



# Handbook on Pædiatric AIDS in Africa

by the African Network for the Care of Children Affected by HIV/AIDS – ANECCA

Fourth Edition  
2017

## Editors

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Brian Eley  
Ruth Nduati  
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Charles Mwansambo  
Dorothy Mbori-  
Ngacha  
Mary Pat Kieffer



**USAID**  
FROM THE AMERICAN PEOPLE

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The African Network for the Care of Children Affected by AIDS (ANECCA) is a Pan African network of health workers and social scientists committed to finding ways of improving the quality of prevention and care for HIV exposed and infected children and adolescents in Africa. Members of the network continue to identify and share scientific and programmatic experiences that could, if put to greater use, rapidly accelerate the attainment of elimination of new HIV infections in children and reduction of HIV related maternal and childhood mortality. One of the methods our members use to share their knowledge is this handbook.

We have as much as possible and where they do exist, endeavoured to remain within the available international guidelines from WHO, UNICEF or UNAIDS, and these are acknowledged.

ANECCA members who are authors of this handbook also form the core of their respective national technical working groups on PMTCT and paediatric AIDS care, and some sections bear resemblance with what appears in their national guidelines. We therefore acknowledge, through the individual authors, those national guidelines.

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## Acronyms and abbreviations

3TC	lamivudine
ABC	abacavir
AIDS	acquired immune deficiency syndrome
ANC	antenatal care
ART	antiretroviral therapy
ARV	antiretroviral drugs
AZT	zidovudine
BCC	behaviour change communication
BCG	Bacillus Calmette-Guérin
CBC	complete blood count
CDC	United States Centers for Disease Control and Prevention
CFR	case fatality rate
CSF	cerebrospinal fluid
CMV	cytomegalovirus
CNS	central nervous system
CRC	United Nations Convention on the Rights of Children
CT	computerized tomography
CTX	cotrimoxazole
d4T	stavudine
ddI	didanosine
DNA	deoxyribonucleic acid
DOT	directly observed therapy
DST	drug susceptibility testing
EBV	Epstein Barr virus
EEG	electroencephalograph
EFV	efavirenz
ELISA	enzyme-linked immunosorbent assay
EPI	expanded programmes on immunisation
FANC	focused antenatal care
FHI	Family Health International
FTC	emtricitabine
gp	glycoprotein
HAART	highly active antiretroviral therapy
HEI	HIV-exposed infant
HIV	human immunodeficiency virus
HPV	human papillomavirus
HRSA	health resources and services administration
HSV	herpes simplex virus
HTS	HIV testing services
IDU	injecting drug user
IMCI	integrated management of childhood illnesses
I/O	input and output
IU	international units
IPT	intermittent preventative therapy; isoniazid preventive therapy
IRIS	immune reconstitution inflammatory syndrome
ITNs	insect-treated bed nets

KS	Kaposi's sarcoma
LBM	lean body mass
LBW	low birth weight
LIP	lymphoid interstitial pneumonitis
LLINs	long-lasting insecticide treated nets
LPV/RTV	lopinavir/ritonavir
LRTI	lower respiratory tract Infection
MCH	maternal and child health
MCP	multiple concurrent sexual partners
MNCH	maternal, neonatal and child health
MRI	magnetic resonance imaging
MTB	<i>Mycobacterium tuberculosis</i>
MTCT	mother-to-child transmission
MUAC	mid-upper-arm circumference
NASBA	nucleic acid sequence-based amplification
NCHS	National Center for Health Statistics
NFV	nelfinavir
NNRTI	non-nucleoside reverse transcriptase inhibitors
NRTI	nucleoside reverse transcriptase inhibitors
NSI	non-syncytium inducing
NVP	nevirapine
OI	opportunistic infection
OVC	orphans and vulnerable children
PACTG	Pediatric AIDS Clinical Trials Group
PCP	<i>Pneumocystis pneumonia</i>
PCR	polymerase chain reaction
PEP	post-exposure prophylaxis
PGL	persistent generalized lymphadenopathy
PI	protease Inhibitor
PLHA	people living with HIV/AIDS
PML	progressive multifocal leukoencephalopathy
PMTCT	prevention of mother-to-child transmission
PrEP	pre-exposure prophylaxis
RAL	raltegravir
ReSoMal	rehydration solution for malnutrition
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT	reverse transcriptase
RTV	ritonavir
RV	rotavirus
SFT	skin-fold thickness
SMX	sulfamethoxazole
SRH	sexual and reproductive health
SSA	sub-Saharan Africa
STI	sexually transmitted infection
TasP	HIV treatment as a prevention
TB	tuberculosis

TLC ..... total lymphocyte count  
TMP ..... trimethoprim  
UNAIDS .... United Nations Joint Program on HIV/AIDS  
UNFPA ..... United Nations Population Fund  
UNICEF ..... United Nations Children's Fund  
URTI ..... upper respiratory tract infection  
USAID ..... United States Agency for International Development  
VCT ..... voluntary counselling and testing  
VL ..... viral load  
VZIG ..... varicella-zoster immune globulin  
WBC ..... white blood count  
WHO ..... World Health Organization





# Chapter 1

## Introduction



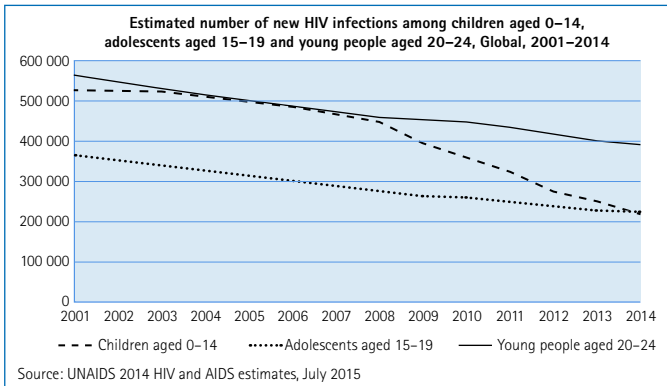
## Introduction

HIV/AIDS is a major cause of infant and childhood mortality and morbidity in Africa.

Globally, of the 36.7 million people living with HIV, in 2015, 1.8 million were children under age of 15 years there were 150 000 new infections and 110 000 HIV-related deaths in this age group. Eighty-seven percent of all HIV infected children below 15 years, 84% of new infections and 86% of HIV-related deaths were in sub-Saharan Africa. Although there has been a 50% decline in paediatric infections since 2010, the numbers of new paediatric HIV infections in sub-Saharan Africa are still unacceptably high.

**Figure 1.1** shows the trends of new HIV infections among children, adolescents and young people

**Figure 1.1** New infection trends among children, adolescents and young people



The high rate of HIV infection in children in Africa results directly from the high rate of HIV infection in women of childbearing age, the high fertility rate and the efficiency of mother-to-child-transmission (MTCT). As in adults, the prevalence of HIV in children varies widely within countries and within different regions in Africa. However, this rate continues to decline because of prevention of mother-to-child-transmission (PMTCT) interventions.

This handbook outlines the science of HIV infection and the technologies and tools that are used to prevent it, to improve the quality of life of those who are infected, and to otherwise mitigate the impact of HIV on children and their families. The handbook also outlines the strategies that are required to reach those who need these services and sets the standards for such services.

### Historical perspective

Adult AIDS, and particularly the syndrome ‘slim disease’, was first described in Africa in the early 1980s. Paediatric HIV cases were first seen in clinical services in the east African region in the early- to mid-1980s.

In Rwanda and Democratic Republic of Congo (DRC) (Kinshasa) the first cases of paediatric AIDS were identified in 1983 – 1984 in clinical services and later in seroprevalence and perinatal studies. In Uganda, reports of paediatric HIV were documented in 1985 and a specialist clinic started in 1988.

In the mid- to late-1980s, longitudinal cohort studies were started in the cities of Kigali, Kampala, Kinshasha, Nairobi, and Blantyre, among others, to study the MTCT rate and the natural history of HIV-exposed and -infected children.

### The magnitude of the HIV/AIDS epidemic in children in sub-Saharan Africa

Of the 36.7 (range 34.0–39.8 million) million people living with HIV in 2015, 70% live in sub-Saharan Africa (SSA), and about 80% of infected women are in sub-Saharan Africa. In 2015, of the 1.4 million pregnant women living with HIV, 90% were in SSA, a main source of paediatric HIV.

For the most part, HIV infection in children is preventable. In industrialized countries in North America and Europe, paediatric HIV infection has largely been controlled. In these settings, HIV testing as part of routine antenatal care, combinations of antiretroviral (ARV) drug regimens, elective caesarean section, and complete avoidance of breastfeeding have translated into absolute vertical transmission rates of less than 2%.

While there has been tremendous improvement, lack of access to currently available and feasible interventions in Africa translates into a high burden of paediatric HIV disease.

**Table 1.1** is a summary of HIV epidemic in women and children.

**Table 1.1** Global summary of the HIV epidemic in women and children, 2015

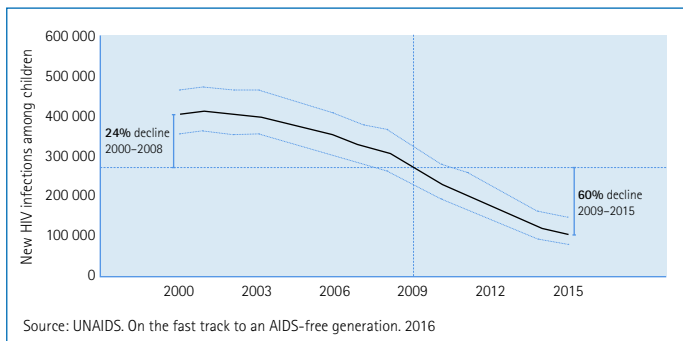
	Global	Sub-Saharan Africa	% of Global
Women (15+) living with HIV	17 800 000	14 200 000	80
Pregnant women living with HIV	1 400 000	1 300 000	90
<b>Children (&lt;15) living with HIV</b>	<b>1 800 000</b>	<b>1 600 000</b>	<b>87</b>
Children (<15) newly infected with HIV	150 000	120 000	84
Children (<15) dying of AIDS-related causes	110 000	91 000	86

Source: UNAIDS, July 2016

## The impact of the AIDS epidemic on children

**Figure 1.2** shows the trend of new infections among children less than 15 years old.

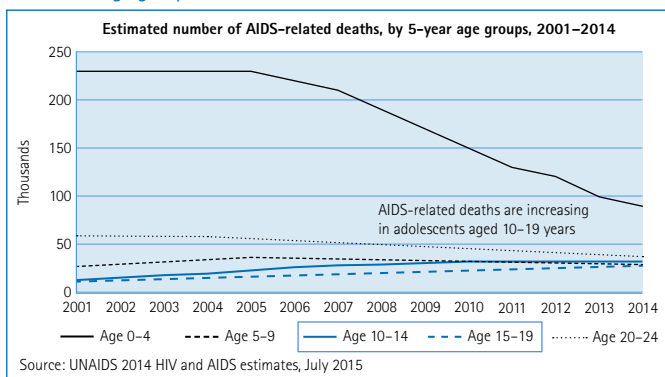
**Figure 1.2** The trend of new infections among children less than 15 years old



AIDS has a devastating effect on children.

The global under-5 mortality rate fell from 90.6 deaths per 1 000 live births in 1990 to 42.5 in 2015. However, the global under-5 mortality rate was reduced by only 53% (50–55%) in the past 25 years and so missed the MDG 4 target, which was to reduce this by two-thirds. It is estimated that about 11 000 children under 15 died of AIDS-related causes in 2015 alone, 86% in SSA. The vast majority of these deaths were preventable, either through antibiotic treatment of opportunistic infections or through antiretroviral treatment. **Figure 1.3** shows the estimated number of AIDS-related deaths in children and adolescents by age group.

**Figure 1.3** Estimated number of AIDS-related deaths in children and adolescents by age group



There were more than 34 million orphans in SSA by end of 2015 and some 11 million of them are orphaned by AIDS. Globally, eight out of every 10 children whose parents have died of AIDS live in sub-Saharan Africa.

The impact of AIDS on families and communities also affects non-orphaned children. With the deepening poverty that results from sick and dying parents, children suffer mental, psychological, and social distress and increasing material hardships. Children may be the only caregivers for their sick or dying parents, may drop out of or interrupt

school, and are at risk of discrimination and abuse, both physical and sexual.

### **Modes of HIV transmission to children**

There are several potential modes of transmission of HIV to children, including MTCT, sexual transmission between adolescents, sexual abuse of children, transfusion of infected blood or blood products, unsterile injection procedures and scarification.

More than 95% of HIV-infected infants in Africa acquire HIV from their mothers during pregnancy, at the time of delivery, or postnatally through breastfeeding. Without any intervention, between 30 and 40% of breastfeeding HIV-positive women transmit HIV to their newborns. The risk factors that increase MTCT are detailed in **Chapter 3**.

Sexual transmission is a significant mode of transmission to adolescents. Adolescent girls are particularly vulnerable to transactional sex – sex in exchange for goods or gifts.

**Chapter 9** reviews some of the combination prevention approaches that can be effective in HIV prevention in adolescents.

The role of child sexual abuse as a source of HIV infection in children is not well documented, but this mode of transmission is of particular concern in countries where both HIV and child sexual abuse are major public health concerns. Orphans are particularly vulnerable to sexual abuse.

Transfusion of infected blood or blood products is another possible source of HIV infection in children, but this mode of transmission has been greatly reduced by national blood safety programmes and improved blood transfusion services.

HIV can also be transmitted to children by using unsterile injection needles and procedures, but this is considered rare, even in Africa. WHO estimates that unsafe injections account for about 2.5% of HIV infections in both adults and children.

Scarification by traditional healers may also be a source of infection to children. While scarification may be more frequent in HIV-infected

children, the process may represent desperate attempts by mothers and guardians to treat recurrent illnesses in the child, rather than being the source of the HIV infection. However, any communal traditional rituals and therapeutic procedures that involve bleeding are potential modes of transmission and communities must be educated about the potential dangers of these practices.

## Progress made

In the last 6 years tremendous progress has been made in the prevention, care and treatment of HIV in children in Africa, resulting in a 50% decline in paediatric infections since 2010. Both research in Africa and programmatic experience have greatly contributed to global knowledge and further reduction in new infections and mortality in HIV-exposed and -infected children.

The HIV prevalence in the general population has declined in many countries, and national programmes have increased the number of HIV-infected pregnant women receiving services for PMTCT as well as treatment of their own illnesses and those of their families.

By 2015, more than 80% of pregnant women living with HIV in sub-Saharan Africa had access to medicines to prevent transmission of the virus to their child – up from just 36% (excluding the less-effective, single-dose nevirapine) in 2009.

By 2015, most countries in SSA, were routinely offering lifelong HIV treatment to all pregnant women living with HIV. The massive scale-up of treatment has helped to reduce AIDS-related deaths among women of reproductive age, which declined by 43% between 2009 and 2015.

New HIV infections among children in SSA dropped from 270 000 (range 230 000–330 000) in 2009 to 110 000 (range 78 000–150 000) in 2015.

Major successes have also been seen in increasing access to treatment for children living with HIV in SSA: access has increased more than threefold since 2009 – from 15% in 2009 to 51% in 2015. However, this is still only half of all children in need of treatment. Major efforts



are required to ensure that all children born to HIV-positive mothers are tested for HIV within the first 2 months of life. Without immediate access to treatment, around 30% of children living with HIV will die within the first year of life and more than 50% will die before they reach their fifth birthday.

Seven years ago PCR testing for children in Africa seemed impossible for most HIV exposed children outside research settings. However, the availability of dried blood spots (DBS) has revolutionized and dramatically improved access to PCR testing for children in Africa. Relatively easy specimen collection and easy storage of samples has allowed some HIV exposed infants in remote rural areas to access PCR testing.

### **The challenges that remain**

The quality of most PMTCT programmes is sub-optimal, with significant drop offs between the first contact and the completion of a service package, and there are still many women who do not reach the health system. The follow-up of mother-baby pairs after first identification as HIV positive is still very weak in most of Africa, with low rates of facility delivery and weak linkages to care and treatment services.

Early infant diagnosis by PCR still remains a challenge, with only about half of children born to HIV-infected mothers having an HIV test within 2 months-of-age. While this is attributed to poor follow up of mother-baby pairs and weak integration and linkage of services, the quality of counselling that mothers receive is also poor and there is low general community knowledge about the benefits of early testing of HIV-exposed children. There are significant delays between specimen collection and return of test results to the mother or care giver. This calls for strengthening of the laboratory system, including training on and use of point of care technologies. However, even when results are available, infants with a positive PCR confirming HIV infection are not started on treatment in a timely manner, and so this is not having an impact on the high mortality associated with HIV in this age group.

Provider-initiated testing and counselling (PITC) for all children coming into contact with the health system is not widely practised

as internationally recommended for high prevalence (HIV prevalence >1% in pregnant women) areas, partly as a result of inadequate numbers of knowledgeable, skilled and confident service providers and weak commodity management systems.

Other challenges that remain for the care and treatment for HIV infected children are:

- Poor supply chain management systems
- Child-friendly ARV formulations including fixed drug combinations
- Simplified paediatric regimens
- Options for second line regimens for children
- Trained (and stable) manpower
- Services that respond to the needs of adolescents and young people
- Weak data management systems and data use for service and quality improvement
- Greater community engagement, and especially involvement of people living with HIV.

### The future

Scientific and programmatic evidence from Africa has demonstrated that virtual elimination of paediatric AIDS is possible and the international community has committed itself to achieving this goal. We must support these exceptional global and national efforts so that all women, especially pregnant women, have access to high quality, life-saving services for prevention, care and treatment of HIV for themselves and for their children.

The future holds exciting opportunities for improving health services using electronic technology as has already been seen with mobile phones, SMS printers, patient databases, and point-of-care equipment. We must, therefore, embrace technological advances and participate in their use and/or assessment for applicability in producing quality prevention care and treatment services for children.

This handbook is intended for use primarily by service providers at facility level (clinicians and nurses), medical and nursing students and their lecturers, as well as community health workers in resource-constrained settings where there is a high burden of HIV infection.



# Chapter 2

## HIV virology, pathogenesis, and natural history

### Summary

---

- The HIV life cycle in the host cell can be divided into several steps: binding, fusion, entry, transcription, integration, replication, budding and maturation.
- Knowledge of the structure of HIV is important in understanding the basis for HIV diagnosis and the mechanism of action of antiretroviral (ARV) drugs.
- Current ARV drugs act mainly by antagonizing the various HIV enzymes necessary for viral replication.



## HIV virology and pathogenesis

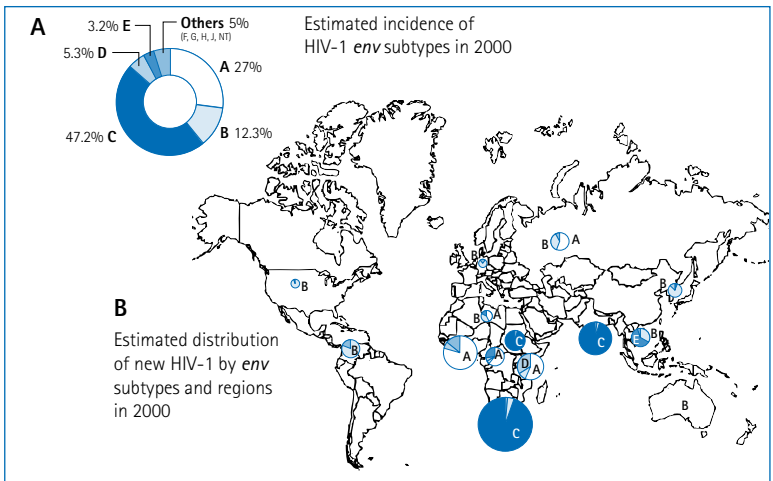
### Basic virology

There are two types of HIV: HIV-1, which is found worldwide and is responsible for the worldwide pandemic, and HIV-2 which is found mainly in West Africa, Mozambique and Angola. HIV-2 is less pathogenic and makes little or no contribution to paediatric AIDS. Therefore, all discussion in this handbook refers to HIV-1.

HIV-1 has many subtypes, often varying in transmissibility and virulence, as well as other characteristics. Africa has mainly subtypes A and D (east and central), C (southern), and A recombinants (west). Subtype C is responsible for over 90% of infections in southern Africa.

As the epidemic has matured, dual infections with different subtypes have occurred and recombinant viruses (containing multiple subtypes) are increasingly common. The proliferation of these more complex forms of the virus may contribute to increased difficulty in treatment management and vaccine development.

**Figure 2.1** The estimated prevalence of HIV-1 *env* subtypes by region in 2000 (Osmanov *et al*, 2002)

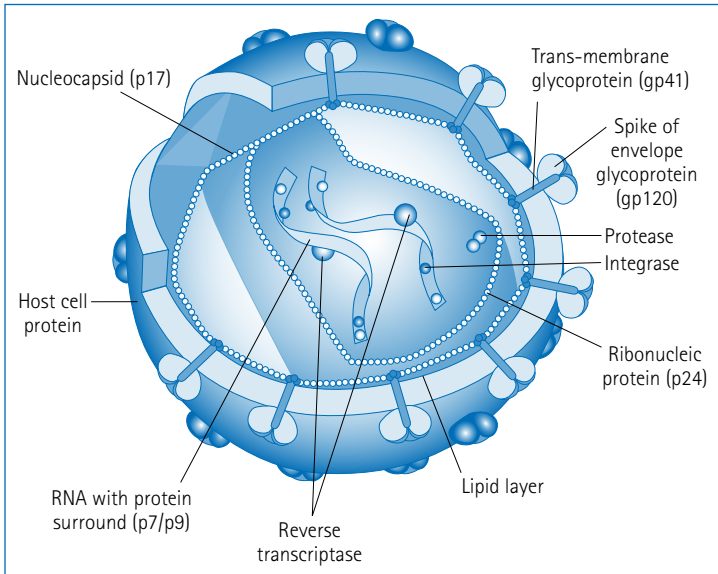


## HIV structure

HIV is a spherical ribonucleic acid (RNA) virus particle with a diameter of 80–100 nanometres (nm) (Figure 2.2). The particle has an outer double lipid layer derived from the host cell membrane. Within the lipid layer is the surface glycoprotein (gp120) and the trans-membrane protein (gp41), which facilitate entry of the virus into the host cell.

The core (capsid) is made of several proteins: p24 (the main protein), p17, p9, and p7. Within this capsid are two single identical strands of RNA, which are the genetic material of the virus (virion). The virion contains a number of enzymes, the most important of which are reverse transcriptase (RT), protease, and integrase.

Figure 2.2 HIV structure



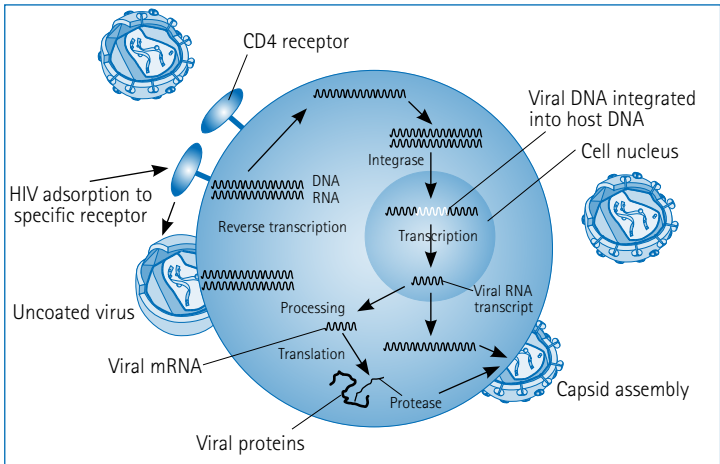
## The HIV life cycle

The HIV life cycle in the host cell can be divided into several steps (Figure 2.3): binding, fusion, entry, transcription, integration, replication, budding, and maturation.



**Binding.** HIV binds to cells via interaction between the HIV envelope glycoprotein (gp120) and the host cell receptors (CD4 molecule) and co-receptors. The receptors are the CD4 antigen found on some T lymphocytes, macrophages, monocytes, glial cells of the brain, and Langerhans cells. The major co-receptors are CCR5 and CXCR4. These receptors and co-receptors determine which cell the HIV virus will infect. HIV strains that use the CCR5 co-receptor are associated with more rapidly progressive illness.

**Figure 2.3** The HIV replication cycle



**Fusion.** The HIV envelope protein (gp120) binds to the host cell receptors and co-receptors on the outside of the cell. This results in the insertion of the trans-membrane glycoprotein (gp41) into the cell membrane of the host cell, with fusion of the two membranes.

**Entry.** The virus particle leaves its membrane behind (un-coating) and the core of the virus is released into the cytoplasm of the host cell. The host cell enzymes interact with the core of the virus, resulting in the release of viral enzymes.

**Reverse transcription.** For the virus to multiply, the viral (single-strand) RNA must first be converted into (double-strand) DNA. This

is done by the viral enzyme reverse transcriptase, which changes the single-stranded viral RNA into double-strand DNA.

**Integration and replication.** The viral DNA is then able to enter the host nucleus and the viral enzyme integrase is used to insert the viral DNA into the host cell's DNA. This is called *integration*. Once a cell is infected, it remains infected for life because the viral genetic material is integrated into the cell's DNA. The production machinery of the host cell produces viral proteins and RNA from which new, immature viral particles are formed in the cytoplasm of the CD4 cell (*replication*).

**Budding.** Newly formed immature viral particles gather at the membrane of the CD4 cells and push through the cell membrane by budding, taking the lipid bilayer with them, ready to form new viral particles.

**Maturation.** The gp160, embedded in the cell membrane, is cleaved by the enzyme protease to produce functional gp41 and gp120 to form a mature virus, which is then ready to infect a new cell.

**Table 2.1** shows the usefulness of the various virus particles in the diagnosis and treatment of HIV.

**Table 2.1** Viral particles (antigen/enzyme) that are useful in the diagnosis and treatment of HIV

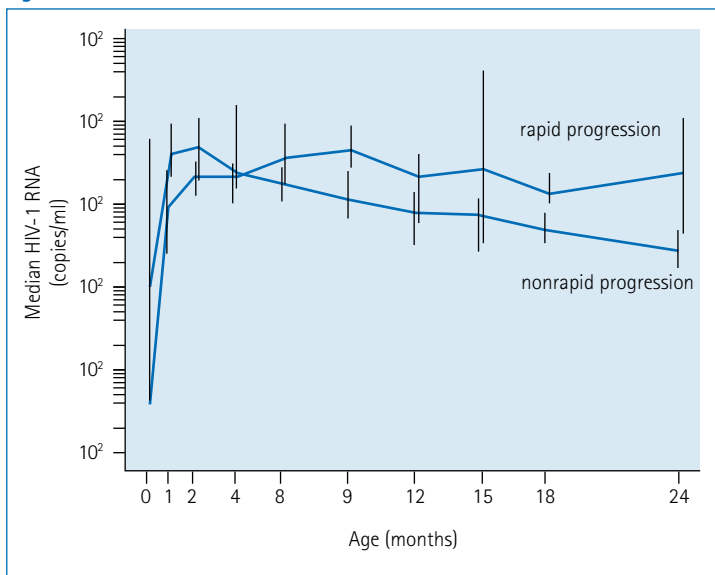
Viral particle	Diagnostic test/ARV target action
Viral DNA	DNA PCR test
Viral RNA	RNA PCR (viral load) test
p24 antigen (core protein of HIV)	p24 antigen test
Reverse transcriptase	<ul style="list-style-type: none"> <li>• Target for nucleoside reverse transcriptase inhibitors (NRTIs), e.g. AZT</li> <li>• Target for non-nucleoside reverse transcriptase inhibitors (NNRTIs), e.g. nevirapine</li> </ul>
Integrase	Target for integrase inhibitors, e.g. raltegravir
Protease	Target for protease inhibitors, e.g. lopinavir
CCR5/ CXCR4 receptor	Target for entry inhibitors, e.g. maraviroc

## HIV replication in infants and children

In the initial stages of HIV disease in adults, the immune system can control viral replication. Use of polymerase chain reaction (PCR) to detect either the viral DNA or viral RNA can reveal HIV in the blood of HIV-infected individuals in these early stages. Several methods can be used to quantify HIV RNA and many of the commonly used assays have a lower limit of detection of 50 copies/ml.

The HIV RNA pattern in perinatally infected infants differs from the pattern in infected adults. HIV RNA levels increase to high values (>100 000 copies/ml) by 2 months of age, remain high throughout the first year of life, and then decline slowly over the next few years. This pattern probably reflects the inability of the infant's immature immune system to contain viral replication and possibly, the greater number of HIV-susceptible cells.

**Figure 2.4** Median HIV-1 RNA levels in infants and children (Shearer *et al*, 1997)



## The effect on the immune system

The basic effect of HIV on the immune system is CD4 cell *depletion* and *dysfunction*. The functional defects can occur before cell numbers decline. Other immunological defects caused by HIV include lymphoid tissue destruction, CD8 cell dysfunction, B-cell abnormalities, thymic dysfunction, and autoimmune abnormalities.

Non-HIV-infected infants and young children normally have higher CD4 counts than adults. The normal CD4 count varies with age, reaching adult levels at 5 to 6 years of age. Interpretation of the HIV-related changes reflected in the absolute CD4 counts are therefore complicated by the age-related differences in values of the normal counts. The CD4 T-cell % that defines each immunologic category does not change with age; CD4 >25% is normal, while CD4 <15% defines severe immune suppression. CD4% is thus the preferred immunologic marker for monitoring disease progression in younger children.

## The mechanism of decline in CD4 count

Several mechanisms are involved in causing the decline in CD4 count. These include:

- CD4 T-cell depletion through single-cell killing caused by the accumulation of HIV DNA in the cell or by the inhibition of cell function
- Cell membranes of infected cells fusing with cell membranes of uninfected cells (syncytium induction), resulting in giant multinucleated cells that are readily destroyed by the immune system
- Programmed death (apoptosis) also contributes to T-cell depletion. It is postulated that cross-linking of the CD4 molecule with gp120-anti-gp120 antibody complexes programmes the cell for death without direct infection of the cell with HIV.
- HIV-specific cytotoxic T-cells (CD8 cells) also play a role in mediated killing of HIV-infected cells.

These events contribute to depletion of CD4 cells and to deteriorating immune function.

## Antiretroviral treatment and HIV vaccines

Antiretroviral therapy (ART) improves the quality of life of individuals infected with HIV by reducing the viral load, but does not cure the infection. HIV infects the cells of the immune system and has highly effective strategies to evade the two major arms of the adaptive immune system: humoral (antibody-mediated) and cellular (T-cell mediated) immunity. In addition the virus has multiple subtypes with a high degree of genetic divergence.

The optimal way to reduce the spread of the AIDS pandemic is through development of a vaccine that will protect individuals from infection, including infants and children. However, after many years of research, HIV remains a difficult target for a vaccine because the virus is highly mutable, resulting in the evolution of numerous divergent strains. Multiple trials are ongoing in adults, but very few have involved children who also would benefit from a successful vaccine.

The discovery of HIV-induced neutralizing antibodies, VRCO1 and VRCO2, that attach the CD4 binding site of HIV and appear to prevent the virus from attaching to and infecting T-cells, could be a candidate for a future preventive vaccine.

On the other hand, with the new drug regimens and programmes for the prevention of mother-to-child-transmission (PMTCT), it is now possible to prevent over 98% of infections from mother to child.

## Natural history

### The clinical course of the infection

There are critical differences between disease progression in children and in adults. These stem largely from the lower efficiency of a child's immature (but developing) immune system and result in much more rapid disease progression and a much shorter duration for each stage.

Perinatally acquired HIV infection in Africa is associated with a poorer prognosis compared with industrialized countries. The higher mortality in HIV-infected children in Africa is attributed to the high burden of inter-current infections (co-infections), malnutrition, and lack of

access to basic healthcare, lack of or delayed definitive diagnosis, and lack of access to primary HIV care and ART.

With no interventions, the majority of perinatally HIV-infected children in Africa develop HIV-related symptoms by 6 months of age and the disease progresses rapidly, with up to 50% of infected children developing AIDS and dying within the first 2 years of life.

There are limited data on clinical and biological indicators of disease progression in HIV-infected children in Africa. Some reports and clinical experience indicate that children perinatally infected with HIV fit into one of three categories:

- **Category 1 (25–30%):** Rapid progressors, who die by the age of one and who are thought to have acquired the infection *in utero* or during the early perinatal period.
- **Category 2 (50–60%):** Children who develop symptoms early in life, followed by a downhill course and death by the age of 3 to 5 years.
- **Category 3 (5–25%):** Long-term survivors, who live beyond the age of 8 years.

## Factors predicting prognosis

Factors used to predict a prognosis are derived mainly from studies performed in industrialized countries. However, these predictors are also useful in the African context. In the clinical management of HIV-infected children, HIV RNA and CD4% provide complementary and independent information about the prognosis for HIV-infected children as well as the response to ART.

HIV-infected children are at higher risk of disease progression if there was a high infecting viral dose (maternal viral load at delivery), and especially if the child was infected before 4 months of life. High infant peak viraemia with slow progress to a low CD4 count and percent, as well as rapid decline in CD4 count, are associated with more

rapid disease progression, as is presence of clinical AIDS and p24 antigenemia.

The mother's disease status also affects the prognosis of infant infection. More rapid progression to death is observed in infants born to women with a high maternal viral load at time of delivery, CD4 counts  $<350$  cells/mm<sup>3</sup> and rapidly progressive maternal disease. Maternal death is associated with a 2–5-fold increase in infant mortality, regardless of the infant's HIV infection status.

### Factors predicting mortality in HIV-infected children

A study done in resource-limited settings showed that low CD4% and CD4 count were the strongest predictors of mortality in untreated HIV-infected children. Other strong predictors of mortality in these children were low weight for age and low haemoglobin. The young children, particularly those aged 1–2 years, who were both severely malnourished and anaemic had high mortality, even at high CD4 values. On the other hand, total lymphocyte count (TLC) was not a good predictor of death in these children.

Because of these difficulties and the high mortality rates, WHO now recommends that all HIV infected children are started on ART, regardless of clinical stage or immunologic status.

### Knowledge gaps

There are limited published data on the natural history of paediatric HIV infection in Africa and other resource-constrained settings beyond the first 3 years of life.

### Recommended reading

Cross Continents Collaboration for Kids (3Cs4kids) Analysis and Writing Committee. Markers for predicting mortality in untreated HIV-infected children in resource-limited settings: a meta-analysis. *AIDS* 2008, 22: 97–105.

Essex, M. et al. *AIDS in Africa*. Kluwer Academic Publishers, 2002.

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# Chapter 3

## Preventing paediatric HIV infection

### Summary

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- Mother-to-child transmission (MTCT) of HIV accounts for over 95% of childhood paediatric infections in sub-Saharan Africa. Recent advances suggest that elimination of paediatric infections is now well within the realm of possibility, even in low and middle income countries.
- All HIV-infected pregnant and breastfeeding women must receive antiretroviral therapy (ART) as a priority, at any gestational age.
- Antiretroviral treatment or prophylaxis for the mother and/or infant prevents breast milk transmission of HIV and affords the baby the benefits of breastfeeding.
- PMTCT programmes provide the opportunity for early infant diagnosis (EID) and timely initiation of ART in children less than 24 months.
- Integration of PMTCT into maternal, neonatal and child health (MNCH) presents an opportunity to avert maternal mortality from complications related to pregnancy and childbearing and from HIV – the two top causes of death in women of reproductive age in sub-Saharan Africa. This platform also offers the opportunity for early detection of HIV exposure/infection and averts morbidity and mortality from HIV/AIDS in infants.
- Comprehensive PMTCT programmes offer unique opportunities to interface with women and men in the reproductive age group for primary HIV prevention.
- Systematic introduction of family planning (FP) services and the introduction of HIV services (HTS/HTS, care and ART) in FP significantly improve the effectiveness of PMTCT programmes.
- Integration of PMTCT and ART clinics, together with streamlined systems for ART provision, follow up and referrals are critical for the success of PMTCT programmes.



## Mother-to-child transmission of HIV

Mother-to-child transmission of HIV accounts for over 95% of childhood paediatric HIV infections in sub-Saharan Africa. Infants who acquire HIV infection from their mothers do so during pregnancy, labour and delivery or after birth through breastfeeding. The absolute transmission risk is shown in **Table 3.1**, while **Table 3.2** shows the magnitude and attributable risk among breastfed infants.

**Table 3.1** Estimated timing of transmission and absolute transmission rates

Time of transmission	Absolute transmission rate (%)
During pregnancy	5–10
During labour and delivery	10–20
During breastfeeding	5–20

**Table 3.2** Transmission rates among breastfed infants born to HIV infected mothers

Time of transmission	Absolute transmission rate (%)
Overall without breastfeeding	15–30
Overall with breastfeeding through 6 months	25–35
Overall with breastfeeding through 18 to 24 months	30–45

Source: Decock et al., *JAMA*, 2000, 283:1175–1182

## Risks and associated factors for transmission

Women who have severe immunosuppression ( $CD4 < 350$  cells/mm<sup>3</sup>) are at the highest risk of transmitting HIV to their infants. Similarly, women who are newly infected during pregnancy or lactation also have a much higher likelihood – documented in Zimbabwe to be as high as 66% – of transmitting HIV to their infants because of the surge in viral load during a new infection. The other factors that increase the risk of MTCT of HIV are shown in **Table 3.3**. The impact of these factors is dependent upon their strength and the frequency of the factor within the population.

**Table 3.3** Risk factors for mother-to-child transmission of HIV, strength of association and impact on overall rate of transmission

Risk factor	Strength of association	Impact
<b>Maternal</b>		
RNA viral load	Strong	Large
AIDS	Strong	Small to medium
Immune deficiency	Strong	Medium
Genetic	Weak	Small
Other STIs	Medium	Small to medium
Chorioamnionitis	Medium	Small
Vitamin A deficiency	Medium	Small
<b>Obstetric</b>		
Mode of delivery	Strong	Large
Duration of membrane rupture	Strong	Large
RNA in vagina/cervix	Medium	Medium
Invasive procedures	Strong	Small
<b>Pædiatric</b>		
Prematurity	Strong	Medium
Breastfeeding	Strong	Large
Breast health	Strong	Small
Genetic	Weak	Small

## Preventing pædiatric HIV infection

The United Nations (UN) four-pronged approach remains the framework for prevention of pædiatric HIV infection. While efforts have often focused on Prongs 3 and 4, programmes must include all four prongs in order to provide comprehensive services to pregnant women and to begin to approach elimination of pædiatric HIV.

### The four prongs of PMTCT:

Prong 1: Primary prevention of HIV infection

Prong 2: Preventing unintended pregnancy among HIV-infected women

Prong 3: Prevention of mother-to-child-transmission of HIV in a pregnant woman

Prong 4: Providing care and support to HIV-infected women, their infants and their families.

### Prong 1: Primary prevention of HIV infection

The majority of women attending PMTCT services are HIV negative. Efforts must continue to keep these women and their partners HIV negative.

In countries with generalized epidemics, the majority of new infections occur in the general population through heterosexual transmission, either as a result of people having multiple concurrent sexual partners (MCP) or in stable discordant couples. The prevalence of HIV discordance among married and cohabitating couples in Africa is high, ranging from 3–20% in the general population and 20–35% within couples in which one partner seeks HIV care services. For this reason, couple counselling and testing, and male involvement must be strengthened in PMTCT clinics.

There is now consensus on ‘combination prevention’, which encompasses the approaches in generalized epidemics shown in the box below.

#### Approaches for combination prevention

- Behavioural change to reduce multiple concurrent sexual partnerships, improve condom use and delay in age of first intercourse
- Biomedical strategies, such as medical male circumcision, partner testing, provide services for discordant couples, PMTCT, post-exposure prophylaxis (PEP), family planning, pre-exposure prophylaxis (PrEP) and use of microbicides
- Treatment of HIV, other viruses and sexually transmitted infections (STIs)
- Structural approaches, addressing the social, economic, political, environmental and legal factors directly affecting HIV risk and vulnerability.

Also see [Chapter 9](#).

#### *Practical steps for preventing HIV in the PMTCT context*

PMTCT programmes can meaningfully contribute through a focus on:

##### 1 Adolescents and young women

- a Particular attention should be paid to younger mothers – negative or positive – and especially to providing couple counselling.

Some programmes have organized additional support for younger mothers.

- b** Keeping young women in school is an effective strategy for delaying sexual debut and empowering them to make safer choices.

## **2 Prevention education for both the HIV negative and the HIV positive**

- a** Education programmes in maternal and child health/sexual and reproductive health (MNCH/SRH) settings should be strengthened to address HIV prevention with emphasis on prevention of multiple concurrent partners (MCP) and condom use.
- b** Prevention with Positives is important for HIV-positive women and their partners, who are often excluded from important prevention counselling.

## **3 Provider initiated testing and counselling (PITC)**

PITC should be recommended as a standard of care for women and their partners in antenatal clinics, at delivery and during the postpartum period, with subsequent care guided by sero-status:

- a** Women should be tested and counselled for HIV and subsequent interventions tailored according to the woman's and partner's sero-status.
- b** Couple or partner testing and counselling can identify negative partners of a positive partner who are at very high risk of HIV infection.
- c** Women and partners who test HIV negative present an opportunity for prevention (see below).
- d** HIV-negative women should be retested later in pregnancy, at delivery and during breastfeeding, especially in countries with higher HIV prevalence. This allows for institution of PMTCT measures for women at highest risk of MTCT.

- e** Women and their partners who are identified as priority population, sex workers, MSMs, IDUs, among others, should have tailored interventions to prevent HIV.
- f** All pregnant women should be offered syphilis testing and treatment.
- g** To minimize the risk of horizontal transmission among HIV discordant couples:
  - The HIV-infected partner should be initiated on ART.
  - The couple should avoid unprotected sex or the HIV-uninfected partner should use PrEP if unprotected sex is unavoidable until the HIV-infected partner is virologically suppressed.
- h** Once viral suppression is confirmed re-testing should be performed as per the HIV testing services (HTS) guidelines.

#### **4 Male partner engagement**

- a** Male partner involvement is associated with a high uptake of PMCT interventions and condom use with a regular partner. Male partners can be engaged in MNCH/SRH/HIV programmes through innovations and outreach such as provision of an invitation letter/email/SMS to attend the MNCH clinic with their partner where consent has been granted.
- b** Services should be planned and provided for male partners, both HIV negative and positive. Clinic times should avoid coinciding with working hours given that a majority of men are often in unstable, casual employment.
- c** Provision or referral for medical male circumcision for partners and male infants can be arranged through PMTCT programmes.
- d** Condoms (both male and female) and other supplies must be available and health workers should promote correct and consistent condom use.

## 5 Community mobilization

- a Partnership between facilities and communities is important, engendering ownership of services, promoting services and providing the space for on-going, community-led dialogue on factors driving the HIV epidemic and how to address them.
- b HIV prevention efforts already exist in many communities, spearheaded by community-based organizations (CBOs), faith based groups and local NGOs. These efforts often reach a large segment of the population. However, they do not always adequately address HIV prevention needs for women and children. Effective outreach and partnership with these groups and established networks can have a multiplier effect on the prevention outcomes of PMTCT programmes.

### Prong 2: Preventing unintended pregnancy among HIV-infected women

Countries with the greatest burden of HIV also have high levels of unmet need for family planning with low coverage and uptake of services, leaving women in these countries at risk for both unintended pregnancy and HIV, and as a result, more infected children.

As PMTCT programmes mature, an increasing number of already diagnosed HIV-infected women are attending antenatal services with new pregnancies. While some of these pregnancies are planned and wanted, many are not. Estimates of unintended pregnancies among HIV-infected women are as high as 51–91% in Africa.

Hormonal contraception is the most effective method of family planning. However, it can increase women's vulnerability to viral and bacterial STIs and increases genital shedding of the virus in HIV-infected women, thus making them more infectious to their sexual partners. Therefore, a combination of hormonal and barrier methods (dual protection) will effectively guard against unintended pregnancies as well as STIs, including HIV.



### **Specific actions to integrate and link HIV to SRH/family planning services in the context of PMTCT**

- 1 Utilize HIV services (HTS, care, ART) to provide family planning information and services for women.
- 2 Utilize family planning services to provide HIV services, including HIV testing and counselling, for women and their partners.
- 3 Ensure that providers in HIV and SRH/FP clinics have the knowledge and skills to provide HIV and SRH/FP services, including the active promotion and demonstration of correct and consistent condom use for dual protection.
- 4 Where provision of FP services is not possible at the point of HIV services, and vice versa, the services should collaboratively agree and plan management of referrals.
- 5 Commodities and supplies, especially for FP, should be planned for and made available at both FP and HIV clinics.
- 6 Task sharing with appropriately trained extension health workers and lay staff including 'expert patients' in both SRH and HIV should be initiated.

### **Prong 3: Prevention of mother-to-child transmission (PMTCT) of HIV from HIV-infected pregnant women to their infants**

In sub-Saharan Africa, as a standard of care, HIV prevention and treatment services must be integrated into MNCH, both at the facility and community level

#### ***Focused antenatal care (FANC)***

PMTCT programmes provide an opportunity to strengthen and improve the quality of focused antenatal care (FANC), labour and delivery and postnatal care for all women. The FANC approach emphasizes the quality of care and diagnostic tests that have proven health benefits, *including HIV testing and counselling*. WHO recommends four antenatal visits in pregnancy, but HIV-infected women will require more than the four visits in order to access and monitor ART.

#### **Focused antenatal care consists of:**

- Health promotion, disease prevention
- Identification of pre-existing health conditions
- Early detection of pregnancy complications
- Screening and treatment for STIs
- Screening for anaemia
- HIV testing, counselling, care and treatment
- Micronutrient prophylaxis (iron, folate and multivitamins)
- Screening for opportunistic infections (OIs) such as TB
- Cotrimoxazole prophylaxis for HIV-infected women (also takes care of malarial prevention)
- Insect-treated bed nets (ITNs), preferably long-lasting insecticide-treated nets (LLINs)
- Tetanus immunization
- Birth planning, complication-readiness planning
- Infant and young child feeding counselling.

#### ***HIV testing and counselling***

HIV testing and counselling is recommended as a standard of care for all women seeking care – during pregnancy as part of FANC, during labour and delivery, or during the post partum period (provider-initiated HIV testing and counselling). It is critical that male partners are engaged and likewise offered HTS.

Repeat HIV testing in later pregnancy, labour and delivery or during breastfeeding should be done according to national guidelines to facilitate identification of previously unknown or recently HIV infected women who would benefit from care and treatment as well as prevention of infections in their infants. Ideally, if the last negative HIV test was more than 2 months before delivery, the test should be repeated when a woman presents in labour.

### Counselling HIV negative women and negative partners

- Educate and counsel on safer sexual practices including promotion of correct and consistent use of condoms, provision of condoms (male and female as appropriate), *particularly during pregnancy and breastfeeding*. This information is crucial because the highest MTCT HIV transmission rates have been documented in women who have seroconverted late in pregnancy.
- Promote HTS for the male partner and invite him to the clinic to receive information, HTS, male circumcision, as appropriate.
- Educate about the importance of and promote repeat HIV testing where nationally recommended.

### Counselling for women and partners newly HIV positive

- Provide HIV test results in a clear manner, allow for processing of information.
- Provide immediate emotional support.
- Provide post-test counselling (should include positive prevention, HTS for partner, medical male circumcision as appropriate).
- Respond to other immediate questions.
- Discuss available support structures and systems, provide contacts – hotline, on-site counselling services, peer support groups.
- Discuss disclosure and whether the client needs support and assistance to disclose.
- Discuss with patients the immediate ‘what next’ – clinical assessment, laboratory diagnostics, initiation of ARVs, cotrimoxazole.
- Make a follow-up counselling appointment and/or communicate open door policy for counselling.
- Supplementary counselling by peer counsellors on the day of diagnosis can help individuals see that there is life after a positive diagnosis.

## Counselling for women known to be HIV positive on arrival at ANC

- Check their treatment status and time of last viral load (VL) or CD4 count where VL not available.
- Counsel on importance of ART and on adherence to treatment during pregnancy and breastfeeding.
- Determine HIV status of partner; if unknown, offer testing or retesting if last negative test was not recent.
- Discuss with patients the immediate ‘what next’ – clinical assessment, laboratory diagnostics, initiation of ARVs, cotrimoxazole.

## Clinical management of the pregnant woman with HIV

### 1 Use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants

In 1994 the Pediatric AIDS Clinical Trials Group (PACTG) in the United States published the first randomised controlled trial demonstrating that prophylactic ARVs could reduce perinatal transmission of HIV. In the PACTG 076 study, an intensive AZT regimen starting at the end of the first trimester in the mother and from birth to 6 weeks in the infant, reduced transmission from 25.5% to 8.3%. Since then several successful trials have shown that a combination of interventions may reduce transmission rates significantly, shown in the Kesho Bora study and the Mma Bana study.

There are two basic approaches recommended for the prevention of transmission to infants, depending on the mother’s stage of HIV disease:

- 1 Lifelong ART for ALL HIV-infected pregnant and breastfeeding women, plus 4–6 weeks of infant ARV prophylaxis.
- 2 Triple ARVs for all HIV-infected pregnant women who are not in need of ART for their own health, plus infant ARV prophylaxis for as long as the babies are breastfeeding or for 4–6 weeks for non-breastfed infants.

Most countries in Africa have adopted or are in the process of adopting the approach of lifelong ART for ALL HIV-infected pregnant or breastfeeding women. This approach is intended to:

- Reach more eligible women (who would otherwise have been missed because of none availability of CD4 test, or not clinically staged)
- Prevent more infant infections (especially with prolonged breastfeeding)
- Prevent spousal infections (in discordant relationships).

It also avoids the need to stop and re-start ARVs for PMTCT in populations with high fertility rates. See [Table 3.4](#).

**Table 3.4** Practical considerations for provision of ART within MCH settings

Key element	Questions to consider
Simplicity for providers	Is the regimen easy for midwives and other providers to understand and implement?
Laboratory requirements	Access to VL or CD4 where VL not available, for every pregnant woman, but CVL or CD4 not a hindrance to ART start
Supply chain	Can the supply chain be integrated with the ART supply chain?
<b>Infant feeding considerations</b>	What will the impact of lifelong ART for all pregnant and breastfeeding women (Option B plus) be on breast feeding? Weaning?
Monitoring and evaluation	Consider the reporting tools, ease of documentation, data use by facility teams
Adherence messages	Are there standardised messages? What messages need to be provided? Are the midwives able to provide these?
Integration with other services	Can PMTCT services be integrated easily with post natal care, family planning, ART clinic?
Psychosocial support	What support is available at national level, facility level, effect of support groups?
Appointment monitoring	Are there mechanisms in place for appointment management for mother-infant pair?
Follow up mechanisms	How will mothers and exposed infants be followed up? Are there streamlined systems for follow up?

ART should be started at any gestational age, including first trimester, with the recommended regimen seen in [Table 3.5](#). This allows for decentralized and integrated ART so that service providers at primary care level and/or in MCH settings can easily provide ART to pregnant and breastfeeding women at the earliest opportunity. This should enable rapid scale up of services for quicker achievement of targets for elimination of mother-to-child transmission.

The baby should receive daily nevirapine (NVP) or twice daily zidovudine (AZT) from birth to 4–6 weeks of age (See [Tables 3.6a and b](#)). The infant should be exclusively breastfed and complementary feeds should be appropriately introduced at 6 months, with the baby continuing to breastfeed until at least 12 months of age (see [Chapter 12](#)).

**Table 3.5** Antiretroviral treatment options recommended for HIV-infected pregnant women

<b>Maternal ART + infant prophylaxis</b>
<b>Mother</b>
<p>Maternal antepartum daily ART, starting as soon as possible, irrespective of gestational age and continued throughout pregnancy, delivery and thereafter. Recommended regimens include:</p> <p>A once daily FDC of TDF + 3TC (or FTC) + EFV (applies for both lifelong and for triple ARVs initiated for PMTCT but discontinued at end of MTCT risk).</p> <p>If TDF + 3TC (or FTC) + EFV is contraindicated or not available, one of the following options are recommended:</p> <p>AZT + 3TC + EFV            AZT + 3TC + NVP            TDF + 3TC (or FTC) + NVP</p> <p>This approach calls for increased pharmaco-vigilance for toxicity for the woman, fetus, and neonate exposed to the ARVs.</p>
<b>Infant</b>
<p>Daily NVP or twice daily AZT from birth until 4–6weeks of age (irrespective of mode of infant feeding)</p>

FDC – triple fixed-dose combination; TDF – tenofovir; 3TC – lamivudine; FTC – emtricitabine; EFV – efavirenz; NVP – nevirapine

**NB:** A combination infant prophylaxis regimen NVP with AZT, is recommended for infants at higher risk of HIV acquisition including those born to HIV-infected women who have not received antepartum or intrapartum ARV drugs or who have received only intrapartum ARV drugs or have received antepartum ARV drugs but do not have viral suppression near delivery (refer to national guidelines). The duration can also be prolonged to 12 weeks.

**Table 3.6a** Infant nevirapine dosing table (nevirapine suspension: 10 mg/ml)

Weight and/or age	Oral dosing
< 2 000 grams	Consult with an experienced clinician Starting dose 2 mg/kg/day (or 0.2 ml/kg/day)
At birth until 6 weeks: 2–2.5 kg > 2.5 kg	10 mg/day (or 1 ml/day) 15 mg/day (or 1.5 ml/day)
6 weeks to 5.9 months	20 mg/day (or 2 ml/day)
6 to 8.9 months	30 mg/day (or 3 ml/day)
9 months to breastfeeding cessation	40 mg/day (or 4 ml/day)

**Table 3.6b** Infant zidovudine (AZT) dosing table (AZT syrup: 10 mg/ml)

Age	Zidovudine dose
10–12 weeks	Birth weight <2 500g 10 mg/kg twice a day Birth weight >2 500g 15 mg/kg twice a day

## 2 Prevention of opportunistic infections during pregnancy

Women with HIV are vulnerable to opportunistic infections. Assessment during pregnancy should include a focused evaluation for opportunistic infections.

**Malaria** during pregnancy is one of the most common causes of low birth weight infants. Dual infection with HIV and malaria is associated with an increased risk of maternal, perinatal and early infant death compared with the risks of either disease alone. Unlike HIV-negative women who acquire placental immunity against malaria, HIV-infected

women continue to be at risk. Chorioamnionitis from malaria has been associated with increased MTCT.

STIs increase genital shedding of HIV, precipitate premature delivery, and increase an infant's risk of HIV infection.

**TB:** There are data from South Africa to suggest that maternal TB appears to be an important risk factor associated with HIV MTCT. In addition 'provider-initiated TB screening' among HIV-infected pregnant women in South Africa, a country with large epidemics of both, appeared to be a high yield intervention, identifying many women with incident TB, many of whom are in need of ART.

***Pneumocystis jirovecii* pneumonia (PCP):** This rapid onset pneumonia has a high fatality rate and has been associated with premature delivery, leading to increased risk of HIV transmission to the infant. Cotrimoxazole prophylaxis, which also protects against other bacterial infections and malaria, should be provided to pregnant HIV-infected women according to national guidelines.

The following should be done:

- **TB:** Clinical screening for TB according to national protocols. Typically this will include eliciting relevant history of cough of any duration and contact with TB.
- **Malaria:** promotion of use, and provision of ITNs, preferably long lasting insecticidal treated nets (LLINs). Intermittent preventive malaria therapy as per national guidelines for women not yet on cotrimoxazole (CTX). Intermittent preventive treatment (IPT) of malaria during pregnancy significantly reduces malaria-related adverse outcomes. (Note that women on CTX prophylaxis are protected from malaria and do not require IPT).
- **Sexually transmitted infections (STIs) and urinary tract diseases:** actively seek symptoms by taking a clinical history and carrying out a genital examination (because STIs are usually asymptomatic in women). Routinely screen for syphilis.



- Cotrimoxazole (CTX) preventive therapy: Initiate CTX prophylaxis according to national guidelines (replacing IPT if earlier started in malaria endemic areas).

### 3 Nutritional education and support (see also Chapter 12)

Nutritional education and support (including multivitamin supplementation) is associated with a decrease in the incidence of low birth weight and congenital defects, thus improving birth outcomes in HIV-infected women. HIV-infected women have increased calorie requirements depending on their stage of HIV disease. There is no indication for increased protein or vitamins above the recommended daily allowance (RDA). Provide:

- Micronutrient supplementation (excluding vitamin A) during pregnancy and lactation. As for other pregnant women, iron supplementation should be provided to prevent maternal anaemia and ensure adequate stores for mother and baby.
- Calorie supplementation. Compared to HIV negative women, infected women who are relatively well require 10% more calories and 30–40% more calories in the presence of opportunistic infections.

### 4 Infant feeding counselling (see also Chapter 11)

Infant feeding is an important element of PMTCT because of the major influence that feeding practices exert on child survival. Breastfeeding by an HIV-infected mother increases the risk of HIV transmission by 10–20%. However, *lack* of breastfeeding increases the risk of malnutrition, other infectious diseases (other than HIV) and death.

Infant feeding practices by mothers known to be HIV infected should support the greatest likelihood of HIV-free survival of their children and not harm the health of mothers. With the currently available technology, MTCT from breastfeeding is substantially preventable through the provision of ARVs to the mother, and to her infant.

The effectiveness of ARVs in reducing HIV transmission, in conjunction with the known benefits of breastfeeding in reducing mortality from other causes, justifies an approach that strongly

recommends exclusive breastfeeding with ARV cover as the strategy that is the most likely to give infants born to mothers known to be HIV infected the greatest chance of HIV-free survival.

National PMTCT programmes and MNCH services should seek to institutionalize support for exclusive breastfeeding and young child nutrition as an integral part of care for all pregnant and breastfeeding women by:

- Ensuring HIV and infant feeding is a systemic part of national PMTCT planning and budgeting, financing, implementation, monitoring and evaluation
- Ensuring HIV and infant feeding are included as part of PMTCT training
- Ensuring infant feeding counselling, and support for optimal infant feeding practice is a standard of care
- Using ARV delivery systems during the postnatal period to reinforce exclusive breastfeeding
- Good weaning practices with the introduction of nutritious complementary foods
- Supporting the recording, measurement and tracking of infant feeding practice as part of national PMTCT reporting.

## **5 Safer delivery practices and care during the immediate postpartum period**

Most HIV transmission occurs around the time of labour and delivery and the risk increases with prolonged rupture of membranes, invasive procedures, and prematurity even in the presence of ARV prophylaxis.

Elective caesarean section (before the onset of labour or the rupture of membranes) may reduce the MTCT risk. However, caesarean section is not advocated for PMTCT in settings where its feasibility and safety are questionable. For women on ART, caesarean section is probably only indicated in women with an undetectable viral load.

Chlorhexidine vaginal douches have been shown to reduce the incidence of some neonatal and maternal infections, but not of HIV transmission unless the membranes are ruptured for longer than 4 hours.

The following measures are recommended during delivery and postnatal care:

- Discourage invasive obstetric procedures such as artificial rupture of membranes before full dilatation, fetal scalp monitoring, vacuum extraction, and episiotomy.
- Institute normative immediate newborn care practices, including wiping off the infant, keeping the baby warm through bodily contact with the mother and early initiation of breastfeeding.
- Avoid vigorous suctioning of the infant (if the procedure is indeed necessary).
- Clarify any outstanding questions about breastfeeding (or replacement feeding) with the mother.
- Support the mother in initiating exclusive breastfeeding within the first 30 minutes of birth, including instruction and support for good latching-on technique.
- Support and assist mothers who elect to replacement feed with demonstrations on how to correctly prepare replacement feeds.
- Counsel mothers on food hygiene and personal hygiene, as well as issues related to maternal infant bonding, particularly for those whose infants receive replacement food.
- Counsel on ARV adherence during breastfeeding; confirm follow up appointment for postnatal/child health services.
- For HIV-positive mothers who present late with their babies: check the maternal VL, take a dried blood spot (DBS) sample from the baby for HIV DNA PCR; initiate ARV prophylaxis according to guidelines if breastfeeding.

#### **Prong 4: Providing care and support to HIV-infected women, their infants, and their families**

HIV-infected women, their infants and their families should be enrolled in care programmes, and offered ART and other forms of care as required. For details see [Chapter 4](#).

#### *Horizontally transmitted HIV among children*

Children may also acquire HIV from modes other than mother-to-child transmission. These include:

- Sexual abuse by an HIV-positive perpetrator.
- Transfusion with contaminated blood and blood products.
- Nosocomial transmission occurring through contaminated or incompletely sterilised instruments.
- Ingestion of HIV-infected breastmilk, e.g. through hospital breastmilk banks or wet-nursing by an HIV infected woman.
- Traditional practices that involve cutting with shared unsterilized instruments.
- In a small number of infants with sero-negative parents, the mode of transmission is uncertain.

#### *Sexual abuse*

Relative to MTCT, sexual abuse accounts for a small proportion of HIV infection in children world-wide. However, there are several factors that contribute to underestimating infections arising from child sexual abuse:

- Sexual abuse is often not reported.
- Perpetrators are often family members.
- Those who are especially vulnerable to abuse, e.g. orphans, are often least empowered both to report or seek care.
- It may be difficult to tell if an older child was infected perinatally or as a result of sexual abuse.

Survivors of sexual abuse experience complex needs relative to the development of systems for care provision in resource-limited settings. In addition to the risk of infection with HIV and STIs, sexual abuse can also result in serious physical injuries, profound psychological trauma, and unwanted pregnancy. Prevention of child sexual abuse is the ultimate goal.

The comprehensive care of a sexually abused child includes:

- Counselling (trauma, pre- and post-test HIV counselling, legal, adherence counselling if appropriate, follow up)
- Legal and forensic referral
- Treatment and management of injuries
- Presumptive treatment for sexually transmitted infections (STIs) according to national guidelines; collect appropriate forensic evidence, including appropriate perineal swabs according to local guidelines
- Post-exposure prophylaxis (PEP) for HIV with triple ARVs for HIV-uninfected children
- Care and treatment for those who are already HIV positive
- Prevention of hepatitis B through vaccination
- Pregnancy prevention, emergency contraception (EC) for older girls who have reached menarche or who show secondary sexual characteristics. It is important to note that a baseline pregnancy test should be offered where feasible, and EC is most effective when given early and in any case within 72 hours.

### *Transfusion of blood products*

Children in Africa are often transfused because of severe anaemia, particularly in areas where malaria is endemic. Routine donor screening has largely eliminated blood products as a route for transmission. However, a small number of such transmissions do occur where there is no safe blood supply or because HIV-infected donors were not detected during the *window period*.

## Preventing other modes of horizontal transmission

Methods for preventing other modes of HIV transmission include:

- Instituting hospital infection control measures such as protective clothing (including gloves and eye protection), use of antiseptic techniques, sterilization of instruments and equipment, and adequate waste storage and disposal systems.
- Reviewing infection control measures regularly to minimise nosocomial infection. Pay attention to practices that are specific to each clinical discipline. Eliminating the reuse of needles and syringes.
- Taking special care with the administration of expressed breastmilk. Do not use communal breast pumps. Place expressed milk into labelled bottles and check the labelled bottles before giving milk to any baby.

### Post-Exposure Prophylaxis (PEP)

- Initiate post-exposure prophylaxis (PEP) after rape (including sodomy) as soon as possible. PEP is most effective if begun within 24 hours of the assault and is probably ineffective after 72 hours.
- Perform HIV testing at presentation.
- Repeat HIV testing at intervals of 6 to 8 weeks, 3 months, and 6 months after the assault. Most sero-conversions occur within 6 to 8 weeks of exposure.

For children found to be HIV-negative:

- Administer AZT *plus* 3TC for a period of 28 days. On discharge from facility, issue children enough medication to complete the 28-day course (see [Table 3.5](#)).
- Administer 3-drug prophylaxis if significant exposure has occurred, e.g., penetrative sexual assault with perineal lacerations (see [Appendix A](#) for assessment of risk of exposure). Use LPV/RTV in combination with AZT and 3TC for 28 days.

For HIV-positive children:

- If a child is found to be HIV-infected, refer for care and ART (see [Chapter 4](#)).

**Table 3.7** Drug dosage for post-exposure prophylaxis

Drug	Paediatric dose	Adolescent dose
AZT	180 mg/m <sup>2</sup> /12 hours	300 mg 12 hourly
3TC	4 mg/kg/12 hours	150 mg 12 hourly
LPV/RTV	LPV: 230-350 mg/m <sup>2</sup> /12 hours	400/100 mg 12 hourly

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# Chapter 4

## Approach to the care of HIV-exposed and HIV- infected children

### Summary

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- Comprehensive care of the HIV-exposed child that includes PMTCT, nutrition counselling, prevention of infections and growth monitoring is feasible within resource-constrained settings and significantly improves the survival of these children.
- Early diagnosis ensures timely treatment and entry into ARV programmes.
- All HIV-infected children should be started on antiretroviral therapy irrespective of their clinical or immunological stage, to reduce morbidity and mortality.
- Establishment of follow-up services, and appropriate referral system for HIV-exposed children and their families are critical components of their care.
- Ensuring the survival of HIV-infected mothers through provision of appropriate care and treatment is critical to the survival of the child.
- Extending HIV care to other family members provides a support network for the affected child, and improves the survival of the child.
- Clear communication with the caregiver and the affected child that includes participatory planning for long-term care increases the likelihood of treatment success.



## Introduction

The scale up of early infant diagnosis and provider-initiated HIV testing and counselling (PITC) for children has improved identification of infected infants and children. Antiretroviral therapy for children has become increasingly more accessible and affordable. With the launch of the 2016 WHO guidelines and with the scaling up of PMTCT services, health providers in Africa now have the tools and the opportunities to prevent the vast majority of paediatric HIV infections and to provide high quality, comprehensive services for those who are infected. Even with these advances, however, too many HIV-infected children are still being diagnosed late in the course of illness or not at all. Much more needs to be done to accelerate the scale-up of HIV testing, counselling and PMTCT services.

This chapter provides an approach for comprehensive care and treatment catering to the needs of HIV-exposed or -infected children, their mothers and families, within the broader context of services for children affected by HIV. Programme-related issues are discussed in [Chapter 13](#).

## Comprehensive paediatric HIV care

The following comprehensive care package should be provided for HIV-exposed or infected children in the broader context of other child health strategies. See the box for the 10 point package for the comprehensive care of HIV-exposed and -infected children.

### Ten point package of comprehensive care for HIV-exposed and infected children

- 1 Determine HIV status at first contact.
- 2 Counsel and support the mother and family on optimal infant feeding and monitor growth and development of the child.
- 3 Provide prophylaxis (ARV, cotrimoxazole and INH) according to national guidelines as appropriate.
- 4 Ensure that immunizations are started and completed according to national guidelines.
- 5 Actively look for and treat infections early.

- 6 Provide ART for **all** HIV-infected children and adolescents .
- 7 Provide regular monitoring of clinical and laboratory parameters and adherence; refer to higher levels of specialized care as necessary.
- 8 Educate the caregiver and family on all aspects of care for the child.
- 9 Provide ongoing psychological and social support for the family and child and refer to community-based support programmes as appropriate.
- 10 Ensure that the mother and family members are receiving appropriate care, support and treatment.

### 1 Determine HIV status at first contact

HIV disease progresses rapidly in infants and children and HIV diagnosis is a critical first step in assuring access to appropriate care and treatment. Health workers should discuss with the mother/caregiver the possibility of HIV infection in their child and the importance of HIV testing at the first point of contact.

Many countries now have child health cards showing HIV exposure status, but often the information is missing and determination of exposure must be done by antibody testing at the well-child or immunization clinic. A rapid antibody test for the mother or the child under 18 months of age will show whether the child has been exposed to HIV.

ARV prophylaxis for HIV-exposed and breastfeeding infants can now be initiated in the under-five or well-baby clinics at any time during breastfeeding, which makes it even more important to strengthen counselling and testing for HIV at all points of contact for exposed breast feeding infants. Providers should identify all exposed infants, especially those whose mothers did not receive PMTCT services or who have become newly infected since pregnancy.

Antibody-based tests (e.g. HIV rapid tests, ELISA) are useful for establishing HIV exposure status of children aged less than 18 months and making a definite diagnosis in older children. DNA-PCR testing is recommended for definitive diagnosis in children less than 18 months (see [Chapter 5](#)). Once HIV exposure or infection status is established, appropriate care and treatment should be initiated immediately.

The best way to ensure adequate follow up care for an exposed infant is to have a well-informed mother who knows that the infant should have a dried blood spot (DBS) sample taken for PCR and that the child should receive an HIV antibody test at 18 months. Even without laboratory tests, the clinician should always have a high index of suspicion and can use clinical criteria to make a presumptive diagnosis of HIV infection (see [Chapter 5](#)) for a sick child. The clinical diagnosis should be confirmed with the appropriate laboratory test as soon as possible.

Infants with unknown or uncertain HIV exposure who are seen in health care facilities at or around birth, or at the first postnatal visit or other child health visit (usually 4–6 weeks of age), should have their HIV exposure status ascertained using a rapid test. Known HIV-exposed infants should have PCR testing at 6 weeks of age or at the earliest opportunity thereafter. In some countries, HIV testing is being done at birth to identify infected children early to achieve the best possible outcomes with ART.

HIV testing should be prioritised for the following categories of children:

- Children born to HIV-infected women
- Children with symptoms suggestive of AIDS
- Children with TB
- Hospitalized children
- Children in therapeutic feeding centres/severely malnourished children
- Children with family members with HIV and/or TB
- Children who have been orphaned by AIDS.

Health workers who are providing care to HIV infected adults or adults with TB or those caring for orphans, need to ask the patients to bring their children for testing.

In high prevalence areas, providers should routinely recommend HIV testing for all children accessing health services.

## 2 Counsel and support the mother and family on optimal infant feeding and monitor growth and development

It is essential for all HIV-infected pregnant and postpartum women to receive comprehensive and repeated counselling on the importance of exclusive breastfeeding for the first 6 months, with appropriate complementary feeds thereafter.

In the clinic, trained providers can counsel and support women in exclusive breastfeeding. Facilities need adequate resources – human, financial, space, support supervision and time – to encourage and support mothers in appropriate infant feeding practices. Women should be encouraged to invite their partners or other family members to join them for infant feeding counselling to ensure that the issues are clear to everyone involved. See **Chapter 12** for further information on infant feeding and nutrition.

Growth and development monitoring and promotion are critical child survival strategies. Slowing of growth and regression of developmental milestones may be the first signs of HIV infection in children. Monitoring growth and development identifies the vulnerable child and is an important intervention to monitor the effects of ART (see **Chapter 12**).

Steps that providers can take to prevent malnutrition and promote good nutrition include:

- Providing accurate information and skilled support to mothers and others responsible for feeding infants and young children
- Ensuring adequate nutrient intake based on locally available foods; providing universal (vitamin A) or targeted micronutrient and mineral supplementation (e.g. iron, folate, zinc)
- Providing food fortification and nutrient supplementation for the most vulnerable
- Providing prompt treatment of common infections and opportunistic infections (OIs) (e.g. oropharyngeal candidiasis)
- Ensuring good health and nutritional status of women and other caretakers of infants and young children.

### Providing services specifically to support mothers in appropriate infant feeding

Skilled counselling and support in appropriate infant feeding practices and ARV interventions to promote HIV-free survival of infants should be available for all pregnant women and mothers.

WHO 2016 Guidelines on HIV and infant feeding.

## 3 Provide prophylaxis – antiretroviral (ARV), cotrimoxazole (CTX) and isoniazid (INH) – according to national guidelines as appropriate

### *ARV prophylaxis for infants*

Children born to HIV-infected mothers should receive nevirapine (NVP) or NVP plus zidovudine (AZT) prophylaxis from birth to at least 6 weeks of age, depending on their risk of infection. Coordination with antenatal care clinics (ANC) and maternity units for follow up of HIV-exposed infants is essential to alert providers to the need for prophylaxis for the infant.

The 2016 WHO guidelines provide for ARV prophylaxis to make breastfeeding for HIV-infected women safer (see **Chapter 3**). This intervention requires improved follow up care for both the woman and the child to ensure that prophylaxis is provided, that the mother is able to administer the correct dosing (for herself or the infant) and that the supply is adequate for the entire breastfeeding period.

Also, ARV prophylaxis should be initiated for mothers or their HIV-exposed, breastfeeding infants who are identified in the under-5 or well-baby clinics. These infants should receive appropriate HIV testing to confirm that transmission has not already occurred.

### *Prophylaxis for opportunistic infections*

*Pneumocystis pneumonia* (PCP) is a significant cause of morbidity and mortality among young HIV infected infants in Africa. Cotrimoxazole (CTX) prophylaxis significantly reduces the incidence and severity of PCP. Additional benefits of cotrimoxazole include protection against common bacterial infections, toxoplasmosis, and malaria. The Children with HIV Antibiotic Prophylaxis (CHAP) trial in Zambia

demonstrated an overall 45% reduction in mortality among HIV-infected children who received cotrimoxazole prophylaxis, regardless of their CD4 count. All children born to HIV-infected mothers should receive CTX prophylaxis, starting at 6 weeks of age and continuing through the first year of life, or until they are proven to be uninfected (see [Table 4.1](#)). WHO recommends that the HIV-infected child should continue to receive CTX indefinitely.

**Table 4.1** Criteria for initiation and discontinuation of cotrimoxazole prophylaxis (WHO 2016)

Population	Criteria for initiation of cotrimoxazole prophylaxis	Criteria for discontinuation of cotrimoxazole prophylaxis
Children and adolescents with HIV	Initiate in all regardless of WHO clinical stage or CD4 cell count <b>As a priority:</b> (1) initiate in all < 5 years of age, regardless of WHO clinical stage or CD4 cell count; (2) initiate in all older than 5 years of age and with severe /advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count $\leq 350$ cells/mm <sup>3</sup>	<b>In settings with a high prevalence of malaria and/or severe bacterial infections:</b> should be continued until adulthood  <b>In settings with a low prevalence of both malaria and severe bacterial infections:</b> may be discontinued for those > 5 years of age who are clinically stable, with evidence of immune recovery* and/or viral suppression on ART
HIV-exposed uninfected infants	Initiate in all starting at 4–6 weeks of age	Until the risk of HIV transmission ends or HIV infection is excluded*
Children living with HIV and TB	Initiate in all with active TB regardless CD4 count	Until criteria for discontinuation in children are met

\* Parameter for immune recovery in children when >5 years old: CD4 cell count >350 cells/mm<sup>3</sup>, with viral load suppression

\* In settings with a high malaria transmission, consideration may be given to extend CTX prophylaxis in HIV-exposed uninfected infants up to 2 years of age



The doses of cotrimoxazole for disease prophylaxis in infants and children of various ages are shown in [Table 4.2](#).

**Table 4.2** Doses of cotrimoxazole in infants and children (WHO 2006)

Age (weight)	Recommended daily dosage <sup>a</sup>	Suspension (5 ml of syrup 200 mg /40 mg)	Child tablet (100 mg /20 mg)	Single strength adult tablet (400 mg /80 mg)	Double strength adult tablet (800 mg /160 mg)
< 6 months (< 5 kg)	100 mg sulfamethoxazole/ 20 mg trimethoprim	2.5 ml	One tablet	¼ tablet, possibly mixed with food <sup>b</sup>	-
6 months–5 years (5–15 kg)	200 mg sulfamethoxazole/ 40 mg trimethoprim	5 ml <sup>c</sup>	Two tablets	Half tablet	-
6–14 yrs (15–30 kg)	400 mg sulfamethoxazole/ 80 mg trimethoprim	10 ml <sup>c</sup>	Four tablets	One tablet	Half tablet
> 14 yrs	800 mg sulfamethoxazole/ 160 mg trimethoprim	-	-	Two tablets	One tablet
Frequency – once a day					

<sup>a</sup> Some countries may use weight bands to determine dosing. The age and corresponding weight bands are based on the CHAP trial.

<sup>b</sup> Splitting tablets into quarters is not considered best practice. This should be done only if syrup is not available.

<sup>c</sup> Children of these ages (6 months–14 years) may swallow crushed tablets.

Alternative drugs if CTX is contraindicated include:

- **Dapsone:** (children > 1 month): dose – 2 mg/kg/24 hours (up to 100 mg) orally once daily.

If both CTX and dapsone are contraindicated (e.g. in children with G6PD deficiency who get haemolysis with CTX and dapsone) then use:

- **Pentamidine** (children > 5 years): dose – 4 mg/kg/dose every 2–4 weeks IM/IV; 300 mg in 6 ml water via inhalation once monthly; higher dose 45 mg/kg/day for age 3–24 months
- **Atovaquone:** dose – 30 mg/kg/day; higher dose 45 mg/kg/day for age 3–24 months.

If these alternative drugs are not available, the health provider should weigh the risks versus the benefits of giving CTX. In some children with an allergy to CTX, desensitisation to the drug can be carried out successfully and it should therefore be tried in such circumstances. It should be noted, however, that desensitisation should not be carried out in individuals with a history of a grade 4 adverse reaction to cotrimoxazole or other sulphur-containing drugs. Desensitisation is done according to the protocol in [Table 4.3](#).

**Table 4.3** Protocol for cotrimoxazole desensitisation among adolescents and adults (WHO 2006)

Step	Dose
Day 1	80 mg sulfamethoxazole + 16 mg trimethoprim (2 ml of oral suspension <sup>a</sup> )
Day 2	160 mg sulfamethoxazole + 32 mg trimethoprim (4 ml of oral suspension <sup>a</sup> )
Day 3	240 mg sulfamethoxazole + 48 mg trimethoprim (6 ml of oral suspension <sup>a</sup> )
Day 4	320 mg sulfamethoxazole + 64 mg trimethoprim (8 ml of oral suspension <sup>a</sup> )
Day 5	One single strength sulfamethoxazole-trimethoprim tablet (400 mg sulfamethoxazole + 80 mg trimethoprim)
Day 6 onwards	Two single strength sulfamethoxazole-trimethoprim tablets or one double strength tablet (800 mg sulfamethoxazole + 160 mg trimethoprim)

<sup>a</sup> Cotrimoxazole oral suspension is 40 mg trimethoprim + 200 mg sulfamethoxazole per 5 ml

### *Preventing TB with isoniazid preventive therapy (IPT)*

The WHO 2011 TB/HIV guidelines recommend:

- Children living with HIV who do not have poor weight gain, fever or current cough are unlikely to have active TB. Children living with HIV who have poor weight gain, fever or current cough or contact history with a TB case may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, they should be offered IPT regardless of their age.
- Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening and have no contact with a TB case should receive 6 months of IPT (10 mg/kg/day) as part of a comprehensive package of HIV prevention and care.
- In children living with HIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB (using investigations) should receive 6 months of IPT if the evaluation shows no TB disease
- All children living with HIV, after successful completion of treatment for TB, should receive IPT for an additional 6 months.

### *BCG for the prevention of TB in HIV endemic areas*

In 2007 WHO recommended that BCG should not be given to infants or children with known HIV infection. The practical implementation of this recommendation is complex, as HIV infection cannot reliably be determined at birth and the majority of infants born to HIV-infected mothers will be HIV-uninfected. HIV-exposed but -uninfected infants, not at risk for disseminated BCG disease, will be at increased risk of disseminated TB disease if not vaccinated with BCG. Therefore, BCG should continue to be given to infants born to HIV-infected mothers in settings where TB and HIV are endemic unless the infant is confirmed as HIV-infected.

### *Prevention of malaria*

A study in HIV-infected and uninfected- children showed that, whereas use of insecticide treated nets (ITNs) was associated with

a 43% reduction in malaria incidence, the combined use of ITNs and cotrimoxazole was associated with a 97% reduction in malaria incidence.

It is therefore recommended that in malaria-endemic areas combined ITNs and cotrimoxazole should be offered to all HIV-infected children.

#### **4 Actively look for and treat infections early**

HIV-exposed and infected children are susceptible to common infections and OIs. Infants who are not known to be HIV-exposed or -infected and who present with frequent and/or severe infections should be screened for HIV infection. Careful counselling of caregivers to seek care early is essential so that the infant can receive the appropriate care and treatment.

With increased access to ART, the frequency of common infections should decrease dramatically. When they do occur, however, HIV may alter the incidence, presentation, and response to conventional therapy. Thorough history taking and clinical examination should be conducted at each visit to detect and treat infections as early as possible. In some cases more aggressive and longer treatment courses may be necessary, as treatment failures are more frequent among HIV infected children.

Tuberculosis (TB) must be ruled out as it is prevalent in most African settings (see [Chapter 7](#)).

In HIV-infected children, common childhood illnesses such as fever or diarrhoea can quickly become severe and life-threatening. Therefore, in HIV-infected children the healthcare provider should actively look for and aggressively treat common childhood illnesses (see details in [Chapters 6 and 7](#)).

The WHO integrated management of childhood illness (IMCI) and integrated management of adolescent and adult illness (IMAI) are recommended in the management of these conditions.

## 5 Ensure that immunizations are started and completed according to national guidelines

HIV-infected children are more susceptible to immunizable diseases than their HIV-uninfected counterparts. It is therefore crucial that they receive the full course of the WHO expanded programme on immunization (EPI) recommended vaccines.

HIV-exposed and -infected children may have an impaired response following immunization with a variety of antigens. In spite of this, these children should receive the full course of immunizations but with some special considerations/modifications as outlined below:

- When considering BCG vaccination at a later age (re-vaccination for no scar or missed earlier vaccination), exclude *symptomatic* HIV infection.
- Do not give yellow fever vaccine to symptomatic HIV-infected children. However, asymptomatic children in endemic areas should receive the vaccine at 9 months of age.
- Give the measles vaccine to children, even when symptoms are present, at 6 and 9 months. Studies from Uganda indicate that children experience much more severe disease with the wild measles virus, which outweighs the risk of a milder illness from the vaccine.
- HIV-infected children can receive prophylactic measles immunoglobulin (0.5 ml/kg, maximum of 15 ml) within 6 days of exposure.
- Varicella immunoglobulin (0.15 ml/kg) is advised within 3 days of exposure if children are exposed to chicken pox.
- Pneumococcal vaccine should be given.
- Rotavirus vaccine should be given: studies in South Africa and Malawi have shown that it is safe and effective in HIV-infected children and the vaccine has been introduced in clinical practice in those countries.

## **6 Provide ART for all children irrespective of their clinical or immunological stage**

Antiretroviral treatment is a life-saving intervention that is becoming more accessible across Africa. Without appropriate treatment, half of HIV-infected children would die before their second birthday. The importance of following HIV diagnosis in an infant with initiation of ART (preferably within 2 weeks of diagnosis) cannot be overstated. The 2016 WHO guidelines recommend that all children who are diagnosed with HIV should be started on ART as soon as possible, irrespective of their clinical status and/or immunological severity (see **Chapter 8**). Early infant diagnosis (EID) and treatment within country programmes should be closely linked to ensure that children with HIV are promptly started on ART. Getting results of DNA-PCR testing to families and engaging them in discussion about ART for the infant must be an urgent priority at facility level. For older children, ART eligibility is determined through long-term care and monitoring for disease progression (also described in **Chapter 8**).

Families are sometimes reluctant to initiate life-long therapy in children. In these cases, additional strategies, support, patience and time are needed to try to provide the best possible care for the child. Many countries struggle with a lack of trained medical staff to treat children and with staff who don't yet have the skills to counsel parents and children. These can both be overcome with training and mentoring providers to meet the needs of HIV-infected children and their families. (See **Chapter 10** and ANECCA's counselling curriculum, available at [www.anecca.org](http://www.anecca.org)).

## **7 Educate the caregiver and family on all aspects of care**

Developing a strong relationship with the caregiver is an important part of providing care and support to the child. Parents and/or caregivers need to participate in making decisions and in planning appropriate care for the child, including decisions about therapy and where the child should receive care. In this respect, health workers must ensure that they communicate effectively with the family on

what to expect and how to care for the child. Empowering caregivers to be ‘partners’ with the health provider can focus on key aspects of caring for the child in the home, including:

- How to dispense prophylaxis and treatment, maintain adherence and comply with the follow up schedule (see [Chapter 8](#))
- Good personal and food hygiene to prevent common infections (see [Chapter 11](#))
- Seeking prompt treatment for any infections or other health-related problem (see [Chapter 6](#)).

With young children, prophylaxis and other medications are often given as syrups. Helping families to become comfortable with dispensing medications and providing them with tools to assist in maintaining adherence will provide better clinical outcomes and reduce the stress on the caregiver.

Good personal and food hygiene are important to maintain overall good health and are particularly important for families affected by HIV. Some facilities have established ‘nutrition’ corners as a way of providing information and instruction to caregivers. Encouraging community organizations to include such activities in their programmes for children can also be of benefit.

Caregivers should be instructed on which symptoms require the child to be brought to the clinic urgently and which symptoms should be noted for discussion at the next regular visit. In HIV-infected children, common childhood illnesses such as fever or diarrhoea can quickly become severe and life-threatening infections.

Information on the needs of children during illnesses and how caretakers can ease pain, provide proper feeding, and manage other symptoms is always of value for families. In addition, caretakers can bring important information on the condition of the child that may not be readily apparent during a routine evaluation.

## **8 Provide regular monitoring of clinical parameters and adherence; refer to higher levels of specialized care as necessary**

Regular follow-up is the backbone to caring for HIV-exposed and infected children and ensures optimal healthcare and psychosocial support to the family. Recommendations on frequency of follow-up for HIV-exposed children are as shown in **the box below**. This is the minimum and more frequent contacts with the healthcare system are indicated for infected children, especially if they are on ART.

### **Recommendations for follow-up of an HIV-exposed child**

- At birth (for infants delivered at home)
- At age 1 to 2 weeks (mainly for infant feeding counselling)
- At 6 weeks, DNA PCR testing and starting cotrimoxazole prophylaxis
- At age 6, 10, and 14 weeks (for immunization and infant feeding counselling)
- After age 14 weeks, monthly through 12 months
- At 12 months, consider stopping breastfeeding
- After age 12 months, every 3 months through 24 months
- At 18 months a confirmatory HIV test should be done as necessary
- After 2 years, a minimum of yearly visits
- At any time in follow up refer those identified as HIV infected for care, and refer to higher levels of specialised care as necessary.

HIV-infected children over the age of 59 months should be followed at least every 6 months if asymptomatic. Symptomatic children should be followed more frequently as needed.

## **9 Provide ongoing psychosocial support for the family and the child and refer to social- or community-based support programmes**

Psychosocial support is an integral part of care for the HIV infected child and his/her family. This is because HIV/AIDS-related illness or death in the family can lead to several mental, psychological and social problems for the child and the family.



The approaches for psychosocial support include:

- Counselling and support for the child and family
- Assisting the family in readying the child for disclosure
- Use of peer support groups
- Community-based support activities.

For details, see [Chapter 12](#).

### **10 Ensure that the mother and family members are receiving appropriate care, support and treatment**

An HIV diagnosis in a child has many direct implications for the other family members. Likewise, maternal HIV infection has direct implications for a child's well-being, even if that child is not HIV-infected.

The most important thing for a child's health is to have is a healthy mother. In many settings, women will bring their children to the clinic regularly, yet they often do not seek care for themselves. Providers should take every opportunity to ensure that the family, especially the mother, are provided with or referred to appropriate diagnosis, care and treatment. A simple inquiry about the mother's health is sometimes the catalyst she needs to seek care and treatment. A family tree analysis/family matrix can be put in each child's file.

Other care and support services that may be available in MCH and family care centres include:

- HIV testing and counselling for the mother, partner, and other children
- Sexual and reproductive health counselling and support, including family planning services
- Prevention and treatment of reproductive tract infections and STIs
- Mental health and psychosocial care and support
- Screening and treatment for TB

- Nutrition care and support services
- Prophylaxis and treatment of HIV-related infections and conditions
- ART for family members.

When mother and child are in care, and if other family members are also in care, their clinic appointments should be made on the same day.

Family contact details should be obtained and captured on the child's clinic card/chart. There could also be entries for a primary caregiver and other caregivers (other than the primary one/alternative caregivers). Attempts should be made to establish the HIV diagnosis and care status of each of these caregivers, with appropriate action taken. Family counselling and support should be encouraged.

### Knowledge gaps

- What are the optimal models of family care?
- What are the best and most efficient mechanisms to scale up ART for children and adults in resource-poor settings?

### Additional and recommended reading

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# Chapter 5

## Diagnosis and clinical staging of HIV infection

### Summary

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- The rapid progression of HIV in children, especially infants and young children less than 2 years of age, means that there is a limited window of opportunity for effective intervention. Specific care and treatment interventions are linked to the certainty of diagnosis and national programmes should provide the capacity to provide early virological testing of infants for HIV.
- Infants with unknown or uncertain HIV exposure who are seen in healthcare facilities at or around birth or first postnatal visit or other child health visit (usually 4–6 weeks of age) should have their HIV exposure status ascertained using a rapid test.
- Known HIV-exposed infants should have virological testing at 6 weeks of age or at the earliest opportunity thereafter. Virological tests can be performed on dry blood spots (DBS) which are easier to collect, store and process than whole blood and which are therefore appropriate to use at lower level health units and especially in resource-limited settings.
- Serological assays suitable for HIV antibody detection in adults cannot be reliably used for confirmatory diagnosis of HIV in infants because the interpretation of positive HIV antibody testing is complicated by the fact that maternal HIV antibodies can persist for 18 months (although this usually clears by 9–12 months).
- Antibody-negative results suggest that infants are unexposed and/or uninfected. However, if the infant is breastfeeding the risk of acquiring HIV continues throughout the entire breastfeeding period.

- Combining clinical and laboratory criteria to stage HIV disease ensures timely and rational initiation of care, treatment, and appropriate counselling. Clinical algorithms are not reliable, and have poor predictive value in young children, especially during the first year of life.

## Diagnosis of HIV infection in children

### Why is it important to make an early diagnosis of HIV infection?

HIV infection is common among children in sub-Saharan Africa (SSA) and is a significant contributor to infant and childhood morbidity and mortality, with more than half of perinatally HIV-infected children dying before their second birthday.

Consequently, identifying those with infection before they become unwell is only possible through routine diagnostic testing, ideally in services for PMTCT or maternal, newborn and child health (MNCH).

Diagnosis of HIV infection facilitates the following:

- It allows healthcare providers to offer optimal care and treatment of HIV-infected children, assists in decision-making around infant feeding, and avoids needless stress in mothers and families.
- Access to currently available effective interventions, which reduce morbidity and mortality associated with infection.
- Access to needed interventions for other affected family members. Diagnosis of HIV in a child is often the first indication of infection among other family members and provides opportunities to provide care, treatment, and support to parents and siblings.
- Access to social and emotional support for the child and family.
- Appropriate healthcare and social welfare planning at the national, regional, and local levels.

### Approach to diagnosis

In settings characterized by high HIV prevalence (> 10%), routine HIV testing should be considered for all infants and children with unknown HIV status at their first contact with the health service.

Identification of exposed infants is crucial as the first step so that HIV testing can be performed on dried blood spots using the DNA PCR technology that is now widely available.

Exposed infants can be identified by tracking HIV-positive mothers and at other entry points at facilities such as MCH, paediatric wards, outpatient departments (OPD), nutrition services and TB clinics.

HIV-specific laboratory tests can provide a definitive diagnosis, can add to the strength of a clinical diagnosis (e.g. by confirming exposure), or can actively aid the exclusion of HIV disease, allowing clinicians to explore other differential diagnoses.

Another approach to the diagnosis of paediatric HIV infection requires health workers who have a high index of suspicion and are knowledgeable and skilled in diagnosis and management of HIV infection in children. HIV/AIDS should be suspected among children with suggestive clinical signs or HIV-associated conditions (see [Table 5.1](#)).

Basic communication skills are essential to allow health workers to discuss and offer HIV testing to children and their parents.

Health workers should extend diagnosis to children who are sexually assaulted, or those exposed to potentially infectious bodily fluids.

### Laboratory assays (tests)

Laboratory tests provide suggestive and/or confirmatory evidence of HIV infection. There are two types of laboratory tests:

- **Antibody tests:** HIV ELISA, rapid tests, and Western Blot
- **Virologic tests:** HIV DNA PCR assays, RNA assays including viral load, and HIV immune complex-dissociated p24 antigen assays.

### Antibody tests

Antibody tests are the most widely used HIV diagnostic tests and provide reliable evidence of HIV infection in adults and children who are older than 18 months. The HIV antibody test is less reliable in infants aged less than 18 months because they may still be carrying HIV-specific antibodies acquired from the mother *in utero*. The time it takes for an HIV-positive mother's maternal antibodies to be eliminated from an infant's system (sero-reversion) varies. The majority of uninfected non-breastfed children will sero-revert by the



age of 15 months, but a smaller percentage (ranging from a low of 10% to a high of 18% in various studies) will not revert until the age of 18 months. In the rare event, the new ultra-sensitive HIV antibody tests may detect minute amounts of maternal antibodies beyond the age of 18 months. All children who become infected will develop antibodies that cannot be differentiated from the maternal antibodies using the current existing laboratory techniques. Breastfed infants may start out as not infected but carrying maternal antibodies, and then go through a period of being antibody negative when they lose maternal antibodies, but once again re-sero-convert when they become infected and start making their own antibodies.

### **Virologic tests**

In order to make a definitive diagnosis of HIV in infants less than 18 months, assays that detect the virus or its components (virological tests) are required. The recommended tests include: HIV DNA PCR, HIV RNA PCR and the ultra-sensitive p24 antigen assay (Up24Ag).

#### ***HIV DNA PCR***

DNA PCR assays amplify the HIV pro-viral DNA sequences within mononuclear cells present in peripheral blood and the results of such assays are the accepted standard for diagnosis of HIV infection during infancy in developed countries. HIV DNA PCR can be performed on whole blood or dried blood spots (DBS).

The sensitivity of HIV DNA PCR is low during the first 1–2 weeks of life because this test is not able to detect very low levels of HIV DNA in babies infected a few minutes/hours/days earlier, during delivery and early breastfeeding. After 4–6 weeks of life, the sensitivity and specificity of HIV DNA PCR tests approach 100%, except in babies who have continuing exposure to HIV through breastfeeding.

Dried blood spot (DBS) specimens are easiest to collect, store and process. They do not require venepuncture as they can be obtained from a finger-stick or a heel-stick (see [Appendix B](#)). They are stable at room temperature for prolonged periods and are easier to transport, allowing for centralized laboratory testing. Using DBS is very practical for testing HIV-exposed infants in lower level health facilities and

should be more widely implemented to improve access to HIV diagnosis in resource limited settings.

Although the test can be completed within one day, blood samples from a number of patients are often tested in batches to reduce costs, delaying the availability of results for some individuals. HIV DNA PCR tests require specialized laboratory equipment and skilled personnel, and are therefore expensive. Also, samples may become contaminated with HIV DNA from other sources.

New technologies, such as real-time and other point-of-care (POC) PCR technologies, could provide a good alternative because they are rapid, simple, cheap, and adaptable to the different clades of HIV. Their usefulness is still being evaluated.

### *HIV RNA assays*

HIV RNA assays detect viral RNA in plasma and other body fluids using a variety of methods (reverse transcriptase PCR, *in vitro* signal amplification nucleic acid probes [branched chain DNA], and nucleic acid sequence-based amplification [NASBA]). HIV RNA assay can be carried out on plasma or DBS.

RNA assays are also more sensitive for early detection of infection (first 2 months of life) than HIV DNA PCR tests.

Quantitative RNA (viral load tests) tests are used to monitor response to ART and to diagnose treatment failure. Although viral load is the most sensitive indicator of treatment failure, it is expensive as HIV RNA assays require specialized laboratory equipment and skilled personnel. However, VL testing is becoming more available to monitor patients and decide when to switch from first to second line ART.

### *HIV immune complex dissociated p24 antigen assays*

The p24 protein (antigen) is from the core proteins of the HIV virus (see **Chapter 2**). Detection of p24 antigen is definitive evidence of HIV infection. The p24 antigen assays use techniques that can be performed in most routine laboratories. In addition, they can be used for diagnosis in children less than 18 months of age. Although the first-generation tests were highly specific, the sensitivity was lower

than that of DNA PCR and RNA assays. The newer, ultra-sensitive p24 (Up24Ag) assays are more reliable.

### Timing of early virological testing

Regardless of the type of virological testing technology used, the following should be considered:

- One early HIV virological detection test at or after 6 weeks of age for all HIV-exposed children identifies most children infected before, during and immediately after delivery, and therefore identifies most babies who will progress rapidly and who will need life-saving ART.
- Virological testing at 6 weeks of age gives good sensitivity (> 98%) with the various methods and is considered programmatically more efficient.
- In infants with an initial positive virological result, it is recommended that ART is started without delay and at the same time, a second specimen is collected to confirm the initial positive virological result. ART initiation should not be delayed while waiting for the result of the confirmatory test.
- Results from virological testing in infants should be returned to the requesting clinic and mother/carer as soon as possible but at the very latest within 4 weeks of specimen collection. Positive test results should be fast tracked to the mother/carer–baby pair to enable prompt initiation of ART.
- Testing before the age of 6 weeks using the DNA and RNA methods can reveal HIV in infants infected *in utero* but is not recommended for use in routine national programmes. However in the 2015 WHO guidelines, birth testing is recommended for high risk neonates; those born to HIV-infected women who have not received antepartum or intrapartum ARV drugs or have received only intrapartum ARV drugs or have received antepartum ARV drugs but do not have viral suppression near delivery, where this is feasible to avert early infant morbidity and mortality.

- The timing of any repeat testing should consider breastfeeding practices, as the risk of acquiring HIV infection from mothers continues throughout the breastfeeding period.

A testing algorithm has been developed by WHO to aid in the diagnosis of HIV in infants that takes breastfeeding practices into consideration (See [Appendix C](#)).

### **Where laboratory testing is available**

Appropriate pre- and post-test counselling should be available and offered (see [Chapter 11](#)). It is also important that health workers offer HIV counselling and testing to parents.

Pre-test counselling should include information about the limitations of the testing approach, the benefits of early diagnosis for the child, and the implications of a positive HIV antibody test results for the family.

### **Interpretation of test results**

In children more than 18 months of age:

- HIV infection can be confirmed in those with positive antibody results.
- HIV infection can be excluded in those with negative antibody results.
- HIV-exposed children who continue to breastfeed should be provided with cotrimoxazole prophylaxis and retested a minimum of 6 weeks after complete cessation of breastfeeding before HIV infection can be excluded. In addition, the child should be retested at any stage during breastfeeding should features of HIV infection occur.

In children less than 18 months of age:

- A positive antibody test is an indication of HIV exposure. This maybe the mothers test result. It may also be the infant's test result for mother-baby pairs first exposed to HIV testing in the postnatal period at well child clinics. The positive antibody test should then be a trigger for virologic testing.

### *Virologic test available:*

- A negative test in a non-breastfed infant,  $\geq$  4–6 weeks old excludes HIV infection.
- A positive test (with a positive repeat test) confirms HIV infection.
- HIV-exposed infants who continue to breastfeed should be provided with cotrimoxazole prophylaxis and should be retested a minimum of 6 weeks after complete cessation of breastfeeding before HIV infection can be excluded. In addition, the infant should be retested at any stage during breastfeeding should features of HIV infection occur.

### *Virological tests not available:*

- HIV infection can be excluded in those with negative antibody results (particularly if they had a previous positive result) and they are no longer exposed because they are fully weaned from the breast.
- Diagnose probable HIV infection in those with suggestive clinical features and positive antibody results. Confirm the result by repeat antibody testing after the child is more than 18 months of age.
- Retest HIV-exposed children who continue to breast-feed at least 6 weeks after complete cessation of breastfeeding, before HIV infection can be excluded.

### **Clinical diagnosis**

HIV infection presents with conditions that are frequently found in children who are not HIV infected. This makes it difficult to make a diagnosis of HIV infection based on clinical features alone. **Table 5.1** groups these conditions according to whether they are common in both HIV-infected children and uninfected children, common in infected children but less common in uninfected children, and whether they are very specific to HIV infection. The occurrence of these clinical signs or conditions may suggest HIV infection in a child and should alert the health worker to obtain other relevant additional history (such as maternal health), and laboratory data where possible.

**Table 5.1** Clinical signs or conditions in child that may suggest HIV infection

Specificity for HIV infection	Signs/conditions
Signs/conditions very specific to HIV infection	<ul style="list-style-type: none"> <li>• <i>Pneumocystis pneumonia</i></li> <li>• Oesophageal candidiasis</li> <li>• Extrapulmonary cryptococcosis</li> <li>• Invasive salmonella infection</li> <li>• Lymphoid interstitial pneumonitis</li> <li>• Herpes zoster (shingles) with multi-dermatomal involvement</li> <li>• Kaposi's sarcoma</li> <li>• Lymphoma</li> <li>• Progressive multifocal encephalopathy</li> </ul>
Signs/conditions common in HIV-infected children and uncommon in uninfected children	<ul style="list-style-type: none"> <li>• Severe bacterial infections, particularly if recurrent</li> <li>• Persistent or recurrent oral thrush</li> <li>• Bilateral painless parotid enlargement</li> <li>• Generalized persistent non-inguinal lymphadenopathy</li> <li>• Hepatosplenomegaly (in non-malaria endemic areas)</li> <li>• Persistent and/or recurrent fever</li> <li>• Neurologic dysfunction</li> <li>• Herpes zoster (shingles), single dermatome</li> <li>• Persistent generalized dermatitis unresponsive to treatment</li> </ul>
Signs/conditions common in HIV-infected children but also common in ill -uninfected children	<ul style="list-style-type: none"> <li>• Chronic, recurrent otitis with ear discharge</li> <li>• Persistent or recurrent diarrhoea</li> <li>• Severe pneumonia</li> <li>• Tuberculosis</li> <li>• Bronchiectasis</li> <li>• Failure to thrive</li> <li>• Marasmus</li> </ul>

### Diagnosis of HIV infection in settings with limited diagnostic laboratory support

In settings where virologic tests are not available a presumptive diagnosis of HIV infection may be made in children aged less than 18 months using a combination of antibody tests and clinical signs, as shown in [Table 5.2](#).

**Table 5.2** Diagnostic criteria for presumptive diagnosis of severe HIV infection in children <18 months old (WHO 2010)

<p><b>1</b> The child is confirmed to be HIV antibody positive</p> <p><b>AND</b></p>	<p><b>2a</b> The infant is symptomatic with two or more of the following:</p> <ul style="list-style-type: none"> <li>• Oral thrush</li> <li>• Severe pneumonia</li> <li>• Severe sepsis</li> </ul> <p><b>OR</b></p> <p><b>2b</b> Diagnosis of any AIDS-indicator condition(s) such as <i>Pneumocystis pneumonia</i>, cryptococcal meningitis, severe wasting, severe malnutrition, Kaposi sarcoma, or extrapulmonary TB</p>
<p>Other supportive evidence of severe HIV disease in an HIV-seropositive infant:</p> <ul style="list-style-type: none"> <li>• Recent HIV-related maternal death or advanced HIV disease</li> <li>• Child's CD4% &lt; 20%</li> </ul> <p>The diagnosis of HIV infection should be confirmed as soon as possible</p>	

This algorithm has been tested by ANECCA in a study that showed that 68.9% of HIV-infected children were correctly identified by the algorithm, making it a useful tool in settings with limited access to virological confirmatory tests.

## Clinical staging of HIV infection and disease in children

Staging is a standardized method for assessing disease stage/progression and for making treatment decisions. It is important to stage children with HIV infection because staging:

- Clarifies the prognosis of individual patients
- Affects the type of treatment interventions, including indications for changing ART.

The international clinical staging system commonly used that classifies the severity of HIV infection in children is the WHO Paediatric Clinical Staging.

The WHO Paediatric Clinical Staging System for infants and children divides HIV infection into four categories (**Table 5.3**).

**Table 5.3 WHO Paediatric Clinical Staging of infants and children with established HIV infection (WHO 2010)**

<b>Stage 1</b>	<ul style="list-style-type: none"> <li>• Asymptomatic</li> <li>• Persistent generalised lymphadenopathy (PGL)</li> </ul>
<b>Stage 2</b>	<ul style="list-style-type: none"> <li>• Unexplained persistent hepatosplenomegaly</li> <li>• Extensive wart virus infection; facial, more than 5% of body area or disfiguring</li> <li>• Papular pruritic eruptions</li> <li>• Fungal nail infections</li> <li>• Lineal gingival erythema</li> <li>• Extensive human papilloma virus (HPV) or molluscum contagiosum (&gt; 5% of body area/face)</li> <li>• Recurrent oral ulcerations (&gt; 2 episodes/6 months)</li> <li>• Unexplained persistent parotid enlargement</li> <li>• Herpes zoster</li> <li>• Recurrent or chronic upper respiratory tract infection (URTI): otitis media, otorrhea, sinusitis, tonsillitis (with at least 1 episode in the last 6 months)</li> <li>• Unexplained persistent hepatosplenomegaly</li> <li>• Extensive wart virus infection; facial, more than 5% of body area or disfiguring</li> <li>• Papular pruritic eruptions</li> <li>• Fungal nail infections</li> <li>• Lineal gingival erythema</li> <li>• Extensive human papilloma virus (HPV) or molluscum contagiosum (&gt;5% of body area/face)</li> <li>• Recurrent oral ulcerations (&gt;2 episodes/6 months)</li> <li>• Unexplained persistent parotid enlargement</li> <li>• Herpes zoster</li> <li>• Recurrent or chronic upper respiratory tract infection (URTI): otitis media, otorrhea, sinusitis, tonsillitis (with at least 1 episode in the last 6 months)</li> </ul>
<b>Stage 3</b>	<ul style="list-style-type: none"> <li>• <i>Unexplained</i> moderate malnutrition (-2 SD or Z score) not adequately responding to standard therapy</li> <li>• <i>Unexplained</i> persistent diarrhoea (<math>\geq</math> 14 days)</li> <li>• <i>Unexplained</i> persistent fever above 37.5 °C (intermittent or constant) for longer than 1 month</li> <li>• Persistent oral candidiasis (after first 6 weeks of life)</li> <li>• Oral hairy leukoplakia</li> <li>• Lymphnode TB</li> </ul>



	<ul style="list-style-type: none"> <li>• Pulmonary tuberculosis</li> <li>• Severe recurrent presumed bacterial pneumonia (current episode plus 1 or more episodes in previous 6 months)</li> <li>• Acute necrotizing ulcerative gingivitis/periodontitis</li> <li>• Symptomatic lymphoid interstitial pneumonitis (LIP)</li> <li>• Chronic HIV-associated lung disease including bronchiectasis</li> <li>• <i>Unexplained</i> anaemia (&lt; 8 gm/dL), neutropenia (&lt; 500 cells/mm<sup>3</sup>), or thrombocytopenia (&lt; 50 000 cells/mm<sup>3</sup>)</li> </ul>
<b>Stage 4</b>	<ul style="list-style-type: none"> <li>• <i>Unexplained</i> severe wasting or severe malnutrition (–3 SD, as defined by WHO IMCI guidelines) not responding to standard therapy</li> <li>• <i>Pneumocystis</i> pneumonia</li> <li>• Recurrent severe presumed bacterial infections, e.g. empyema, pyomyositis, bone or joint infection, meningitis but <i>excluding</i> pneumonia (current episodes plus ≥ 1 in previous 6 months,)</li> <li>• Chronic orolabial, cutaneous or visceral (any site) HSV infection (lasting &gt; 1 month)</li> <li>• Extrapulmonary tuberculosis</li> <li>• Kaposi's sarcoma</li> <li>• Esophageal candidiasis (or candida of trachea, bronchi or lungs)</li> <li>• CNS toxoplasmosis (after the neonatal period)</li> <li>• HIV encephalopathy</li> <li>• Cytomegalovirus (CMV) infection; retinitis or CMV affecting another organ with onset at age over 1 month</li> <li>• Extrapulmonary Cryptococcosis, including meningitis</li> <li>• Any disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)</li> <li>• Chronic cryptosporidiosis with diarrhoea</li> <li>• Chronic isosporiasis</li> <li>• Disseminated non-tuberculous mycobacterial infection</li> <li>• Acquired HIV-associated rectal fistula</li> <li>• Cerebral or B cell non-Hodgkins lymphoma</li> <li>• Progressive multifocal leukoencephalopathy (PML)</li> <li>• HIV-related cardiomyopathy or nephropathy</li> </ul>

### Rationalizing care

After diagnosis and staging, a plan for tailored care needs to be developed. It is important to note that *however limited the resources, there is always something to be done for an individual child*. **Table 5.4** provides an overview of how to proceed in different care settings.

**Table 5.4** What can be done for different levels of resources and certainty of diagnosis?

IF there are:	AND:	THEN:
No laboratory facilities	HIV is suspected from clinical signs	<ul style="list-style-type: none"> <li>• Monitor growth and development</li> <li>• Provide nutrition care and support</li> <li>• Control infections</li> <li>• Give PCP prophylaxis</li> <li>• Treat opportunistic infections (OIs)</li> </ul>
	AIDS is suspected	<ul style="list-style-type: none"> <li>• Provide all above, plus</li> <li>• Refer for testing and ART</li> </ul>
Simple tests (complete blood count) and child is HIV antibody positive	HIV is suspected for < 18 months	<ul style="list-style-type: none"> <li>• Monitor growth and development</li> <li>• Provide nutrition care and support</li> <li>• Control infections</li> <li>• Give PCP prophylaxis</li> <li>• Treat opportunistic infections (OIs)</li> <li>• Re-test at 18 months</li> </ul>
	< 18 months and meets criteria for presumptive diagnosis	<ul style="list-style-type: none"> <li>• Provide all above, plus provide anti-retroviral therapy (see <a href="#">Chapter 8</a>)</li> <li>• Re-test at 18 months</li> </ul>
	HIV is confirmed for > 18 months	<ul style="list-style-type: none"> <li>• Provide all above, plus ART</li> </ul>
Virologic tests (PCR, p24 antigen tests)	HIV is confirmed	<ul style="list-style-type: none"> <li>• Provide all above, plus ART (see <a href="#">Chapter 8</a>)</li> </ul>

### Operational challenges

- Improving access to inexpensive and simpler diagnostic tests for young infants at all levels of the healthcare system
- Promoting use of widely available HIV antibody tests for infants and children, especially where these are primarily available through VCT service points, which typically exclude children
- Improving basic laboratory diagnostic infrastructure to include complete blood counts (CBC) at primary care levels and, where possible, CD4 counts and viral load tests that are increasingly indispensable in the care of HIV-exposed and -infected infants.

## References and recommended reading

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- World Health Organization (WHO). *Antiretroviral therapy for HIV infection in infants and children: towards universal access. Recommendations for a public health approach, 2010*. Available at: <http://www.who.int>, (accessed 13 November 2010).
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# Chapter 6

## Common clinical conditions associated with HIV

### Summary

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- Babies are born with an immature and naïve immune system, predisposing them to an increased frequency of bacterial infections. The immunosuppressive effects of HIV are added to those of an immature immune system and place HIV-infected infants at particularly high risk of invasive bacterial infections.
- Common childhood infections and conditions are more frequent in HIV-infected children and have a higher case fatality compared to uninfected children. These infections include diarrhoea, acute lower respiratory tract infections, acute suppurative otitis media, sinusitis, and failure to thrive.
- Immunisation and cotrimoxazole prophylaxis significantly decrease the frequency of invasive bacterial infections in HIV-infected children.
- Viral opportunistic infections present significant challenges to management because diagnostic tests and therapies are not readily available.
- Antiretroviral therapy induces immune reconstitution and is the most effective therapy for preventing OIs.



## Introduction

Babies are born with an immature and immunologically naïve immune system, predisposing them to an increased frequency of bacterial infections. The ability to respond to pathogens and other antigens and the ability of immune systems to recall the memory of past exposure is diminished very early in HIV infection. The immunosuppressive effects of HIV are added to those of an immature immune system and, therefore, the common conditions associated with HIV are frequently infections.

Common conditions experienced by HIV-infected children are diarrhoea, acute lower respiratory tract infections, septicaemia, acute suppurative otitis media, sinusitis, and failure to thrive. In young infants the earliest clinical signs and symptoms may be non-specific, such as failure to thrive, acute respiratory infections, and diarrhoea.

There are few comprehensive studies documenting the aetiological cause of infections and death in HIV-infected children in Africa. The published studies are frequently cross-sectional and tend to focus on a single clinical condition or they are post-mortem studies biased towards the severest forms of disease, which result in death. This makes it difficult to obtain a comprehensive picture of the common conditions that occur over the course of HIV infection.

The aetiology of infectious diseases changes significantly during the first few years of life, as the infant's immune system matures. Thus, studies on older children do not necessarily reflect events that occur in younger children. A good example is *Pneumocystis jiroveci* pneumonia (PCP), which is typically found in younger infants.

## Diarrhoea

Acute diarrhoea is one of the most common causes of morbidity and the leading cause of death in HIV-infected children during the first year of life. Diarrhoea in HIV-infected children tends to be prolonged and is usually complicated by dehydration and malnutrition. There is also an increased frequency of acute diarrhoea in HIV-exposed uninfected children whose mothers have symptomatic HIV infection or are dead, or following early introduction of complementary feeding.

The infectious causes of diarrhoea in HIV-infected children are similar to the common causes in non-infected children. The leading cause of diarrhoea is rotavirus (RV), followed by bacterial causes that include *Enterobacter*, *Escherichia coli*, *Shigella* species, *Salmonella* species, *Campylobacter jejuni*, *Giardia lamblia*, *Entamoeba histolytica*, and *Candida albicans*. Children with RV infection tend to be younger, with 60–70% less than one year of age.

HIV-infected children with RV are more likely to present with respiratory symptoms at admission and are more frequently underweight when compared to uninfected children.

Malnutrition is a common co-morbidity in HIV-infected children, and this complicates their management.

In HIV-infected children, other infectious causes of diarrhoea include AIDS-defining illnesses such as cryptosporidiosis, isosporiasis, Cytomegalovirus (CMV) infection, atypical *Mycobacteria* species, HIV enteropathy, and parasitic infections, including *Strongyloides stercoralis* and *Tricuris tricuris*. Healthcare workers should conduct standard stool microscopy and stool culture on all HIV-infected children with diarrhoea because of the occurrence of unusual pathogens.

Persistent diarrhoea occurs with increased frequency in HIV-infected children (particularly those with significant immune suppression and failure to thrive) and infants of women with symptomatic HIV disease. Persistent diarrhoea is associated with an 11-fold increase in risk of death in HIV-infected children when compared to uninfected children. Up to 70% of diarrhoeal deaths in HIV-infected children result from persistent diarrhoea. Prolonged use of antibiotics and antiretroviral drugs such as nelfinavir and ritonavir can also contribute to HIV-related diarrhoea.

In the context of new PMCT regimens that reduce risk of infection to < 2%, early weaning which had hitherto been a recommended practice for PMCT, has now been shown to be dangerous and associated with high incidence of severe diarrhoea with dehydration that requires in-patient management. Current recommendations discourage early



weaning and instead recommend infant ARV prophylaxis and maternal treatment as a method of protecting breastfeeding for the infant (see **Chapters 3 and 11**).

The principles of management of acute diarrhoea in HIV-infected children are the same as in other children and should follow the integrated management of childhood illness (IMCI) guidelines, which include management and correction of dehydration, aggressive nutritional management to minimize the occurrence of persistent diarrhoea, and malnutrition and nutrition counselling, including a review of household hygiene practices, especially handling of the baby's water and food.

In the management of acute diarrhoea, health workers should:

- Counsel mothers to begin administering available home fluids immediately upon the onset of diarrhoea in a child (while avoiding home-made salt and sugar solution).
- Treat dehydration with oral rehydration salts (or with an intravenous electrolyte solution in cases of severe dehydration)
- Emphasise continued feeding or increased feeding during and after the diarrhoeal episode.
- Use antibiotics only when appropriate, that is, in the presence of bloody diarrhoea or shigellosis, and **abstain** from administering anti-diarrhoeal drugs. The 2010 WHO IMCI guidelines recommend ciprofloxacin (15 mg/kg, 2 times/day for 3 days).
- Provide children with 20 mg/day of zinc supplementation for 10–14 days (10 mg/day for infants under 6 months of age ).
- Provide mothers or caregivers with two 1 L packets of oral rehydration salts for home use until diarrhoea stops.

Source: WHO. Recommendations on the management of diarrhoea and pneumonia in HIV-infected infants and children: integrated management of childhood illness (IMCI). 2010

### Management of persistent diarrhoea

- Manage as acute diarrhoea (see **box above**)
- Examine the child for non-intestinal infections and treat as appropriate.

Children with persistent diarrhoea who are malnourished should be managed as in-patients using the IMCI guidelines for the management of children with severe malnutrition: correct the hydration status (rehydration solution for malnutrition (ReSoMal) is preferred to standard ORS) and any electrolyte imbalances, take measures to prevent hypothermia and hypoglycaemia, and, where possible, conduct a full septic screen (blood, urine, and stool cultures, chest X-ray (CXR), and complete blood count (CBC), as well as blood urea, electrolytes, and blood sugar estimation). Lactose-free feeds may be used until the gut settles if there are increased bouts of diarrhoea on milk feeding. Lactose-free feeds include fermented animal milk, yoghurt or soy milks. Children with persistent diarrhoea should be investigated and the appropriate antimicrobial agent used accordingly.

## Malnutrition

Childhood malnutrition is common among HIV-infected children and the magnitude is even higher in developing countries, where it is already endemic. Severe malnutrition is predictive of HIV, as early studies showed that 30–50% of severely malnourished children were HIV infected in settings where both conditions were endemic. Acute malnutrition (low weight for height) is associated with increased case-fatality of common childhood infections while chronic malnutrition (low height for age) is associated with long term effects on cognition, intellectual abilities and loss of human capital among other adverse effects.

HIV-infected children are at increased risk of malnutrition for many reasons, including:

- Decreased food intake because of anorexia associated with the illness, mouth ulcers and oral thrush
- Increased nutrient loss resulting from malabsorption, diarrhoea, HIV enteropathy
- Increased metabolic rate because of infections, opportunistic infections (OIs), and the HIV infection itself

- During periods of accelerated growth following initiation of ARV therapy
- Release of cytokines (TNF-alpha, cachetin) into plasma or tissues may mediate weight loss in HIV-infected children
- Reduced food production in the family owing to sick parents/guardians being unable to grow or buy food because they may be out of work
- HIV-positive mothers have higher rates of low-birth-weight babies and premature birth, which are risk factors for childhood malnutrition.

Characteristics of HIV-infected children associated with malnutrition include:

- Micronutrient deficiencies (low serum levels of zinc, selenium, vitamins A, E, B6, B12 and C) are common among HIV-infected children, reduce immunity, and predispose them to more infections and worsening nutritional status.
- Characteristically, deviations in linear growth and weight are apparent as early as 3 months of age in HIV-infected children.
- Stunting (low height for age) is more prominent than wasting.
- Malnutrition and cachexia are characteristic symptoms of AIDS.

The clinical presentation of malnutrition in HIV-infected children is similar to that in HIV-negative children. However, marasmus/severe wasting is more common than kwashiorkor/oedematous malnutrition among HIV-infected children.

### Clinical evaluation for nutrition status

Evaluation for malnutrition should be carried out at each clinical contact with the HIV infected child.

Ask mother/caregiver or check the medical records to determine whether the child lost weight during the past month. Take a brief history to determine whether the child has conditions that put them

at nutrition risk such as a cough for more than 21 days, diarrhoea for more than 14 days, chronic OI or malignancy.

The classification of the nutritional status of children is shown in [Table 6.1](#).

**Table 6.1: Classification of nutrition status**

<b>Severe acute malnutrition</b>	Signs of severe visible wasting, or Oedema present in both feet, or Weight-for-height less than $-3$ z-scores below median WHO reference value, or MUAC less than: <ul style="list-style-type: none"> <li>• 115 mm in infants and children <i>6 months–5 years</i></li> <li>• 135 mm in infants <i>6 years–9 years</i></li> <li>• 160 mm in infants <i>10 years–14 years</i></li> </ul>
<b>Poor weight gain</b>	Reported weight loss, or Very low weight (weight for age less than $-3$ z-scores), or Underweight (weight for age less than $-2$ z-scores), or Confirmed weight loss ( $> 5\%$ ) since the last visit, or Growth curve flattening, or MUAC less than: <ul style="list-style-type: none"> <li>• 120 mm in infants <i>6 months–12 months</i></li> <li>• 130 mm in infants <i>1 year–5 years</i></li> <li>• 145 mm in infants <i>6 years–9 years</i></li> <li>• 185 mm in infants <i>10 years–14 years</i></li> </ul>
<b>Growing well</b>	Child is gaining weight
<b>Has conditions with increased nutrition needs</b>	HIV infection, or Chronic lung disease, or TB, or Persistent diarrhoea, or Other chronic OI or malignancy

(Source: WHO and UNICEF 2009)

Caregivers of children who are growing well should be encouraged and given information on how to continue supporting their children nutritionally:

- Children who are growing well but have a chronic illness such as HIV require 10% more energy calories than usual requirements. (refer to [Chapter 11](#))

- Children who are growing poorly or have a condition that increases nutrition requirements such as TB require 30–40% increase in the energy calories (refer to [Chapter 11](#)).
- All children classified as severely malnourished require therapeutic feeding.

## Management of severe acute malnutrition (the 'Ten Steps')

(Adapted from WHO 1999 guidelines for treatment of severely malnourished children)

There are ten essential steps for managing severe acute malnutrition.

These steps are accomplished in two phases: an initial **stabilisation phase** where the acute medical conditions are managed, and a longer **rehabilitation phase**. Note that treatment procedures are similar for marasmus/severe wasting and kwashiorkor/oedematous malnutrition.

The ten steps are:

- 1 Treat/prevent hypoglycaemia
- 2 Treat/prevent hypothermia
- 3 Treat/prevent dehydration
- 4 Correct electrolyte imbalance
- 5 Treat/prevent infection
- 6 Correct micronutrient deficiencies
- 7 Start cautious feeding
- 8 Achieve catch-up growth
- 9 Provide sensory stimulation and emotional support
- 10 Prepare for follow-up after recovery

See [Appendix D](#) for the detailed management of children with severe acute malnutrition.

### *How long do you treat the child?*

The 1999 WHO guidelines recommend that children with severe acute malnutrition are managed in the institution until there is nutritional recovery, i.e.  $\geq 90\%$  weight for height. Generally this would require admission for up to 4 weeks. This is inconvenient for the mother and family and may contribute to additional poverty because normal family economic activities are disrupted. Most children are discharged before full recovery. Studies that have followed up children to determine long-term success of nutritional rehabilitation found that only 25% of the children recover fully, 10% die, 20% are re-admitted for further nutritional rehabilitation while 45% continue to be malnourished.

Children can be discharged once they have achieved weight gain of  $>10$  gm/day, are taking a solid diet, have a good appetite, show no oedema, and the mother is the primary care provider. After returning home, the child should be fed at least 5 times per day, with the usual home foods modified to contain approximately 460 kilojoules and 2–3 g/kg proteins per 100 g of food. High-energy snacks should be given between meals along with electrolyte supplements. Ready-to-use food (RTUF), a new peanut-butter based ‘F100 preparation’ is increasingly being used as a therapeutic and supplemental feed in the management of severe malnutrition.

For further discussion on food preparation see [Chapter 11](#).

### *Ready-to-use therapeutic food (RTUF)*

RTUF is an energy-dense paste that has nutrients in the same proportion as the WHO F100 formulation. It is made by replacing dry skimmed milk (DSM) in the F100 with peanut butter paste. This gives an energy-rich paste that can be eaten directly by the child without addition of water, thus reducing the risk of bacterial contamination. RTUF is associated with greater weight gain than F100 or corn-soy blends used for therapeutic feeding. RTUF does not rely on mother’s cooking skills for preparation.

RTUF can be used as supplement to provide for some of the child’s nutrient requirements while the rest is provided by the home diet.

This is best for children who are nutritionally at risk or during the transition from RTUF therapeutic feeding to feeding on a family-based diet after recovery from severe acute malnutrition.

### *Community therapeutic feeding*

Children with severe acute malnutrition, who have a good appetite and no obvious complications are good candidates for community rehabilitation. Community feeding means that mothers and their malnourished children do not need to be hospitalized and that children are not exposed to new infections as would be the case with in-patient hospital management. This approach has been evaluated extensively in Malawi and Ethiopia with enormous success. Community therapeutic feeding needs to be closely supervised to ensure appropriate selection of eligible children and to ensure that children who are on this plan actually recover.

### **Invasive bacterial infections**

Invasive bacterial infections that occur with greater frequency and severity are one of the early manifestations of HIV disease in children. Common infections include bacterial pneumonia (see **Chapter 7** for a discussion of pneumonia), meningitis, and sepsis. Aetiology and clinical presentations may be similar to those in other children but the presence of occult infections is more frequent. Fever (axillary temperatures  $> 37.5^{\circ}\text{C}$ ) may be the only symptom of serious infections. HIV-infected children with fever therefore need careful clinical and laboratory assessment to identify the cause of fever. The treatment of infections in HIV-infected children is the same as in other children. However, recovery in HIV-infected children is often slower and treatment failure is more frequent. Presumptive treatment for these conditions should be according to age-appropriate local recommendations and should consist of broad-spectrum antibiotics (penicillin and an aminoglycoside). Treatment for malaria should also be included in malaria endemic areas.

### **Otitis media**

Ear infection is one of the most common infections in HIV-infected children. Acute otitis media refers to an ear infection that resolves

within 14 days of onset. Suppurative otitis media is more common in infected children during the first year of life. By the age of 3 years, most HIV-infected children in the absence of ART will have had one or more episodes of acute otitis media. Signs and symptoms are similar to those in non-HIV infected children and include ear pain, pulling on the ears, excessive crying, ear discharge, and irritability. At otoscopy the eardrum is hyperaemic, bulging and immobile and there may be perforation. Management includes ear wicking 8-hourly when there is discharge and appropriate antibiotic cover.

Chronic suppurative otitis media occurs with increased frequency in HIV-infected children and is associated with chronic ear discharge, which is usually painless, and a perforated eardrum. Frequent ear wicking is the main mode of management; additionally you may syringe the ear using dilute vinegar (1–4 ml of clean water) and instillation of antibiotics. It is preferable that experienced ENT practitioners carry out the ear syringing.

## **Malaria**

Malaria is a major cause of morbidity and mortality in most sub-Saharan African countries. Infants born to HIV-infected women are more likely to suffer from congenital malaria than children born to uninfected women. Likewise, an increased frequency of malaria has been noted in HIV-infected children, with associated higher levels of parasitaemia than in other children. Additionally HIV-infected children are more likely to be anaemic during an episode of malaria compared to uninfected children.

Clinical presentation and response to treatment is similar to that in uninfected children and treatment recommendations should follow the guidelines provided by the national malaria programme.

Because in many areas it will not be possible to differentiate cerebral malaria and meningitis at admission, you should treat all children in malaria endemic areas with a presumptive diagnosis of cerebral malaria for bacterial meningitis until proven otherwise. This is particularly relevant for HIV-infected children who have an increased frequency of both conditions.



## Prevention

Take standard measures for preventing malaria in HIV-infected children living in endemic areas (wearing long sleeves and trousers in the evenings, impregnated mosquito nets, and topical insect repellents, as long as child does not have dermatitis or other skin problems).

The CHAMP trial in HIV-infected and -uninfected children in Uganda showed that whereas use of insect treated bednets (ITNs) was associated with a 43% reduction in malaria incidence, the combined use of ITNs and cotrimoxazole was associated with a 97% reduction in malaria incidence. It is therefore recommended that in malaria-endemic areas the combined use of ITNs and cotrimoxazole should be offered to all HIV-infected children.

## Haematologic abnormalities associated with HIV infection

HIV-1 infection has been associated with cytopenias, suggesting that the virus may disrupt haematopoiesis. The postulated mechanisms for the cytopenias include: underlying opportunistic infections, autoimmune reactions, blunted erythropoietin production, medications and nutritional deficiencies. Low platelet counts have been described in 2.5–10% of HIV infected children and typically tend to be asymptomatic. Leucopenia has been found in 10–43% of HIV infected ARV-naïve children, while the prevalence of granulocytopenia in published studies ranges between 7–17.5%. The commonest abnormality is anaemia.

## Anaemia

Anaemia is the commonest haematological condition in HIV-infected ARV-naïve children and contributes significantly to morbidity. The reported prevalence of anaemia (Hb of < 10.5 g/dL) is 74–92%. Anaemia in these children is generally mild, with reported median haemoglobin levels ranging from 10–10.6 g/dL. Anaemia with haemoglobin levels below 8 g/dL is associated with increased mortality in HIV-ART naïve and ART-experienced children. The prevalence of anaemia in HIV-infected infants is influenced by the prevalence of other conditions that cause anaemia, such as malaria and helminthic infestation. The occurrence of malnutrition,

and especially micronutrient malnutrition, also contributes to the prevalence of anaemia. There is also some evidence that the severity of anaemia is associated with HIV disease progression and malnutrition.

HIV-infected children have an equal prevalence of anaemia compared to uninfected children but have a higher case fatality rate. A study in Abidjan found an equal frequency of anaemia in HIV-infected and uninfected children. In the same study, the case fatality rate (CFR) from anaemia was 13% in HIV-infected children (third commonest cause of death) compared to a CFR of 8% in uninfected children (fifth commonest cause of death).

Anaemia in HIV infected children is predictive of mortality on ART, as was shown by a study in Kenya where an Hb of < 9 g/dL at ART initiation was a risk factor for death among children started on treatment.

### **Other haematological disorders in HIV-infected children**

Multiple interacting factors contribute to the haematological manifestations of HIV disease. The effects of HIV-1 infection influence all haemopoietic cell lineages resulting in a spectrum of haematological abnormalities. Even in the absence of other pathological processes, bone marrow morphology is invariably abnormal, and anaemia, neutropenia and thrombocytopenia are all common during the course of HIV disease. Inter-current opportunistic infections may cause bone marrow suppression or induce specific cytopenias. Therapies used to treat HIV and its complications, e.g. AZT and cotrimoxazole, are frequently implicated as the cause of haematological dysfunction, and many have significant myelotoxic side-effects.

Further to this, the treatment of neutropenia is based upon the underlying cause, severity, and the presence of associated infections or symptoms as well as the overall health status of the child. As well as making sure the underlying cause is treated, there are treatments that directly address neutropenia and these may include (as appropriate for the setting):

- Antibiotic and/or antifungal medications for prophylaxis or treatment
- Administration of white blood cells growth factors (such as recombinant granulocyte colony-stimulating factor (G-CSF) in some cases of severe neutropenia
- Granulocyte transfusions, or
- Glucocorticosteroid therapy or intravenous immune globulin for some cases of immune-mediated neutropenia.

The treatment of thrombocytopenia varies according to the cause. If thrombocytopenia is drug-induced, then removal of the offending agents should correct the condition. Specific treatment may include the following:

- Corticosteroids may be used to increase platelet production.
- Lithium carbonate or folate may also be used to stimulate the bone marrow production of platelets.
- Platelet transfusions may be used to stop episodic abnormal bleeding caused by a low platelet count. However, if platelet destruction results from an immune disorder, platelet infusions may have only a minimal effect and may be reserved for life-threatening bleeding.
- Immune modulators such as glucocorticosteroids and intravenous immunoglobulin therapy may be used.
- Splenectomy may be necessary to correct thrombocytopenia caused by platelet destruction. A splenectomy should significantly reduce platelet destruction because the spleen acts as the primary site of platelet removal and antibody production.
- Patients with idiopathic thrombocytopenic purpura (ITP) may require high-dose intravenous immunoglobulin. Patients with thrombotic thrombocytopenic purpura (TTP) will probably require large-volume plasmapheresis (plasma exchange).

### Effect of antiretroviral treatment on haematological parameters

Following 6 months of treatment with ART, haematological reconstitution occurs progressively for all blood lineages except RBC, WBC, granulocytes and total lymphocytes. The positive effect of ART is probably due to the reduction in viral load, decreased destruction of mature hematopoietic cells of multiple lineages, improvement in the blunted erythropoietin response, and decreased incidences of opportunistic infections. Significant increase in haemoglobin and mean corpuscular volume occur within the first 6 months of treatment with AZT-based ART in children with and without anaemia at treatment initiation and regardless of haematinic use. Some patients develop red cell macrocytosis, which is largely attributed to AZT use. Total red cell counts decline following treatment with ART despite an increase in haemoglobin levels and mean corpuscular volume. It is thought that there may be a defect in the production of erythrocytes from erythroid progenitor cells leading to the generation of fewer but larger cells. Total white blood cells also decrease significantly with ART probably due to improved immunity and subsequent reduction of chronic immune stimulation from viral replication, and reduction in infections. Granulocytopenia is observed in a minority of patients on ART and is an indication for ARV drug substitution. (Refer to [Chapter 8](#).)

### Measles

Measles is one of the major causes of morbidity and mortality in sub-Saharan Africa and is a severe illness in children with HIV infection, particularly those with advanced immunodeficiency. Severe cases can occur without the typical rash and may be complicated by pneumonia or encephalitis. HIV-infected children with measles have a high case fatality and should be treated in hospital. Management should include two doses of vitamin A, administered on successive days, calculated on the basis of the child's age (50 000 IU per dose if aged < 6 months; 100 000 IU per dose for age 6–11 months and 200 000 IU per dose in children aged 12 months to 5 years).

Measles may occur in early infancy in HIV-infected children because of inadequate transfer of maternal antibodies and infection may occur despite a history of immunization.

Nonetheless it is still recommended to give measles immunization to HIV-infected children at 6 months and to repeat at 9 months. In ARV-naïve children there are low levels of measles antibody following immunization due to the impaired immune response associated with HIV infection. Once ART is started, measles antibody levels do not increase on their own. Repeat measles immunization following immune reconstitution with ART treatment has been shown to result in brisk antibody response and maybe considered as part of routine care.

### **Hepatitis B/HIV co-infection**

Due to shared modes of transmission, co-infection with hepatitis B virus (HBV) and HIV is common. With a reduction in AIDS-related deaths due to ART, liver disease has emerged as an important cause of death in patients with HBV-HIV co-infection.

The antiretroviral drugs lamivudine (3TC), emtricitabine (FTC) and tenofovir (TDF) (for older adolescents) have activity against hepatitis B. They should therefore be included in the regimen for HIV infected children with hepatitis B co-infection.

### **Hepatitis C/HIV co-infection**

Mothers with hepatitis C virus (HCV) and HIV co-infection are the major source of HCV/HIV co-infection in infancy and childhood. There is no known intervention capable of interrupting HCV spread from mother to child, while the majority of infant HIV infections can be prevented by antiretroviral prophylaxis in the mother and child and other measures (see **Chapter 3**). In the era preceding treatment of HIV infection with ART, HCV co-infection was of little concern because the short-term survival of patients with HIV infection prevented the slowly developing consequences of chronic hepatitis C. As the life expectancy of patients with HIV infection increased with therapy, HCV has emerged as a significant pathogen. Several lines of evidence in adult patients suggest that liver disease may be more severe in patients co-infected with HIV and that progression of HIV disease may be accelerated by HCV co-infection. Whether co-infected children share these clinical patterns remains a matter of speculation. Chronic hepatitis C in otherwise healthy children is usually a mild

disease; liver damage may be sustained and fibrosis may increase over the years, suggesting slow progression of the disease. Interferon-alpha has been the main drug used to treat hepatitis C in children and adolescents, with average response rates of 20%. Preliminary results of treatment with interferon-alpha and ribavirin suggest that the efficacy would be greater with combined therapy. These treatment protocols are yet to be applied to children co-infected with HIV on a wide scale, but the increasing number of long-term survivors will probably prompt further investigation. At present, treating HIV disease and monitoring HCV infection and hepatotoxicity induced by antiretroviral drugs seem to be the more reasonable approach to HCV/HIV co-infection in childhood.

## Neurological manifestations

HIV is a neurotropic virus that invades the central nervous system by infecting monocytes, which cross the blood-brain barrier and establish HIV infection in macrophages and microglial cells. Neurological symptoms are widely prevalent, occurring at all stages of HIV infection and affecting any part of the nervous system. It is estimated that 50–90% of HIV-infected children in the absence of ART, develop symptomatic neurological disturbances, and the brain is the most commonly affected part of the nervous system in children.

### HIV encephalopathy

HIV encephalopathy is caused by HIV infection of the brain. It manifests clinically with various neuro-developmental, cognitive, motor, and behavioral abnormalities. The disease may follow one of three trajectories: (1) a static form in which the overall neuro-developmental potential is marginally reduced, (2) a plateau form in which arrest of brain development occurs, resulting in marked neuro-developmental delay, and (3) a regressive form (the most severe form of the disease) in which marked neuro-developmental delay plus loss of attained milestones (regression) are central features.

HIV encephalopathy has been reported in about 21% of HIV-infected African children. Age of onset of developmental delay is unpredictable, but the onset of encephalopathy may be related to the

presence of other symptoms of HIV disease (e.g. hepatosplenomegaly and lymphadenopathy).

### *Diagnosis*

Diagnosis is mainly clinical and depends on the presence of least 2 of the following for at least 2 months:

- Failure to attain or loss of developmental milestones or loss of intellectual ability
- Impaired brain growth or acquired microcephaly
- Acquired symmetrical motor deficit manifested by 2 or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbances
- Cerebrospinal fluid is normal or has non-specific findings and CT scan shows diffuse brain atrophy.

### *Management*

Managing encephalopathy should include evaluating the child with the help of a neurologist, if possible. If nothing other than HIV is found, the treatment goal is to reduce viral load. Depending on the severity, the patient will need a support system, which includes physical therapy, a social worker, and surgery to minimize contractures.

ART is possibly the only way to reverse the effects of HIV infection on the CNS and allow restoration of growth, development, and milestones. However, ART and other medications used can also have neurological side effects, the most common of which is peripheral neuropathy. In the management of children with HIV encephalopathy selection of ARV drugs should take into account CSF penetration of the drug. Fortunately, zidovudine, and abacavir, two of the the most commonly used first line drugs, have good CNS penetration.

## **Other neurological manifestations**

### **Neuropathy**

Several types of peripheral neuropathy affecting single or multiple nerves have been documented (e.g. axonal neuropathy, demyelinated

neuropathy, polyradiculopathy, and radiculopathy). HIV-related neuropathy is a troublesome condition that occurs in as many as one-third of patients with a CD4 count < 200/ $\mu$ L. It presents with dysaesthesias and numbness in a 'glove and stocking' distribution.

Neuropathy in children is more difficult to diagnose and less well described than in adults. Diagnosis is based on clinical presentations such as pain or numbness that has a 'glove and stocking' distribution.

Treatment is mainly symptomatic. Pain due to neuropathies may respond to analgesics combined with amitriptyline, carbamazepine, and lamotrigine. Morphine is recommended for pain management in end-stage disease.

### Seizures

Seizures are common non-specific manifestations of neurological illnesses associated with HIV. Seizures may result from:

- Space-occupying lesions (most often cerebral toxoplasmosis or tuberculoma)
- Meningitis (could be cryptococcal meningitis in older children)
- Metabolic disturbances
- No identified cause other than HIV infection.

Treatment is aimed at the underlying disorder and seizure control through standard anti-epileptic medication. Drug interactions may be a problem for patients on ART. For those on ART the drug of choice is sodium valproate.

For patients presenting with focal seizures, consider treatment for toxoplasmosis if no other cause is apparent.

### CNS opportunistic infections (OIs)

CNS OIs are seen in cases of severe immunosuppression (CD4 < 200/ $\mu$ L) in older children and adolescents ([Table 6.2](#)).



**Table 6.2** Opportunistic infections of the central nervous system

Neurological disease	Clinical presentation	Diagnostic tests	Management
Cytomegalovirus (CMV) infection	<ul style="list-style-type: none"> <li>• Presents with encephalitis with retinitis, radiculomyelitis, or neuritis</li> </ul>	CSF PCR, MRI, if available	Intravenous ganciclovir 10 mg/kg per day in 2 divided doses for 2–3 weeks Foscarnet 180 mg/kg/day in 3 divided doses for 14–21 days may be used when there is sight threatening CMV retinitis
Cryptococcosis (Cryptococcal meningitis)	<ul style="list-style-type: none"> <li>• Presents with fever, headache, seizures, change in mental status</li> <li>• Focal neurological signs uncommon</li> </ul>	CSF-Indian ink positive Cryptococcal antigen test, MRI, if available	Induction with combination of amphotericin B (0.7–1.0 mg/kg/day) and flucytosine 100 mg/kg/day for 2 weeks followed maintenance therapy with fluconazole 5–6 mg/kg/dose (max 800 mg/day) in children and 400 mg/day in adolescents and adults for a minimum of 10 weeks, then 200 mg/kg maintenance therapy
Toxoplasmosis	<ul style="list-style-type: none"> <li>• Most common manifestations are encephalitis, mental changes, fever headache, and confusion</li> </ul>	Serology, MRI, if available Do not do lumbar puncture if there is mass lesion	Pyrimethamine loading dose 2 mg/kg/day (max 50 mg) for 2 days, then maintenance dose 1 mg/kg/day (max 25 mg) plus sulfadiazine 50 mg/kg every 12-hours plus folic acid 5–20 mg 3 times weekly Treat until 1–2 weeks beyond resolution of signs and symptoms
Herpes simplex virus	<ul style="list-style-type: none"> <li>• Associated with fever-altered state of consciousness, personality changes, convulsions, and usually focal neurological signs, particularly temporal lobe signs</li> </ul>	Rising serum HSV titres and increased ratio of CSF-to-serum concentration of HSV antibody Viral isolation	IV acyclovir 20 mg/kg given 3 times a day for 21 days

The most common OI in children is, reportedly, CMV infection. Other viruses, especially herpes simplex and varicella-zoster virus, can also cause acute encephalitis.

Fungal infections, particularly candida and aspergillus meningitis, are reported to be the second most common infection in children.

Cryptococcal meningitis is rarely seen in young children with AIDS, but has been reported among older children and adolescents. Toxoplasma encephalitis has rarely been reported.

## Dermatitis and other skin manifestations

HIV-infected children have a significantly higher prevalence of skin conditions compared to non-infected children. The most common skin conditions among HIV-infected children are infections followed by eczematous dermatitis, unlike HIV-uninfected children where the most frequent condition is eczematous dermatitis followed by infections. Frequency of skin conditions increases as HIV disease progresses. Among the infections, fungal conditions are the most common, followed by bacterial infections. There are subtle differences in the clinical presentation of skin conditions in HIV-infected children. **Table 6.3** contrasts the clinical presentation of skin conditions in HIV-infected and uninfected children.

**Table 6.3** Comparing common skin disorders in HIV infected and uninfected children

Disorder	HIV-1 uninfected child	HIV-1 infected child
Impetigo	Discrete areas of erythema with honey-crusting, small blister formation	Lesions similar in appearance but may be extremely widespread or evolve into cellulitis
Oral thrush	Discrete white-yellow patches and plaques on tongue, palate, buccal mucosa; usual rapid response to topical therapy	Lesions may be more extensive, with involvement of entire oral cavity and posterior pharynx; poor response to topical therapy

Disorder	HIV-1 uninfected child	HIV-1 infected child
Monilial diaper dermatitis	Confluent erythema with satellite pustules; responds to topical imidazole creams	Lesions may be more widespread; rapid recurrence after cessation of therapy
Tinea capitis	Discrete areas of scale and hair loss; responds well to treatment Discrete areas of scale and hair loss; responds well to treatment	Areas of involvement may extend to face and recur after treatment
Herpes simplex	Primary herpetic gingivostomatitis is sometimes followed by recurrences of vermillion border of lip; lesions on other parts of face or on fingers may also occur	Severe and persistent infection of oral mucosa, fingers or other skin surface may occur
Herpes zoster (Figure 6.1b, page 110)	Relatively rare. Correlates with occurrence of chicken pox during infancy and childhood	Lesions tend to be more painful and result in scarring; may develop chronic varicella-zoster infection
Warts	Single or multiple lesions on hands and other skin locations common	Lesions may be extremely widespread or persistent; extensive flat warts and giant condyloma acuminata may occur
Scabies	Discrete, intensely pruritic papules or nodules in axilla, diaper area; rapid response to topical treatment	Widespread papular lesions or diffuse eczematous eruption; may recur after treatment
Molluscum contagiosum (Figure 6.1a, page 110)	1–2 mm umbilicated papules on face, trunk, extremities	Lesions may be extremely widespread; giant lesions may occur
Seborrheic dermatitis	Erythema covered with greasy looking scales over areas rich in sebaceous glands; scalp, face, chest, back and flexural areas.	More severe and lesions of the extremities are more common.

Source: Okello P (2006), MMED thesis, University of Nairobi

The treatments for some common skin manifestations are shown in **Table 6.4**.

**Table 6.4** Common skin manifestations and treatments

Skin manifestation	Treatment
Scabies treatment Children < 1 year	<ul style="list-style-type: none"> <li>• 25% benzyl benzoate for 12 hours or gamma benzene hexachloride</li> <li>• 2.5% sulphur ointment 3 times daily for 3 days</li> <li>• Screen and treat other household contacts where appropriate</li> <li>• Wash and iron bedding and clothing or hang it out in the sun</li> </ul>
Eczema treatment	<ul style="list-style-type: none"> <li>• Avoid soap and expose affected areas to sunlight</li> <li>• Use aqueous cream instead of soap for washing; use moisturizer on dry areas</li> <li>• Apply zinc oxide cream 2 times daily; if not responding, use 1% hydrocortisone cream 2 times daily</li> <li>• Cut nails short</li> </ul>
Ringworm treatment	<ul style="list-style-type: none"> <li>• Apply benzoic acid with salicylic acid ointment (Whitfield's ointment) 2 times daily for 2–5 weeks for body lesions; if not successful try 2% miconazole cream</li> <li>• For scalp lesions give griseofulvin 10 m/kg/day for 8 weeks; if not responding consider ketoconazole</li> </ul>
Herpes zoster prophylaxis	<ul style="list-style-type: none"> <li>• Hospitalize all cases and treat, if possible, with IV acyclovir 30 mg/kg/day divided into doses every 8 hours for a total of 7 days or 2 days after cessation of new lesion formation, whichever is longer. Oral acyclovir may be used if the IV is not available</li> <li>• Children who have been exposed to herpes zoster may receive prophylaxis using varicella-zoster immune globulin (VZIG) 125 U per 10 kg (max 625 U) within 48–96 hours of exposure</li> </ul>
Herpes simplex treatment	<ul style="list-style-type: none"> <li>• Local antiseptic (gentian violet)</li> <li>• Analgesia (paracetamol)</li> <li>• Admit all children with disseminated or severe herpes simplex and give acyclovir 5 mg/kg intravenously 3 times a day or 200–400 mg orally 5 times a day, for 7–10 days</li> </ul>
Impetigo treatment	<ul style="list-style-type: none"> <li>• Hygiene, proper washing, cut fingernails, soak crusts off in soapy water</li> <li>• Apply 10% iodine solution 3 times daily or zinc oxide cream, miperazin (bactroban)</li> <li>• Antibiotics indicated only if there is pyrexia and lymphadenopathy If lesions are resistant to first treatment (first-line = amoxycillin for 10 days; second-line = flucloxacillin or erythromycin for 10 days)</li> </ul>

Other skin manifestations in HIV infected children include:

- **Papular pruritic eruptions (PPE)** ([Figure 6.1c, page 110](#)): The most common skin manifestation in HIV which results from allergic reactions to anthropod bites. The lesions may be super-infected by bacteria. Treatment is with antihistamines.
- **Verucca planus** ([Figure 6.1d, page 110](#))
- **Atopic dermatitis**
- **Eczema**
- **Psooriasis**
- **Skin lesions associated with nutritional deficiency** (more prevalent in children than in adults)
- **Drug eruptions**, which occur less frequently in children than in adults: cotrimoxazole can cause a reaction in children who are immunocompromised.

## Oral and dental conditions

Oral and dental conditions are also common in HIV-infected children, particularly those who are malnourished. Therefore, good dental hygiene is important. The most common oral condition in HIV-infected children is candidiasis, which may present as oropharyngeal or oesophageal candidiasis. Oral candidiasis/thrush ([Figure 6.2](#)) is predictive of HIV infection if seen after the neonatal period without prior antibiotic treatment, if lasting for more than 30 days, or if it is recurrent. Oral thrush is associated with difficulty or pain in swallowing or vomiting. Children therefore present with reluctance to take food, excessive salivation, or crying while feeding. Exclude other conditions that cause painful swallowing and are frequently found in HIV-infected children such as CMV, herpes simplex, and lymphomas.

For the treatment of candidiasis see the box on [page 111](#).

**Figure 6.1** Skin manifestations in HIV infected children (photographs courtesy of Israel Kalyesubula)



**6.1a** *Molluscum contagiosum*



**6.1c** Papular pruritic eruptions (PPE)



**6.1b** Herpes zoster



**6.1d** *Verucca planus*

**Figure 6.2** Oral candidiasis (photo courtesy of Israel Kalyesubula)



#### **Treatment of candidiasis**

##### **Oral candidiasis:**

- Nystatin: 2–4 million units/day divided every 6 hours until resolution
- Ketoconazole: 3.3–6.6 mg/kg/day (note: there are no doses for children under 2 years, but from field experience,  $\frac{1}{2}$  to  $\frac{1}{4}$  200 mg tablets can be used successfully)
- Miconazole: which may be in the form of a once daily buccal tablet.

##### **Oesophageal candidiasis:**

- Fluconazole: 3–6 mg/kg once daily

Other common oral and dental conditions in HIV-infected children include:

- Dental caries
- Viral diseases of the teeth
- Ulcerative necrotizing gingivitis
- Ulcerative stomatitis
- Cancrum oris aphthous ulceration (herpes simplex-related ulcer; if diagnosed early it will be amenable to acyclovir)
- Oral hairy leukoplakia
- Angular stomatitis
- HIV-associated gingivitis.

## Malignancy

The major malignancies associated with HIV infection in African children are Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (Burkitt's lymphoma, B-cell lymphoma). B-cell lymphoma is more prevalent in southern Africa than Burkitt's lymphoma. Clinical experience indicates that the frequency of occurrence of some malignancies is increasing with HIV endemicity.

### Kaposi 's sarcoma (KS)

Before the HIV pandemic, KS was rare in children, and adults tended to have the less aggressive endemic type. Currently, KS is more prevalent in East and Central Africa and less prevalent in West and southern Africa.

KS can present as early as the first month of life. KS is associated with human herpes virus type 8 and usually presents as generalised lymphadenopathy, black/purple mucocutaneous lesions (skin, eye, and mouth); the chest lesions may mimic those of TB.

Diagnosis is confirmed by biopsy of the lesion and histological examination. Biopsy confirmation is recommended because



several conditions may mimic KS, including pyogenic granuloma, bacillary angiomatosis and dermatofibromata. Treatment includes chemotherapy (vincristine and bleomycin or liposomal preparations of danorubicin and doxorubicin). This may require referral to cancer treatment centres. ART also often leads to regression of the lesions.

**Figure 6.3** Kaposi's sarcoma (KS) (Photographs courtesy of Israel Kalyesubula)



**6.3a** Skin and lymphadenopathic KS



**6.3b** Oral KS

## Parotid enlargement

Bilateral parotid gland enlargement is one of the most specific signs of HIV infection in children. Parotid enlargement is usually not tender and is commonly found in older children who are slow progressors; it may be associated with lymphoid interstitial pneumonitis (LIP). When parotid enlargement is exceptionally large, it may be disfiguring and lead children to be teased and/or emotionally distressed.

Periodically the parotid glands may enlarge and regress over several months, and intermittently they may become tender from bacterial super-infection. When they are tender, prescribe antibiotics and analgesics. Surgery is not required.

## Persistent generalised lymphadenopathy

Persistent generalised lymphadenopathy is one of the most common early clinical presentations in HIV-infected children. It may also be associated with parotid enlargement or hepatosplenomegaly. A biopsy may show non-specific inflammation of the nodes. It is important to

remember that disseminated TB, Kaposi's sarcoma (KS), and leukaemia can also present with generalised lymphadenopathy. Other causes include acute toxoplasmosis, rubella, CMV, EBV infection, herpes, and syphilis.

## Other medical conditions

Organ diseases are WHO stage conditions. In resource-limited settings the conditions are often not recognized and even when suspected, diagnosis is limited by lack of resources.

### Cardiac disease and HIV

Studies from developed countries indicate that most HIV-infected children referred for cardiovascular assessment were found to have abnormalities that were often clinically non-apparent. Few similar studies have been reported for African children.

One such study in Uganda involved 230 symptomatic mostly ART-naïve HIV-infected children. Of these, 51% had abnormal echocardiographic changes. One-quarter of those with abnormal echocardiographic changes had cardiovascular symptoms.

A similar study in the same city nearly 10 years later, in the ART era, showed a lower occurrence of cardiac abnormalities/cardiac dysfunction (prevalence: 13.7%).

Therefore, clinicians should evaluate HIV-infected children for cardiovascular symptoms and manage appropriately.

Common cardiac manifestations include asymptomatic left ventricular dysfunction, HIV-related cardiomyopathy, arrhythmias and pericardial disease especially pericardial effusion due to bacterial or tuberculous infection.

### Renal disease

Patients infected with HIV-1 and having persistent proteinuria or clinical evidence of renal involvement should be considered as having HIV nephropathy, also referred to as HIV-associated nephropathy (HIVN/HIVAN). Children with HIVN/HIVAN may

have the general manifestations of HIV or have renal specific manifestations such as nephritic syndrome (NS), haemolytic uraemic syndrome (HUS), systemic lupus erythromatoses (SLE), renal tubular necrosis, acute renal failure, IgA nephropathy and infiltrative renal disease. In children, as in adults, proteinuria may be the earliest clinical presentation of HIV nephropathy and may rarely be the first manifestation of HIV infection in a patient with unsuspected disease. Subsequently they may develop reduction in glomerular filtration rate that progress to end stage renal disease in a few weeks to months. Clinical manifestations may be gross features such as anasarca, oliguria, seizures, abnormal blood pressure, and glomerular filtration rates as well as deranged fluid and electrolytes, urinary tract infections, or a chance finding of proteinuria on routine clinical evaluation. Acute renal failure is rare in children and is usually secondary to complications such as intercurrent illnesses, hypotension and the use of nephrotoxic drug therapy. Persistent sterile leukocyturia has been reported in children receiving indinavir, accompanied by reversible impairment in renal function. Ultrasound evaluation of the kidneys of children with nephropathy may reveal normal kidneys or large kidneys compared to the child's age and height in both early and late stages of HIVAN/HIVN.

There is limited data on the prevalence of HIVN/HIVAN in African children. In a Kenyan study Galgalo and colleagues studied the renal function of 87 HIV-infected ARV-naïve children. In this study the prevalence of proteinuria of > 1+ was 32.2% (95% CI 23.7%-40.7%) and persistent proteinuria > 1+ on the repeat urinalysis performed 2 weeks later was 16.1% ( 95% CI 9.4%-22.8%). In addition, 21 (24.1%) of the children had borderline systolic hypertension and 18.4% definite diastolic hypertension. Abnormal glomerular filtration rate was found in 26.4 % of the patients. Overall, persistent proteinuria and/or decreased glomerular filtration rate was seen in 31/87 of the study subjects giving a conservative prevalence of HIV nephropathy of 35.6% ( 95% CI 26.8%-44.4%). If patients with non-gastrointestinally related deranged bicarbonate levels were included, the prevalence of HIV nephropathy would be 55%. American studies have documented

prevalence of HIVN to be 29% on clinical assessment and 4–7% based on renal biopsy.

To identify children with nephropathy both glomerular (i.e. proteinuria and reduced GFR using urine dipsticks, microscopy and creatinine levels) and tubular (i.e. metabolic acidosis, proteinuria and electrolyte imbalances) functions should be evaluated.

The authors of this book recommend that routine evaluation of an HIV-infected child should include a complete urinalysis, estimation of serum electrolytes levels (sodium, potassium), metabolic screen ( $\text{HCO}_3^-$ ), blood urea nitrogen, creatinine levels and estimation of GFR every 6 months.

### *Urinalysis*

Urinalysis using urine dipstick is a simple and inexpensive method of screening patients for proteinuria, detects primarily albuminuria and becomes positive only when protein excretion exceeds 300–500 mg/day. Proteinuria is defined as urinary protein excretion exceeding 100 mg/m<sup>2</sup>/day or 4 mg/m<sup>2</sup>/hr which may be transient, orthostatic or postural. It may result from non-pathological causes such as posture, fever, dehydration, exercise or pathological causes such as glomerular or tubular process. Patients with 1+ or greater proteinuria should be evaluated for other congenital urinary tract anomalies, urinary tract infection (UTI), and malignancies. Urinalysis should be repeated at least 2 weeks later; if the test is positive, the patient should be labelled as having ‘persistent proteinuria’; and if negative, as ‘intermittent/transient proteinuria’.

Patients infected with HIV-1 and having persistent proteinuria or clinical evidence of renal involvement should be considered as having HIV nephropathy, and a kidney biopsy should be obtained. The estimate of the degree of proteinuria is further refined by quantifying urinary protein/creatinine ratio. The protein/creatinine ratio from a spot urine specimen, preferably collected after the first voided morning specimen and before bedtime, has an excellent correlation with the protein content of 24-hr urine collection. Urine protein/creatinine ratios to estimate daily proteinuria in HIV-infected

paediatric patients are reliable, despite the low creatinine excretion rates associated with advanced AIDS.

Additional investigations for renal function include a complete metabolic panel, total protein and albumin levels, serology for HBV, C3 and C4, antinuclear antibody testing, and urine cultures. The completeness of this evaluation will of course depend very much on the available resources. Children should be referred to a nephrologist if there is significant proteinuria (grade  $\geq 1+$  by urine dipstick analysis or urine protein to creatinine ratio  $\geq 200$  mg/ $\mu$ mol for two specimens), persistent microscopic haematuria, gross haematuria in the absence of a UTI, oedema, hypertension, recurrent UTI, electrolyte abnormalities, persistent metabolic acidosis, elevated creatinine or elevated BUN. Percutaneous renal biopsy is indicated if there is persistent proteinuria or renal insufficiency.

The importance of routinely evaluating HIV-infected children for renal disease is illustrated by the following Kenyan study (unpublished). There was a significant inverse relationship between WHO clinical stage of disease and persistent proteinuria. Children classified as WHO clinical stage 3 and 4 were less likely to have persistent proteinuria compared to those with stage 1 and 2. Since nephropathy is a WHO stage 3 disease, without dipstick analysis eight (57.1%) of the 14 children with persistent proteinuria were incorrectly staged and as a result failed to access ART in a timely manner, as per the treatment guidelines then in place. Twelve (16.9%) of the 71 children with CD4 > 15% had persistent proteinuria, and they too would have missed ART, following the treatment guidelines then in place, if only WHO staging and CD4 counts without a urinalysis were used for evaluation.

### *Treatment of renal disease in HIV*

Antiretroviral therapy appears to be the most promising way to prevent progression of childhood HIVAN. There is no known treatment for other lesions. In HIV patients with lesions other than HIVAN, viral suppression and use of ART are not associated with a beneficial effect on renal function. Observational studies have suggested that antiretroviral medications and angiotensin-converting enzyme

inhibitors can slow the progression of renal disease with subsequent progression to end-stage renal disease, and result in a reduction in proteinuria among patients with HIVAN. Steroids are particularly useful in patients with nephrotic syndrome but not in HIV-associated nephropathy. Other drugs such as cyclosporine have been shown to reduce proteinuria in some children but there are no randomized trials available. Remission of proteinuria in AIDS-related nephrotic syndrome has been observed in patients on cyclosporine after the failure of prednisone.

## Knowledge gaps

- There are few comprehensive studies documenting the aetiological cause of infections and death in HIV-infected children in Africa.

## Additional and recommended reading

### *Clinical spectrum of disease in HIV-infected children*

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### **Kaposi's Sarcoma**

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# Chapter 7

## Pulmonary conditions

### Summary

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- Pneumonia is the leading cause of hospital admissions and death in HIV-infected children. Recurrent episodes of pneumonia suggest immune suppression, but this should be investigated further to exclude other conditions such as TB, foreign body, and lymphoid interstitial pneumonitis (LIP).
- In children less than one year old, consider *Pneumocystis* pneumonia (PCP) as a possible cause of severe pneumonia. In areas of high HIV prevalence, treat infants with severe pneumonia presumptively for PCP, until it is excluded or it is found that they are DNA PCR or HIV antibody negative.
- PCP in an infant may be the first AIDS-defining condition and an indication of HIV infection in the family. Therefore efforts should be made to provide counselling and testing for HIV for the mother and the family.
- All HIV-exposed children should receive prophylaxis against PCP from 4–6 weeks of age until it is established that the child is not HIV-infected.
- Children who are co-infected with HIV and TB experience higher case fatality and it is important to look actively for TB in children with chronic cough and failure to thrive, and provide treatment as early as possible.
- Lymphoid interstitial pneumonitis (LIP) is common in children. It occurs in about 40% of children with perinatally acquired HIV, is diagnosed by exclusion, and is often mistaken for miliary pulmonary TB because of chronic cough and *miliary-like* pattern on chest X-ray.



## Introduction

Pneumonia and chronic lung diseases contribute to the increased morbidity and mortality of HIV-infected children. Most children present with recurrent bacterial pneumonia, but in children less than one year of age, PCP contributes to the high infant mortality. The incidence of TB in children depends on the prevalence of TB in the adult community, and other HIV-related chronic lung diseases often have a similar clinical presentation leading to over-diagnosis of TB.

In the treatment of different pulmonary conditions, it is important to remember that antimicrobial therapy may require adjustment, by increasing the length of treatment, using different antibiotics, and/or providing primary or secondary prophylaxis.

The different pulmonary conditions may be difficult to differentiate from each other without invasive procedures such as bronchoalveolar lavage, and are often fatal in the immune-compromised child. The most common include:

- Bacterial pneumonia
- *Pneumocystis* pneumonia (PCP)
- Tuberculosis
- Lymphoid interstitial pneumonitis (LIP)
- Bronchiectasis
- Viral pneumonitis.

**Tables 7.1** and **7.2** show the causes of lung disease in HIV infected children of various ages.

**Table 7.1** Causes of lung disease in HIV- infected infants (<1 year of age)

Cause	Importance	Clinical features	Management <sup>a,b</sup>
Bacterial pneumonia, e.g. pneumococcus, staphylococcus, Gram negatives	Very high incidence	Acute onset of cough, fever and fast breathing. Can be very severe with hypoxia	Broad-spectrum antibiotics including coverage of Gram-negative organisms
PcP	Common cause of severe, fatal pneumonia especially in 2-6 months age group	Severe respiratory distress with hypoxia not improving with broad-spectrum antibiotics. Often low grade fever. CXR: diffuse interstitial infiltration or hyperinflation	Add high-dose cotrimoxazole. Consider steroids
CMV pneumonitis	Common co-infection with PcP but few data from resource-poor setting	Severe respiratory distress with hypoxia not improving with broad-spectrum antibiotics and high-dose cotrimoxazole	Add ganciclovir
Viral pneumonia, e.g. RSV	Common and associated with bacterial co-infection	Acute onset of cough, fever, fast breathing. Wheezing less common than in HIV-uninfected	Broad-spectrum antibiotics if suspected bacterial co-infection
Tuberculosis	Depends on prevalence of TB/HIV in adult population	TB contact usually identifiable, often mother. Presentation often acute and severe or disseminated	Anti-TB treatment
Mixed infection	Common problem. PcP, Bbacterial pneumonia, viral, TB	Consider when poor response to first-line empiric management	Anti-TB treatment plus treatment for additional and presumed respiratory infections
Measles	In communities with poor measles immunization coverage	Conjunctivitis, typical rash, fever and cough, respiratory distress	Broad-spectrum antibiotics Vitamin A
LIP	Uncommon in infants and associated with bacterial co-infection	Generalised lymphadenopathy, clubbing, parotid enlargement. CXR: diffuse reticulonodular pattern	If symptomatic and close follow-up, steroids and broad-spectrum antibiotics

PcP= *Pneumocystis pneumonia*; CMV = cytomegalovirus; RSV = respiratory syncytial virus; LIP = lymphoid interstitial pneumonitis

<sup>a</sup> Oxygen may be indicated irrespective of cause; <sup>b</sup> CPT and ART when indicated for all cases

Source: WHO 2010 childhood TB/HIV guidelines

**Table 7.2** Causes of lung disease in HIV-infected children (1–14yrs)

Cause	Importance	Clinical features	Management <sup>a</sup>
Bacterial pneumonia, e.g. pneumococcus, staphylococcus, Gram negatives	Very high incidence Often recurrent	Acute onset of cough, fever and fast breathing. Can be very severe with hypoxia	Broad-spectrum antibiotics including coverage of Gram-negative organisms
Tuberculosis	Common in TB-endemic regions	See text. Persistent respiratory symptoms and often poor nutritional status; positive TB contact especially in younger children. CXR: focal abnormalities and perihilar adenopathy	Anti-TB treatment
LIP	Common, especially around 2–6 years and bacterial pneumonia is a common complication	Persistent or recurrent respiratory symptoms. Generalised lymphadenopathy, clubbing, parotid enlargement. CXR: diffuse reticulonodular pattern and bilateral perihilar adenopathy	If symptomatic, steroids and broad-spectrum antibiotics
Bronchiectasis	Common. Complicates recurrent bacterial pneumonia, LIP or TB	Cough productive of purulent sputum. Clubbing. CXR: honeycombing usually of lower lobes	Broad-spectrum antibiotics Physiotherapy
Viral pneumonia	Associated with bacterial co-infection	Acute onset of cough, fever, fast breathing. Wheezing less common than in HIV-uninfected	Broad-spectrum antibiotics if suspected bacterial co-infection

(Continued on the next page)

**Table 7.2** Causes of lung disease in HIV-infected children (1–14yrs) (continued)

Cause	Importance	Clinical features	Management <sup>a</sup>
Mixed infection	Common problem. Bacterial pneumonia, viral, LIP, TB	Consider when poor response to first-line empiric management	As above
Measles	In communities with poor measles immunization coverage	Conjunctivitis, typical rash, fever and cough, respiratory distress	Broad-spectrum antibiotics Vitamin A
Kaposi's sarcoma	Especially in tropical Africa	Characteristic lesions on skin or palate	Chemotherapy
PcP	Rarely described from African region in this age group	Severe respiratory distress not improving with broad-spectrum antibiotics. CXR: diffuse interstitial infiltration	High-dose cotrimoxazole Consider steroids
Other fungal pneumonia, e.g. cryptococcosis, candidiasis	Little clinical data but data from autopsy studies suggests rare		
Penicilliosis Melioidosis	Older children in South-East Asia		

PcP = *Pneumocystis pneumonia*; CMV = cytomegalovirus; LIP = lymphoid interstitial pneumonitis; TB = tuberculosis  
<sup>a</sup> CPT and ART when indicated for all cases

Source: WHO 2010 childhood TB/HIV guidelines

## Bacterial pneumonia

Pneumonia is the leading cause of hospital admissions and death in HIV-infected children. It is also the most common pulmonary condition and presents the same way in both infected and uninfected children.

*Streptococcus pneumoniae* is the most common pathogen isolated in both HIV-infected and -uninfected children. Other organisms include *Haemophilus influenzae* Type b, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and enteric gram negatives (*Escherichia coli*, *Enterobacter spp.*, non-typhoidal *Salmonella spp.*, *Citrobacter spp.*, *Proteus mirabilis* and *Pseudomonas aeruginosa*). These bacteria generally colonize the nasopharynx before the child develops pneumonia.

Recurrent bacterial pneumonia suggests immune suppression (WHO stage 3, see [Chapter 5](#)). Recurrent pneumonia should be investigated further to exclude other conditions such as tuberculosis (TB), foreign body, gastroesophageal reflux disease, bronchiectasis, LIP, and fungal pneumonias.

### Clinical presentation

Clinical presentation of pneumonia includes the following:

- History of fever, cough, and fast breathing (tachypnoea) with or without chest in-drawing (retractions), cyanosis, and lethargy
- On auscultation, crepitations, decreased breath sounds or bronchial breathing (lobar pneumonia) may be present
- When pulse oximetry is available, persistent hypoxia is demonstrated (oxygen (O<sub>2</sub>) saturation less than 90%).

### Diagnosis

Diagnosis of pneumonia is purely on clinical grounds (see [immediately above](#)). However, some laboratory tests may help in pointing towards an aetiological agent:

- An increased white blood count (WBC) with a neutrophilia (granulocytosis) suggests bacterial pneumonia and growth on blood cultures (bacteraemia) may result from the causative organism. However, because the yield from blood culture in children

with pneumonia is low (<15%), routine blood culture is not recommended.

- A chest X-ray is not necessary for diagnosis of acute pneumonia, but it may be done if there is poor response to appropriate treatment or when suspecting empyema, TB, foreign body, or tumour.
- Chest ultrasonography.
- Because symptoms of pneumonia and those of malaria often overlap, a blood smear for malaria parasites should be done in malaria endemic areas.

## Managing bacterial pneumonia

### *Outpatient management (for mild pneumonia)*

The management of pneumonia should follow the recommended national guidelines. If there are no guidelines, or you are not aware of them, use the following IMCI guidelines:

- Oral amoxicillin (40 mg/kg twice daily or 80 mg/kg/day).

### *PCP*

- Analgesics/antipyretics (e.g. paracetamol 15 mg/kg/dose every 6–8 hours) should be prescribed for fever and pain.
- Avoid using aspirin in children < 12 years.
- If a child has recurrent pneumonia (more than 3 times in one year), the child should be investigated further to rule out TB, foreign body, or chronic lung disease.

### *Managing severe pneumonia*

The features of severe pneumonia are cough or difficult breathing accompanied by at least one of the following:

- Central cyanosis or oxygen saturation < 90% on pulse oximetry
- Severe respiratory distress (e.g. grunting, very severe chest indrawing)



- Signs of pneumonia with a general danger sign:
  - inability to breastfeed or drink
  - lethargy or unconscious
  - convulsions.

Severe pneumonia should be managed in a hospital or other inpatient facility and should include both supportive and specific therapy.

### *Supportive care*

Supportive care of severe pneumonia includes the following:

- Provide supplemental oxygen when a child presents with chest in-drawing, cyanosis, and/or hypoxia.
- Correct severe anaemia (Hb < 5 g/dL) by slow transfusion with packed red blood cells.
- If wheeze is present, give a rapid acting bronchodilator, e.g. nebulised salbutamol.
- Ensure adequate oral hydration, and monitor fluid input and output (I/O chart). If respiratory distress is severe, pass a nasogastric (N/G) tube and give food in small volumes to avoid aspiration. If the child is vomiting, intravenous fluids should be used carefully to avoid fluid overload.
- Provide an analgesic (paracetamol) for fever and pain.
- Provide vitamin A supplementation if the child has not received vitamin A in the last 3 months.

### *Specific therapy*

The specific antibiotic therapy depends on the sensitivity pattern of the common organisms in the region. However, if unknown, the recommended therapy is:

- First-line antibiotics include intravenous benzyl penicillin – 50 000 IU 6 hourly (or ampicillin – 50 mg/kg 6 hourly) and gentamicin (7.5 mg/kg once a day) for 5 days
- If *S. aureus* pneumonia is suspected, add cloxacillin.

- Second-line antimicrobial agents: ceftriaxone/cefotaxime.
- Empiric cotrimoxazole treatment for suspected *Pneumocystis jirovecii* pneumonia (PCP) (see additional information below) is recommended as an additional treatment for HIV-infected and -exposed infants aged from 2 months up to 1 year with chest indrawing or severe pneumonia.

### Other considerations

Other considerations for treating pneumonia in children include the following:

- In children less than one year of age, clinicians must consider PCP a possible cause of severe pneumonia and treat accordingly (see [below](#)).
- If pneumonia is associated with typical staphylococcal skin lesions (e.g. bullae), chest X-ray with pneumatoceles, a positive blood culture for staphylococcus (not contaminant), after measles, or with poor response to first-line antibiotics, then you must consider staphylococcal pneumonia and add cloxacillin or vancomycin to the treatment.
- It is recommended that HIV-infected or malnourished children should receive antibiotic cover for both gram positive and gram negative organisms, for suspected sepsis and pneumonia irrespective of clinical severity.
- If an enteric gram negative organism is suspected, add gentamycin or ceftazidime to the regimen, if available.
- Suspect enteric gram negative infection if the child has had repeated hospitalisation, recurrent pneumonia affecting the same lobe, poor response to first-line antibiotics, green, mucoid sputum, underlying bronchiectasis, or chronic lung disease.
- If CMV co-infection is present, intravenous gancyclovir therapy should be considered

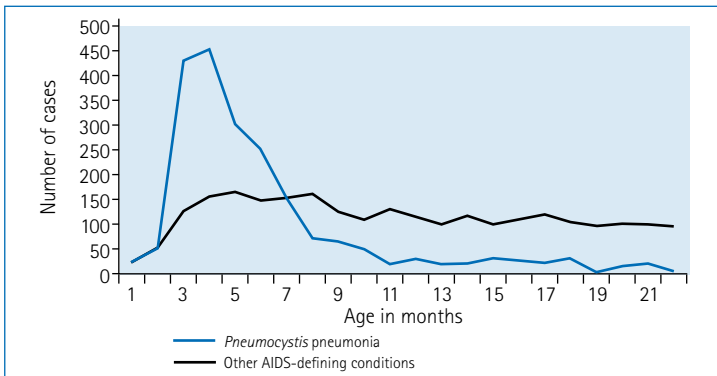
## *Pneumocystis pneumonia* (PCP)

*Pneumocystis pneumonia* (PCP) is caused by a fungus called *Pneumocystis jiroveci* (formerly called *Pneumocystis carinii*). PCP is a major cause of severe pneumonia (15–30%) and death (30–50%) in HIV-infected infants. Infants are usually in a good nutritional state and may not have other clinical features that indicate the presence of HIV/AIDS.

The incidence of PCP is highest during the first year of life and usually peaks at 6 months of age. It can occur after one year of age, but with decreasing frequency. **Figure 7.1** below, although from the United States, probably reflects similar occurrence in Africa.

A study carried out among 121 children aged 2–6 months with severe pneumonia in a hospital setting in Kampala, Uganda, showed that 12.6% (20/121) had PCP. Of these (12/20) 60% were aged < 6 months. The clinical features associated with PCP included: age below one year, a clear chest on auscultation, elevated LDH levels, and having AIDS.

**Figure 7.1:** Threat of PCP; AIDS-defining conditions by age at diagnosis (perinatally-acquired AIDS cases) through 1992, USA



Source: Simonds RJ, et al.; Prophylaxis against *Pneumocystis carinii pneumonia* among children with perinatally acquired human immunodeficiency virus infection in the United States. *Pneumocystis carinii* Pneumonia Prophylaxis Working Group, N Engl J Med, 1995. March 23:332(12): 786-90.

## Clinical features of PCP

Clinical features of PCP in children include:

- Low-grade fever or afebrile
- Marked respiratory distress (chest in-drawing, rapid progression, cyanosis, inability to drink)
- Auscultation: clear chest or diffuse fine crepitations
- Poor response to standard antibiotic treatment
- Pulse oximetry: severe persistent hypoxia ( $\text{paO}_2 < 90\%$ )
- Occasionally, associated HIV symptoms include oral thrush, lymphadenopathy, and/or weight loss.

## Investigations

Sputum induction with nasopharyngeal aspirates or bronchoalveolar lavage may help in diagnosing PCP. A chest X-ray may be useful, although no radiological changes are specific to PCP.

In cases where a definitive diagnosis of PCP cannot be made, but where there is a high index of suspicion of PCP, therapy must be initiated promptly, along with treatment for bacterial pneumonia.

## Management of PCP

Management of PCP is both supportive and specific. In supportive management of PCP:

- Provide oxygen therapy
- Maintain and monitor hydration
- Provide paracetamol for pain
- Continue therapy for bacterial pneumonia

For specific management of PCP:

- Give intravenous high dose cotrimoxazole (CTX) 20 mg/kg of the trimethoprim component per day or 80 mg/kg/day of sulfamethoxazole in 4 divided doses (at 6-hourly intervals) for 21 days. Give the same dose orally if IV preparations are not available.

- Add prednisolone at 2 mg/kg/day for 7–14 days if the child is in severe respiratory distress, then taper over 7–10 days.

If the child is allergic to sulphurs or cannot use cotrimoxazole, the alternatives include:

- Pentamidine: 4 mg/kg/day for at least 14 days intravenously or 600 mg pentamidine isetionate daily for 3 weeks by inhalation.
- Clindamycin: 15–40 mg/kg/day in 3–4 divided doses intravenously, plus primaquine orally, 0.3 mg/kg/day (maximum 30 mg/day) for 21 days may be considered in mild-to-moderate disease, although the efficacy of this strategy has not been evaluated in paediatric practice.

### *Follow-up*

After an acute episode of PCP, provide daily cotrimoxazole. This secondary prophylaxis is life-long. For details of prevention of PCP, including dosage see **Chapter 4**.

PCP may be the first AIDS-defining illness in the child and the first indication of HIV infection within the family. Therefore, efforts must be made to provide counselling and testing for HIV for the mother and the family. If the mother or another family member is identified as HIV-infected, refer the individual to appropriate services for ongoing care and support.

## **Chronic lung disease**

The primary causes of chronic lung disease are TB, LIP, bronchiectasis, and pulmonary Kaposi's sarcoma or lymphoma.

### **Tuberculosis**

#### *TB and HIV co-infection*

The HIV pandemic has led to a resurgence of TB in both adults and children, and the burden of TB in children depends on the burden of the disease in the adult population.

Children also have an increased risk of developing primary progressive TB because of the associated severe immune suppression resulting from a combination of their young age and HIV. Extrapulmonary TB is seen more often in HIV-infected children.

There is a higher case fatality rate for children who are co-infected with TB and HIV. It is important to look actively for TB in children with a chronic cough and to provide treatment as early as possible.

The reported seroprevalence of HIV in children with TB ranges from 10–60%. The highest prevalence of HIV infection in children with TB has been reported in southern Africa, the lowest prevalence in West Africa.

The risk for developing confirmed TB in HIV-infected children in a TB endemic setting has been observed to be over 20 times higher than in -uninfected children.

Diagnosing TB in children was difficult even before the HIV/AIDS pandemic; now it is more difficult because an HIV-positive child may have many other pulmonary conditions and HIV-related chronic lung diseases that 'mimic' the symptoms of TB.

The outcome of treatment is worse in HIV-infected children with TB than in -uninfected children, with high case fatality rates, especially in the first 2 months of treatment.

### *Clinical diagnosis*

**Table 7.3** shows the evaluation of a child suspected to have TB.

**Table 7.3** Evaluation of the HIV-exposed infant for tuberculosis disease

<b>History (symptoms and signs of TB disease)</b>	<ul style="list-style-type: none"> <li>• Unexplained weight loss or failure to grow normally</li> <li>• Unexplained fever, especially if more than 14 days</li> <li>• Chronic cough (more than 14 days)</li> <li>• Failure to respond to appropriate antibiotic treatment of presumed bacterial pneumonia or meningitis</li> <li>• Exposure to an adult with probable or definite pulmonary infectious TB</li> </ul>
<b>Physical examination</b>	<ul style="list-style-type: none"> <li>• Fluid on one side of chest ( stony dullness to percussion, reduced air entry)</li> <li>• Enlarged, non-tender lymph nodes or abscess, especially in the neck</li> <li>• Signs of meningitis, especially if subacute and developing over several days</li> <li>• Cerebrospinal fluid contains predominantly lymphocytes and elevated protein</li> </ul>

<b>Physical examination (continued)</b>	<ul style="list-style-type: none"> <li>• Abdominal swelling, with or without palpable lumps</li> <li>• Progressive swelling or deformity of a bone or joint, including the spine</li> </ul>
<b>Laboratory investigations</b>	<ul style="list-style-type: none"> <li>• Microscopic examination for acid-fast bacilli (Ziehl-Nielsen stain) and culture of specimens, such as early morning gastric aspirates for 3 consecutive days and pleural, ascitic and cerebrospinal fluid as relevant.</li> <li>• Chest radiograph for lobar opacity, pleural effusion, miliary pattern.</li> <li>• PPD tuberculin skin test (&gt; 5 mm is positive).</li> </ul>

Modified from WHO Treatment of TB; Guidelines for National Programs, Third Edition, 2002.

Most TB diagnostic criteria (chronic symptoms, smear positive contact, positive Mantoux, response to treatment) have lower sensitivity and specificity in a co-infected child than in a non-HIV-infected child (see [Table 7.4](#)).

**Table 7.4** Impact of HIV on recommended approach for diagnosis of TB in children

<b>Recommended approach to diagnoses of TB in children</b>	<b>Impact of HIV infection</b>	<b>Maximum dose/day</b>
Careful history including history of TB contact	Especially important due to poor sensitivity of TST to identify TB infection	20 (range: 15–25)
Careful history of symptoms consistent with TB	Lower specificity: clinical overlap between symptoms of TB and HIV	600 mg
Clinical examination including growth assessment	Lower specificity: malnutrition is common with TB or HIV	–
Tuberculin skin testing	Lower sensitivity: TST positivity decreases with increasing immunosuppression	–
Bacteriological confirmation whenever possible	As important for HIV infection	

Recommended approach to diagnoses of TB in children	Impact of HIV infection	Maximum dose/day
Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB	Wider range of diagnostic possibilities because of other HIV-related disease	
Chest X-ray findings	Lower specificity: overlap with HIV-related lung disease	

Source: WHO 2010 childhood TB/HIV guidelines

### *Diagnosis of extra-pulmonary TB*

Clinicians may use the following to diagnose extra pulmonary TB:

- When there are superficial enlarged lymph nodes, biopsy or fine needle lymph node aspirate microscopy and culture may be diagnostic.
- Body fluids: ascitic, pleural, or cerebrospinal can be subjected to microscopy, biochemical analysis, Ziehl-Nielsen (ZN) staining and culture. The yield from ZN staining and culture is usually poor.
- Bone marrow aspirate and culture may be diagnostic in disseminated TB with persistent fever and wasting.
- Ultrasound can help differentiate loculated fluid and consolidation, document ascites and intra-abdominal lymph nodes, and identify features of pericardial TB.
- Computerised tomography (CT) scan, where available, may assist in diagnosing abdominal, pulmonary, and CNS disease.
- Contrast CT scan or MRI can differentiate inflamed mediastinal lymph nodes from thymic shadows in younger children.



### *Newer diagnostic tests*

Several WHO-endorsed diagnostic tests have been evaluated in recent years, including liquid-medium TB culture methods such as BACTEC<sup>®</sup> and MGIT 960, molecular line probe assays, light-emitting diode fluorescence microscopy, and automated nucleic acid amplification tests (NAATs) such as the Xpert<sup>®</sup> MTB/RIF assay.

Xpert<sup>®</sup> MTB/RIF, a fully automated assay will allow a relatively unskilled laboratory assistant to diagnose tuberculosis and detect resistance within 90 minutes of receiving a sputum specimen. The first paediatric study to evaluate Xpert<sup>®</sup> MTB/RIF showed that two tests done on separate induced sputum specimens detected twice as many tuberculosis cases as did smear microscopy (75.9% vs 37.9%), and was highly accurate for detecting rifampicin-resistant strains. Several recent studies have confirmed these findings and have shown that the performance of Xpert<sup>®</sup> MTB/RIF on induced sputum and gastric lavage aspirate specimens is similar. These results suggest that Xpert<sup>®</sup> MTB/RIF testing could replace smear microscopy as part of the first-line TB diagnostic approach for children.

### *Treating drug-susceptible TB in children*

In most instances diagnosis of TB is usually presumptive, based on clinical and radiological features. At the start of treatment the child must be reported to the National TB Programme.

Antituberculous therapy consists of two phases, an intensive phase lasting 2 months during which three or four drugs are administered, and a continuation phase lasting 4 months during which two drugs are administered. In the HIV-uninfected child, three drugs (isoniazid [INH or H], rifampicin [RMP or R], and pyrazinamide [PZA or Z]) are sufficient for treating uncomplicated TB during the intensive phase. In HIV-infected children complicated TB is common and four drugs should be prescribed during the intensive phase, i.e. INH, RMP, PZA and ethambutol (EMB or E). During the continuation phase of treatment, regimens are stepped down to two drugs, INH or H and RMP or R.

National TB guidelines should be adhered to in all cases.

Where national guidelines are not available, [Table 7.5](#) can be used.

**Table 7.5** Recommended treatment regimens for new cases of TB in children (WHO 2014)

TB Diagnostic category	Anti-TB drug regimens <sup>a</sup>	
	Intensive phase	Continuation phase
<i>Low HIV prevalence (and HIV-negative children) and low isoniazid resistance settings<sup>b</sup></i>		
Smear-negative pulmonary TB Intrathoracic lymph node TB Tuberculous peripheral lymphadenitis	2HRZ	4HR
Extensive pulmonary disease Smear-positive pulmonary TB Severe forms of extrapulmonary TB (other than tuberculous meningitis/osteoarticular TB)	2HRZE	4HR
<i>High HIV prevalence or high isoniazid resistance or both</i>		
Smear-positive PTB Smear-negative PTB with or without extensive parenchymal disease All forms of EPTB except tuberculous meningitis and osteoarticular TB	2HRZE	4HR
<i>All regions</i>		
Tuberculous meningitis and osteoarticular TB	2HRZE <sup>b</sup>	10HR
MDR-TB	Individualized regimens	

Source: WHO. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Second edition. 2014

The dosages of the various first line TB medications in [Table 7.5](#) are shown in [Table 7.6](#).

**Table 7.6** Recommended dosages of first line TB drugs for children (WHO 2014)

Drug	Dose (mg/kg/day)	Maximum dose/day
Isoniazid	10 (range: 7–15)	300 mg
Rifampicin (R)	15 (range: 10–20)	600 mg
Pyrazinamide (Z)	35 (range: 30–40)	–
Ethambutol (E)	300 mg/20 (range: 15–25)	--

Source: WHO Guidance for national tuberculosis programmes on the management of tuberculosis in children. Second edition. 2014

### Drug resistant tuberculosis

This is a growing problem throughout Africa. There are no clinical or radiological differences between drug susceptible and drug resistant TB. Children with drug resistant TB are more likely to have a history of a drug resistant contact. Diagnosis of drug resistant TB is dependent on isolating the TB strain and determining the antimicrobial sensitivity profile. Therefore, as many representative specimens as possible should be obtained from the patient for culture.

#### Definitions

*Multi-drug resistant (MDR) TB:* Resistance to at least INH (H) and RMP (R).

*Extensive drug resistant (XDR) TB:* Resistance to INH (R), RMP (R), any fluoroquinolone and at least one second-line injectable agent (kanamycin, amikacin or capreomycin).

#### Treatment

The treatment of MDR-TB and XDR-TB in children is guided by the same principles and uses the same second-line drugs as the treatment in adults, although optimal durations of regimens are not known. MDR-TB is associated with poorer treatment outcomes and higher mortality than drug-sensitive TB in children.

### **Treatment of mono-resistant TB**

Where mono-resistance to isoniazid is known or suspected when treatment is initiated, or when there is high background prevalence of isoniazid resistance, the addition of ethambutol to isoniazid, rifampicin and pyrazinamide in the intensive phase is recommended. For patients with more extensive disease, consideration should be given to the addition of a fluoroquinolone and to prolonging treatment to a minimum of 9 months. Mono-resistance to rifampicin should be treated with isoniazid, ethambutol and a fluoroquinolone for at least 12–18 months, with the addition of pyrazinamide for at least the first 2 months.

### **Treatment of multidrug-resistant TB**

Children with MDR-TB are treated in a similar way to adults with MDR-TB. One practical difference is that confirmation and drug susceptibility testing (DST) may not be possible, so that empirical treatment is often required for children with suspected MDR-TB. Although outcome data in children are limited, the available evidence suggests that outcomes at least as good as those reported in adults can be achieved.

Management should adhere to the following principles:

- Never add a single drug to a failing regimen; this may lead to amplification of resistance.
- All treatment should be given daily and under direct observation.
- Treat the child according to the DST results from the likely source case, unless *M. tuberculosis* culture and DST results are available from the child.
- Do second-line DST in all MDR-TB cases to exclude resistance to the fluoroquinolones and/or second-line injectables, as this may call for additional drugs early in therapy.
- Give at least 3 (only in early primary disease) or preferably 4 drugs to which the patient or adult source case is naive or their isolates susceptible.

- Caregivers need counselling and support at every follow-up visit regarding adverse effects, treatment duration and importance of adherence. In addition, the following assessment of the child should be undertaken as a minimum:
  - symptom assessment
  - assessment of treatment adherence
  - enquiry about any adverse events
  - weight measurement.
- Drug dosages should be adjusted to account for any weight gain.
- Clinical, radiographic and culture response to treatment should be monitored. Monthly smear microscopy and cultures should be done until confirmed negative on three consecutive occasions; thereafter, follow-up cultures can be done every 2–3 months.
- Clinical monitoring for adverse effects should be done at every visit. Special investigations should be guided by the adverse effect profile of the drugs used. While any of the drugs described in [Table 7.7](#) might be used in the treatment of children with MDR-TB, safety data in children currently exist only for fluoroquinolones, and so the WHO recommendation on the treatment of MDR-TB in children addresses the use only of fluoroquinolones. There is a need for safety data on other drugs that are being used for treatment of children with MDR-TB.

Children with proven or suspected pulmonary TB or tuberculous meningitis caused by multi-drug resistant bacilli can be treated with a fluoroquinolone in the context of a well-functioning MDR-TB control programme and within an appropriate MDR-TB regimen. The decision to treat should be taken by a clinician experienced in managing paediatric TB.

Source: Rapid advice: treatment of tuberculosis in children. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13).

**Table 7.7** Summary of drug groups used to treat drug resistant TB

Drug group	Drug name	Daily adult dose in mg/kg	Maximum adult daily dose (mg)	Daily paediatric dose in mg/kg (max. dose in mg) <sup>a</sup>
Group 1: first-line oral drugs <sup>b</sup>	Ethambutol Pyrazinamide	20–25 30–40	2 000 2 000	15
Group 2: injectable agents <sup>c</sup> Aminoglycosides	Amikacin Kanamycin	15–20 15–20	1 000 1 000	15–22.5 (1 000) 15–30 (1 000)
Cyclic polypeptide	Capreomycin	15–20	1 000	15–30 (1 000)
Group 3: fluoroquinolones	Ofloxacin Levofloxacin Moxifloxacin	15–20 7.5–10 7.5–10	800 750 400	15–20 (800) 2x daily 7.5–10 (750) 7.5–10 (400)
Group 4: second-line oral drugs <sup>d</sup>	Ethionamide (or prothionamide) Cycloserine (or terizidone) p-aminosalicylic acid <sup>e</sup> (PAS; 4-g sachets)	15–20 10–20 150	1 000 1 000 12 000	15–20 (1 000) 2x daily 10–20 (1 000) 1x/2x daily 150 (12 000) 2x/3x daily

**Table 7.7 Summary of drug groups used to treat drug resistant TB (continued)**

Drug group	Drug name	Daily adult dose in mg/kg	Maximum adult daily dose (mg)	Daily paediatric dose in mg/kg (max. dose in mg) <sup>a</sup>
Group 5: third-line drugs of unclear efficacy (not recommended by WHO for routine use in MDR-TB patients) <sup>f</sup>	High-dose Isoniazid <sup>g</sup>	15–20	400	
	Linezolid <sup>h</sup>	10–12, 2x daily	300, 1x/2x daily	
	Amoxicillin/clavulanate	15 amoxicillin 3x daily		
	Clarithromycin	7.5–15, 2x daily	500, 2x daily	
	Thioacetazone <sup>i</sup>	3–4	150	
	Imipenem/cilastatin Clofazimine	(only IV) 3–5	300	

<sup>a</sup> In children, doses of all drugs, including the fluoroquinolones, should be at the higher end of the recommended ranges wherever possible, except ethambutol. Ethambutol should be dosed at 15 mg/kg, and not at 25 mg/kg as sometimes used in adults with DR-TB, as monitoring for optic neuritis is more difficult in children.

<sup>b</sup> DST could be unreliable – use an additional drug if DST is not done or result is susceptible.

<sup>c</sup> Choose one drug in each of these groups; amikacin is preferred to kanamycin in children. Intramuscular injection of amikacin is very painful – intravenous infusion should be preferred.

<sup>d</sup> Choose one or more of these drugs to make up total of four new drugs

<sup>e</sup> PAS (including PAS Na) is administered in acidic medium (e.g. yoghurt or orange juice) for improved absorption.

<sup>f</sup> Consider use of these drugs if there are insufficient drugs in other groups to build an acceptable regimen. Each drug is considered as only half a drug – therefore two drugs in this group count as one additional drug.

<sup>g</sup> In adults, high-dose isoniazid is defined as 16–20 mg/kg per day.

<sup>h</sup> Linezolid dosage for TB is uncertain, but lower doses (300 mg twice daily or even 300 mg daily in adults) cause fewer adverse effects and still seem effective.

<sup>i</sup> Thioacetazone should not be used in people living with HIV because of the serious risk of life-threatening adverse reaction.

Source: WHO. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Second edition. 2014

### *TB treatment and antiretroviral drug interactions*

In children co-infected with TB and HIV, the treatment of TB takes precedence. Antituberculous and antiretroviral drugs have overlapping toxicity profiles. It is recommended that the introduction of ART be delayed by 2–8 weeks, to allow time for the early adverse effects of antituberculous drugs to manifest.

The rifamycins, particularly RMP(R), induce the cytochrome p450 system of the liver, causing an appreciable decrease in the serum concentrations of many protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Adjustments to the antiretroviral regimen may be required in patients co-treated with RMP-containing antituberculous medication (see **Chapter 8** for details). Alternatively, rifabutin which has less interaction than rifampicin is used together with the ART.

### **Lymphoid interstitial pneumonitis (LIP)**

Lymphoid interstitial pneumonitis (LIP) is common in HIV infected children. It occurs in at least 40% of children with perinatal HIV, but is rare in adults (LIP develops in about 3% of adults with HIV), and usually occurs in children more than two years of age. Various studies in Africa have documented a 30–40% prevalence of LIP in HIV-infected children, and up to 60% prevalence in those with chronic lung disease. LIP is often mistaken for pulmonary TB (miliary) because of the chronic cough and the *miliary-like* pattern on chest X-ray.

#### *Pathogenesis*

Possible explanations for LIP include a co-infection of the lungs by HIV and Epstein Barr Virus (EBV), leading to immune stimulation with lymphoid infiltration and chronic inflammation.

#### *Clinical symptoms*

Diagnosis of LIP is usually by exclusion. However, the following may be helpful:

- The patient is usually in good general condition despite respiratory distress.
- Recurrent cough and dyspnoea are invariably present.



- Typical radiological features are usually associated with parotid enlargement, generalized lymphadenopathy, and hepatosplenomegaly.
- Finger clubbing may be present.
- Terminally, there is chronic lung disease with hypoxia.
- The child may present with cor-pulmonale and/or right heart failure.

The late stages respond poorly to antiretroviral therapy (ART).

### *Radiological picture*

Radiological indicators of LIP include:

- Diffuse bilateral reticulonodular infiltrates, similar in appearance to miliary TB
- Bilateral hilar or paratracheal lymph node enlargement.

**Table 7.8** highlights similarities and differences between LIP and TB

**Table 7.8** Comparison of miliary TB and LIP

Clinical Features	Miliary TB	LIP
Respiratory distress	-/+	+++
Persistent fever	++	++
Wasting	+++	-/+
Generalized lymphadenopathy	-/+	+++
Parotid enlargement	-	++
Digital clubbing	-	++
Hepatomegaly	++	++
CXR features		
• Diffuse micronodular	++	+
• Diffuse reticulonodular	-	++
Lymphadenopathy	-/+	++

## *Management*

Managing LIP includes the following:

- Steroids, when the children with LIP have significant respiratory distress (exclude TB first). Prednisolone 2 mg/kg/day initially for 4 weeks daily then alternate day maintenance for 2–3 months and review
- Oxygen therapy during episodes of hypoxia
- Bronchodilators (e.g. salbutamol) where wheezing is a problem
- Antibiotics, during episodes of concurrent supra-infection with pneumonia
- Chest physiotherapy and postural drainage if there is secondary bronchiectasis
- Refer for specialist care if no response or resistant to therapy.

## *Bronchiectasis*

Bronchiectasis may occur as a complication of severe or recurrent pneumonia, TB, LIP, or measles. It involves damage to the bronchial lining because of recurrent infection and weakening of the bronchi with cyst formation and secondary infection.

## *Clinical presentation*

The clinical presentation of bronchiectasis includes the following:

- Chronic cough, mainly in the morning
- Copious purulent sputum
- Halitosis
- Digital clubbing
- Recurrent pneumonia.

## *Management of bronchiectasis*

Management includes diagnosis of bronchiectasis and its treatment.

## Diagnosis

- With the above symptoms and signs, a chest X-ray may show localized infiltrates, cystic areas, dilated bronchi (persistent opacity in one area).
- Where possible collect sputum and culture for bacteria and fungi. If the sputum grows a specific organism, adjust treatment appropriately.

## Treatment

- Supportive treatment includes daily chest physiotherapy and postural drainage. Caregivers should be trained in daily physiotherapy and postural drainage.
- Broad-spectrum antibiotics: chloramphenicol, augumentin, cefuroxime, azithromycin/clarithromycin or third-generation cephalosporins (ceftriaxone, ceftazidime, cefodoxime), if available. Ciprofloxacin may be used as a last resort (be careful about prolonged use) for inpatients with possible enteric gram-negative and anaerobic organisms.
- Bronchodilators such as salbutamol/albuterol can be used when bronchospasm is present.
- Prophylactic antibiotics may be needed for several months if the patient has recurrent pneumonia/bronchiectasis. Consider referral to specialist.
- Surgery may be necessary in cases with segmental lung damage.

## Viral pneumonitis

Children with HIV may develop severe viral pneumonitis from a number of viruses, including respiratory syncytial virus (RSV), parainfluenza virus, metapneumovirus, influenza virus, adenovirus, varicella (chicken pox), measles, and cytomegalovirus (CMV). In most African settings it is not possible to confirm the actual aetiological agent. The clinical presentation may be more severe and the case fatality rate higher than in HIV-uninfected children. Viral pneumonitis

in HIV-infected children presents more frequently as pneumonia than bronchiolitis.

Some reports indicate that CMV may be a frequent co-pathogen in infants with PCP, and that using steroids to treat PCP may aggravate the CMV pneumonitis. Specific treatment is ganciclovir ± valganciclovir, but this is rarely available and very expensive. ART may be useful to lessen severity.

Varicella zoster immunoglobulin may reduce the severity of chicken pox pneumonitis if it is given within 72 hours of exposure. Oral acyclovir should ideally be administered to all HIV-infected children with chicken pox to prevent severe or disseminated disease.

Measles immunisation usually prevents infection. However, following measles exposure, measles immunoglobulin (0.5 ml/kg (maximum 15 ml) should be given within 6 days of exposure, regardless of previous measles immunisation status.

## Other pulmonary conditions

A child presenting with an unexplained sudden onset of dyspnoea or subcutaneous emphysema may indicate spontaneous pneumothorax, which may be associated with PCP, LIP, or other causes of pneumonia.

**Asthma/reactive airway disease** may occur in HIV-infected children, and must be managed according to standard treatment guidelines.

**Fungal chest infections** (e.g. aspergillosis, nocardia, cryptococosis, and candida) in Africa are rarely reported. Where laboratory facilities exist, further investigation of patients with poorly responding chest infections should include fungal stains and cultures.

**Kaposi's sarcoma (KS)** is the most common HIV-associated malignancy in the the lungs. In addition to the mucocutaneous lesions and lymphadenopathy, patients present with progressive dyspnoea, cough, and rarely haemoptysis. Chest X-rays will show mediastinal lymphadenopathy, pleural effusion, or bilateral interstitial infiltrates. Diagnosis of pulmonary KS can be made at bronchoscopy, where multiple purplish lesions can be seen. Intra-pulmonary biopsy should not be done, as it can lead to profuse haemorrhage. Treatment

includes chemotherapy (vincristine and bleomycin or liposomal preparations of danorubicin and doxorubicin). This may require referral to cancer treatment centres (refer to [Chapter 6](#)).

**Lymphomas** (both T- and B-cell) may present with non-specific symptoms and signs, and chest X-rays showing mediastinal lymphadenopathy, focal opacities, or pleural effusions.

**Pulmonary hypertension:** With the increased survival of HIV-infected children because of improved prophylaxis for opportunistic infections (OIs) and treatment of AIDS, non-infectious conditions related to HIV are being detected more frequently. Pulmonary hypertension is one such condition and it has a poor prognosis. It has been suggested that HIV-induced mediator and growth factor-related inflammatory reactions altering the pulmonary cell homeostasis might be the cause of cardiovascular conditions. The appearance of unexplained cardiopulmonary symptoms in HIV-infected individuals should suggest pulmonary hypertension. Therapy is based on antiretroviral therapy and pulmonary vasodilators, e.g. sildenafil.

### Knowledge gaps

- Easier and more accurate diagnostic tests for pulmonary conditions
- Improved diagnostic and treatment options for TB in children including drug resistance.

### Additional and recommended reading

Bakeera-Kitaka S, Musoke P, Downing R, et al. *Pneumocystis carinii* in children with severe pneumonia at Mulago Hospital, Uganda. *Annals of Tropical Paediatrics* 2004, 24: 227-35.

Graham SM, Coulter JB, Gilks CF. Pulmonary disease in HIV-infected African children. *International Journal of Tuberculous Lung Disease* 2001, 5: 12-23.

Katiya SK, Bihari S, Prakash S, et al. A randomized controlled trial of high-dose isoniazid adjuvant therapy for multi-drug resistant tuberculosis. *International Journal of Tuberculous Lung Disease* 2008, 12: 139-145.

Mehta NJ, Khan IA, Mehta RN, et al. HIV related pulmonary hypertension: analytical review of 131 cases. *Chest* 2000, 118: 1133-1141.

WHO. *Guidance for national TB and HIV programmes on the management of TB in HIV infected children: Recommendations for a public health approach*. 2010.

WHO. *Revised WHO classification and treatment of childhood pneumonia at health facilities*. 2014

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# Chapter 8

## Antiretroviral therapy

### Summary

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- All HIV-infected children should have access to HIV comprehensive care.
- All HIV-infected children and adolescents should be initiated on ART as soon as possible.
- Adverse events are much less common in children than in adults.
- Access to treatment for children's parents and families is equally critical and has direct implications for treatment outcomes of the child.
- The caregiver should be counselled and made aware of the implications of ART and the importance of adherence.





## Introduction

Antiretroviral therapy (ART) for HIV infected children has lagged behind that of adults for several reasons, including lack of identification of infected children, healthcare providers not being comfortable treating children, the dependence on an adult caregiver, and healthcare worker and community attitudes. New global and national guidelines that recommend earlier initiation of ART, increased availability of HIV diagnostics and improved paediatric formulations provide an opportunity to identify HIV-infected children earlier, start them on ART and enroll them into treatment programmes.

The Children with HIV Early Antiretroviral Therapy (CHER) trial showed that treating HIV-infected infants aged 6–12 weeks with mild or moderate clinical diseases and a CD4 > 25% reduced early infant mortality by 76% and disease progression by 75%. These results support starting ART in all infants diagnosed with HIV. Given the limited access to immunological testing, the high burden of paediatric HIV disease and low ART coverage among children, WHO, in its 2016 guidelines, extended universal ART to all children and adolescents, as a way of simplifying the eligibility criteria for ART initiation. This is expected to increase ART coverage in children infected with HIV and improve their health outcomes. However, priority for ART initiation should be given to children younger than 2 years of age, regardless of WHO clinical stage or CD4 cell count, because of higher mortality risk, children between 2 and 5 years of age with advanced disease (WHO HIV clinical stages 3 and 4) or with CD4 count  $\leq 750$  cells/mm<sup>3</sup> (or < 25%, whichever is lower); and children aged more than 5 years with CD4  $\leq 350$  cells/mm<sup>3</sup>.

The goals of treatment with ARV drugs are to:

- Prolong the survival of HIV-infected children.
- Promote optimal growth and development, and preserve neuro-cognitive potential.
- Preserve, enhance, or reconstitute the immune system and therefore reduce opportunistic infections.
- Suppress HIV replication and thus prevent disease progression.
- Reduce the morbidity of children and improve their quality of life.

Antiretroviral therapy that is made up of at least three antiretroviral drugs (ARV) is the regimen that is potent enough to suppress viral replication and prevent the emergence of resistance for a significant period of time. Such regimens have been associated with immunologic restoration, slower HIV clinical progression, durable therapeutic responses, improvements in quality of life, and reduction in the emergence of drug resistance. ART can be expected to reduce the HIV viral load to undetectable levels in approximately 70% of children with no prior exposure to ARV drugs.

Tools to achieve the above therapy goals include:

- Appropriate early initiation of ART
- Maximising adherence to ART
- Rational sequencing of ARV drugs to preserve future treatment options.

Health workers must continually update their knowledge and skills around ART because it is a rapidly changing field and because it has benefits for child health.

This chapter aims to help healthcare professionals understand the basics of treating HIV-infected children with ARV drugs, and they are encouraged to adapt these recommendations to local circumstances.

## Principles of ART

ART is one component of comprehensive HIV care. The following are guiding principles for the administration of ART in children:

- Before ART is considered ensure that the diagnostic criteria for HIV infection have been fulfilled. In situations where virological testing is not available, e.g. for children aged < 18 months of age, presumptive diagnosis is based on HIV antibody testing and clinical criteria (see [Chapter 5](#)).
- All HIV-infected children and adolescents should be initiated on ART irrespective of their CD4 count/percentage or WHO clinical stage.

- Choose drug regimens with proven efficacy, low risk of serious adverse effects and that are relatively easy to administer to children.
- Consider affordability and availability of drugs and drug combinations.
- Provide ongoing support for the patient and family to maintain adherence.
- Drug interactions and drug resistance may decrease the potency of ARV drugs.
- Adverse drug reactions may occur, but are less frequent in children than adults.

Patients must take at least 95% of their pills to minimize the emergence of drug resistance, which leads to treatment failure. Optimal adherence is key to successful therapy.

There are specific issues to consider when treating HIV-infected children with ART (see [Table 8.1](#)).

**Table 8.1** Specific issues to consider when treating HIV-infected children with ART

Issue	Comment
<b>Virological suppression</b>	Complete virological suppression is more difficult to achieve in children than in adults, therefore be cautious about switching based on virological failure
<b>Pharmacokinetic issues</b>	Pharmacokinetic data is often insufficient to optimise dosing of existing drugs, e.g. efavirenz and newer agents. This is particularly problematic in very young infants who metabolise antiretroviral drugs differently to older children. This is the reason efavirenz is avoided in children below 3 years
<b>Adverse events</b>	Adverse events are much less frequent in children than in adults for most drugs
<b>Drug formulations</b>	Child-friendly formulations such as suspensions, dispersible preparations and scored tablets are becoming more and more available. In addition fixed dose combination drugs are now available for paediatric use, which will make adherence to the medications more favourable

Issue	Comment
<b>Cost</b>	Suspensions are relatively more expensive than capsule or tablet formulations
<b>Palatability</b>	Lopinavir/ritonavir suspension has a bitter taste which may affect adherence. Measures to improve palatability should be utilized, e.g. mixing the suspension with fruit juice or yoghurt
<b>Drug administration</b>	Caregivers for the children need to be assisted to make drug administration easier, e.g. by using colour coding for suspensions/syrups, providing dispensing aids, e.g. colour coded and marked syringes, and others
<b>Drug storage</b>	Drugs should be stored under optimal conditions, e.g. lopinavir/ritonavir (Kaletra) syrup and stavudine syrup should ideally be refrigerated; innovative approaches in resource-limited settings lacking refrigeration include storing these medicines in clay pots containing water
<b>Adherence</b>	Adherence to ART in infants and children depends on the competency and commitment of their caregivers
<b>Concurrent administration of traditional medication</b>	This is an under-researched area. Until evidence to the contrary emerges, the use of concurrent herbal therapies should be discouraged

## Opportunities and entry points for ART in children

Multiple opportunities to reach children who need HIV care and ART exist, and include:

- *Provider initiated testing and counselling (PITC)*: For children of unknown status at their first contact with the health system as well as universal testing of all children admitted to hospital are recommended
- *PMTCT programmes*: Identify HIV-exposed and -infected children.
- *Adult HIV care clinics*: By asking the adults to have their children tested
- *Children with tuberculosis (TB)/TB clinics*: HIV-infected children are at a high risk of developing TB; a risk 24-fold higher than for

HIV-uninfected children has been documented in some studies, and up to 60% of children with tuberculosis may have HIV infection.

- *Nutrition units/wards for management of malnutrition*: Over 20% of children with severe malnutrition are HIV-infected.
- *Siblings of children*: Siblings enrolled in care may also be HIV-infected
- *Community-based programmes*: Door-to-door testing, *programmes targeting orphans and vulnerable children* (OVC) and others.

## When ART should be started in children and adolescents

Every effort should be made to ensure that all children and adolescents are started on ART as soon as possible, ideally within 2 weeks of diagnosis.

The local healthcare team and the family should make the decision to treat a child with ART after considering all medical, family, and social factors. Parents/caregivers should be adequately prepared before treatment is started. Such preparation includes providing general knowledge and understanding about the virus, the natural course of HIV infection in children, antiretroviral drugs including storage and administration, the need for life-long therapy, implications of suboptimal adherence, and ongoing care. However this should not unduly delay ART initiation.

## Clinical evaluation for children starting ART

The following should be assessed before ART is started:

- A pretreatment assessment, which ideally should include: HIV diagnostic testing; complete clinical assessment; neuro-developmental assessment; screening for active TB (see [Chapter 7](#)); screening for malaria where appropriate; identifying other medical conditions, e.g. hepatitis, opportunistic infections, pregnancy in adolescents; taking weight, length/height, and head circumference (where appropriate); staging the HIV infection using the WHO clinical staging classification (see [Table 5.3](#)); and taking the complete blood count (CBC) and differential count, alanine aminotransferase (ALT), CD4 count/percentage, and viral load

(when available). However, the lack of these laboratory tests should not hinder the start of ART

- A clearly defined caregiver(s), who understands the prognosis of HIV infection, side effects of antiretroviral agents, administration and storage conditions, implications of non-adherence, and the fact that it is life-long therapy
- Accessibility to supportive processes, such as counselling services and peer support groups
- Access to nutritional counselling and cotrimoxazole prophylaxis
- Treatment of HIV-infected parents and siblings should be considered to preserve the family unit. The health of the mother is particularly important for survival of the child.

### Criteria for starting children on ART

The criteria for starting children on ART are contained in **Table 8.2**.

**Table 8.2** Recommendations for initiating ART in HIV-infected infants and children and adolescents (WHO 2016)

Age	When to start
Infants (age <1 year)	<b>Treat all individuals</b>
1 year to < 5 years	<b>Treat all individuals</b> (Children $\leq$ 2 years or with WHO stage 3/4 or CD4 count $\leq$ 750 cells/mm <sup>3</sup> or <25% as a priority)
5–10 years	<b>Treat all individuals</b> (Children with WHO stage 3/4 or CD4 $\leq$ 350 cells/mm <sup>3</sup> as a priority)
Adolescents (age 10–19 years)	<b>Treat all individuals</b> (Adolescents with WHO stage 3/4 or CD4 $\leq$ 350 cells/mm <sup>3</sup> as a priority)

\*See **Table 5.3** for WHO clinical staging

### First-line ART therapy

Treatment for HIV-infected children should adhere to national treatment recommendations, which consider local factors. The first-

line regimen consists of two nucleoside reverse transcriptase inhibitors (NRTIs) plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) (see [Table 8.3](#)). For infants who start ART around birth, the regimens should be sequenced according to [Table 8.4](#). Several NRTI options exist (see [Table 8.5](#)). It may be difficult to calculate doses according to body surface area (see box below for formula). For this reason WHO has developed simplified weight-band dosing guidelines (see [Table 8.6](#)).

**Table 8.3** First-line ARV drug regimens for infants, children and adolescents, as well as the adults and pregnant or breastfeeding women (WHO 2016)

First-line ART	Preferred first-line regimens	Alternative first-line regimens <sup>a,b</sup>
Adults	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + DTGc TDF + 3TC (or FTC) + EFV400 <sup>c,e</sup> TDF + 3TC (or FTC) + NVP
Pregnant or breastfeeding women	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP
Adolescents	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF (or ABC) + 3TC (or FTC) + DTG <sup>c,d</sup> TDF (or ABC) + 3TC (or FTC) + EFV400 <sup>c,d,e</sup> TDF (or ABC) + 3TC (or FTC) + NVP
Children 3 years to less than 10 years	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + EFV (or NVP)
Children less than 3 years	ABC (or AZT) + 3TC + LPV/r	ABC (or AZT) + 3TC + NVP

<sup>a</sup> For adults and adolescents, d4T should be discontinued as an option in first-line treatment.

<sup>b</sup> ABC or boosted protease inhibitors (ATV/r, DRV/r, LPV/r) can be used in special circumstances.

<sup>c</sup> Safety and efficacy data on the use of DTG and EFV400 in pregnant women, people with HIV/TB coinfection and adolescents younger than 12 years of age are not yet available.

<sup>d</sup> Conditional recommendation, moderate-quality evidence.

<sup>e</sup> EFV at lower dose (400 mg/day).

3TC lamivudine, ABC abacavir, AZT zidovudine, DRV darunavir, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, LPV lopinavir, NVP nevirapine, r ritonavir, TDF tenofovir.

Source: WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. Second edition. 2016

**Table 8.4** Sequencing of ART regimens/formulations for newborns starting ART around birth (WHO 2016)

	0–2 weeks	2 weeks– 3 months	3–36 months
<b>Preferred</b>	AZT+3TC+NVP	ABC or AZT+3TC+ LPV/r syrup	ABC or AZT +3TC+ LPV/r pellets
<b>Alternative</b>	AZT+3TC+NVP		ABC or AZT +3TC+ LPV/r pellets
<b>Special circumstances</b>	AZT+3TC+NVP	ABC or AZT + 3TC + RAL	

Source: WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2016

Formula for body surface area (**Tables 8.5 and 8.7**)

$$\text{Body surface area} = \sqrt{\frac{\text{weight (kg)} \times \text{length (cm)}}{3\,600}}$$

### First line therapy for children with co-morbidities

For children less than 3 years with concurrent TB, a triple NRTI regimen may be considered because of the potential drug interaction between nevirapine and LPV/r with rifampicin. There is concern that the triple NRTI regimen has lower virological efficacy when compared to a two-class triple drug regimen. So, after the TB therapy, think about reverting to a two class regimen (details below). In adolescents with Hepatitis B, consider using a combination of 3TC plus TDF as the preferred nucleoside reverse transcriptase inhibitor backbone. NVP is preferred to EFV in adolescent girls with a potential for pregnancy or in the first trimester of pregnancy. These special circumstances are summarized in **Table 8.7**.



**Table 8.5** Antiretroviral drugs in paediatric practice

Drug	Formulation	Dosage	Adverse Events	Comments
<b>Nucleoside reverse transcriptase inhibitors (NRTIs)</b>				
<b>Zidovudine</b> AZT, ZDV	Suspension 10 mg/ml Capsules 100 mg Tablets 300 mg	180–240 mg/m <sup>2</sup> bd Neonatal dose: 4 mg/kg bd Maximum dose: 300 mg bd	Neutropenia, anaemia, headache; Myopathy, myositis, liver toxicity, lactic acidosis (uncommon)	Can be given with food Store at room temperature
<b>Lamivudine</b> 3TC	Suspension 10 mg/ml Tablets 150 mg	4 mg/kg bd Neonatal dose: 2 mg/kg bd Maximum dose: 150 mg bd	Headache, fatigue, nausea, skin rash, abdominal disturbances Pancreatitis, peripheral neuropathy; neutropenia, ↑ LFTs, lactic acidosis (uncommon)	Can be given with food Store at room temperature
<b>Abacavir</b> ABC	Suspension 20 mg/ml Tablets 300 mg	8 mg/kg bd Maximum dose: 300 mg bd	Nausea, vomiting, fever, headache, diarrhoea, anorexia Hypersensitivity rash (5%), pancreatitis, lactic acidosis (less common)	Can be given with food Store at room temperature Do not rechallenge after hypersensitivity

bd – twice a day, tds – three times a day, qid – four times a day, m2 – body surface area (BSA) metre squared

**Table 8.5** Antiretroviral drugs in paediatric practice (continued)

Drug	Formulation	Dosage	Adverse Events	Comments
<b>Protease inhibitors (PIs)</b>				
<b>Ritonavir</b> RTV	Suspension 80 mg/ml Capsules 100 mg	Not recommended as a single PI For boosting of other PIs For boosting of Kaletra during TB therapy (refer below)	Nausea, vomiting, diarrhoea, abdominal pain, headache, anorexia, lipid abnormalities Fat redistribution, diabetes mellitus, pancreatitis, hepatitis, allergic reactions (less common)	Give with food Palatability improved by mixing with milk, honey, ice cream, yoghurt or chocolate milkshake Store suspension at room temperature. Refrigeration of capsules recommended, but capsules are stable for 30 days if stored below 25 °C
<b>Lopinavir/ritonavir</b> LPV/r	Suspension 80 mg LPV and 20 mg RTV per ml Tablets: 200 mg LPV/50 mg RTV Paediatric tablets: 100 mg LPV / 50 mg RTV Capsules 133.3 mg LPV and 33.3 mg RTV	Neonate / infant: 300 mg/m <sup>2</sup> LPV / 75 mg/m <sup>2</sup> bd Children ( 2 years): 230 mg/m <sup>2</sup> LPV/57.5 mg/m <sup>2</sup> RTV bd up to a maximum dose of 400 mg LPV/ 100 mg RTV bd Increase dose with NVP or EFV co-administration (refer manufacturer's instructions)	Nausea, vomiting, diarrhoea, abdominal pain, headache, anorexia, lipid abnormalities Fat redistribution, diabetes mellitus, haemolytic anaemia, pancreatitis, hepatitis (less common)	Give with food. A high fat meal increases absorption Oral suspension should be refrigerated, but remains stable at room temperature for 2 months
<b>Atazanavir/ritonavir</b> ATV/r (For those >6 yrs and ≥15 kg)	Atazanavir oral powder: 50 mg Atazanavir caps: 150, 200, 300 mg ATV/r tablet: 300/100 mg	15 – <20 kg: 150/100 mg 20 – <40 kg: 200/100 mg ≥40 kg: 300/100 mg	Nausea, vomiting, diarrhoea, abdominal pain, headache, anorexia, jaundice, lipid abnormalities, Fat redistribution, diabetes mellitus	Store at room temperature

bd=twice a day, m<sup>2</sup>=body surface area (BSA) metre squared

**Table 8.6** Harmonised dosing schedule (WHO 2010)

Simplified table giving number of tablets of child-friendly solid formulations for morning and evening dosing

Drug	Strength of paediatric tab (mg)	Children 6 weeks of age and above												Strength of adult tab (mg)		Number of tablets by weight-band	
		Number of tablets by weight-band morning and evening						Number of tablets by weight-band morning and evening									
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg		25–34.9 kg		am	pm		
<b>SINGLE DRUGS</b>																	
AZT	60	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1			
ABC	60	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1			
NVP	50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200	1	1			
ddl	25	2 <sup>a</sup>	3	2	3	3	4	3	4	4	4	25	5	5			
<b>COMBINATIONS</b>																	
AZT/3TC	60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/150	1	1			
AZT/3TC/NVP	60/30/50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/150/200	1	1			
ABC/AZT/3TC	60/60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/300/150	1	1			
ABC/3TC	60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	<sup>b</sup>					
d4T/3TC	6/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	30/150	1	1			
d4T/3TC/NVP	6/30/50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	30/150/200	1	1			
LVP/r <sup>c</sup>	100/25	NR	NR	2	1	2	2	2	2	2	2	100/25	3	3			

<sup>a</sup> This dose of ddl is only appropriate for children 3 months of age or older and weighing between 5 and 5.9 kg

<sup>b</sup> See ABC/3TC FDC dosing table

<sup>c</sup> Higher doses of LVP/r may be required when co-administered with enzyme-inducing drugs such as NVP, EFV, fosamprenavir (FPV), rifampicin

**Table 8.7 Preferred first line regimens for specific conditions (WHO 2016)**

Situation	Preferred first line
Child or adolescent with severe anaemia	NVP or EFV + 2NRTIs (avoid AZT)
Child < 3 years on TB treatment	NVP* + 2NRTIs (ABC or AZT) or 3NRTIs (AZT + 3TC+ABC) or LPV/r# + 3TC+ ABC or AZT (especially if already on regimen)
Child > 3 years or adolescent on TB treatment	EFV + 2NRTIs (AZT or ABC or TDF)
Adolescent with hepatitis B	TDF + FTC or 3TC + NNRTI (EFV or NVP)

\* Nevirapine should be dosed at the upper-end of the dosing range i.e. 200 mg/m<sup>2</sup> twice daily

# Add ritonavir (r) to achieve the full therapeutic dose; Increase RTV (r) until it reaches the same dose as LPV in mg, in a ratio of 1:1.

## Antiretroviral therapy and TB treatment

Because rifampicin affects the hepatic metabolism of NNTRIs and PIs, and the adverse event profile of ART and TB treatment overlap, combining the two sets of drugs in HIV and TB co-infected children should be carefully considered. In TB/HIV co-infected children who are not on ART, TB treatment should be started immediately (see [Chapter 7](#)). The introduction of ART is usually delayed for a period of 2–8 weeks. It should be noted that a diagnosis of TB is an indication for ART initiation. Alternatively, TB may be diagnosed after initiating ART. In this setting TB treatment should be started at diagnosis, and the ART regimen appropriately modified ([Table 8.7](#)). The ART should not be interrupted.

In children who have been started on a triple NRTI regimen for the purpose of TB/HIV co-treatment, switch to a standard regimen on completion of TB treatment.

In all situations when rifampicin-containing TB medication is combined with ART, the ART regimen may require modification. The WHO-preferred ART regimens are listed in [Table 8.7](#).

- Although rifampicin decreases the serum concentration of nevirapine by 20–55% in adults, some studies have suggested that this effect may not be as great in children. Therefore, where abacavir is not available nevirapine dosed at the upper-end of the dosing range may be considered, i.e. NVP 200 mg/m<sup>2</sup> twice daily.
- In children treated with lopinavir/ritonavir co-formulation boosting with additional ritonavir so that the administered milligram lopinavir/ritonavir ratio is 1:1 throughout the course of TB medication overcomes the effect of rifampicin on lopinavir metabolism; for example for every 1 ml of LPV/r administered add 0.75 ml of ritonavir to ensure that the milligram ratio is 1:1. This alternative strategy is used in settings where LPV/r-containing first line regimens are employed in young children after perinatal nevirapine exposure.
- Alternatively, anti-TB drugs with less interaction than rifampicin, such as rifabutin can be used.
- Ultimately ART options for overcoming the metabolic effects of rifampicin should be guided by local circumstances and national treatment guidelines.

## Monitoring and follow-up

### Clinical monitoring

The frequency of visits for clinical monitoring is as follows:

- Ideally the first visit should take place 2 weeks after initiating therapy. This appointment should focus on ensuring that medicines are being correctly administered and stored, and strengthening adherence. Side effects to the ARV drugs should also be explored and one should take time to answer any questions from the parent/caregiver.
- For infants: monthly follow-up visits focusing on the clinical progress of the child should occur for the first year of life.
- For older children: initiate monthly follow-up visits for the first 3 months. Thereafter, if the child is adherent to the ART and

clinically stable, appointments may be spaced at 3–6 month intervals.

At each visit:

- Plot physical growth (weight, length/height, and head circumference for children less than 2 years of age).
- Conduct a physical examination of the child.
- Address ongoing medical problems, including skin and dental problems and organ-specific complications of HIV infection.
- Treat intercurrent infections, if present.
- Check the doses of the drugs. Adjust doses according to the weight of the child.
- Monitor neuro-developmental progress at 12-month intervals.
- Supply medications at monthly intervals, even though the clinic appointments are more widely spaced. In stable patients, drugs can be supplied at longer periods.
- Provide nutritional counselling and support.
- Provide psychosocial support.

### Laboratory monitoring

Viral load is recommended by WHO (2016) as the preferred monitoring approach to diagnose and confirm ARV treatment failure. If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure.

Treatment failure is defined by a persistently detectable viral load exceeding 1 000 copies/ml (that is, two consecutive viral load measurements within a 3-month interval, with adherence support between measurements) after at least 6 months of using ARV drugs. Viral load testing is usually performed on plasma; however, dried blood spot specimens using venous or capillary whole blood can also be used to determine the viral load. A threshold of 1 000 copies/mL can be used to determine viral failure when using dried blood spot

(DBS) samples, as defined for testing in plasma. It is important to note that plasma specimens are preferred to DBS samples for viral load measurements; the DBS samples are recommended for use in settings where logistical, infrastructural or operational barriers prevent routine viral load monitoring using plasma specimens.

Viral load should be tested early after initiating ART (at 6 months) and then at least every 12 months to detect treatment failure. If viral load testing is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure, with targeted viral load testing to confirm virological failure where possible.

Routine viral load monitoring can be carried out at 6 months, at 12 months and then every 12 months thereafter if the patient is stable on ART to synchronize with routine monitoring and evaluation reporting.

In settings where routine viral load monitoring is available, CD4 cell count monitoring can be stopped in individuals who are stable on ART and virally suppressed.

The recommended laboratory tests at diagnosis of HIV-infection and for monitoring response to ART are summarized in **Table 8.8**.

**Table 8.8** Recommended and desirable laboratory tests at HIV diagnosis, monitoring on ART, and screening for co-infections and non-communicable diseases (WHO 2016)

Phase of HIV management	Recommended	Desirable (if feasible)
HIV diagnosis	HIV testing (serology for adults and children 18 months or older; EID for children younger than 18 months) CD4 cell count TB symptom screening	HBV (HBsAg) serology <sup>a</sup> HCV serology Cryptococcus antigen if CD4 cell count $\leq 100$ cells/mm <sup>3</sup> <sup>b</sup> Screening for STIs Pregnancy test to assess if ART initiation should be prioritized to prevent HIV transmission to the child Assessment for major noncommunicable chronic diseases and comorbidities <sup>c</sup>

Phase of HIV management	Recommended	Desirable (if feasible)
Follow-up before ART	CD4 cell count (every 6–12 months in circumstances where ART initiation is delayed)	
ART initiation		Haemoglobin test for starting AZT <sup>d</sup> Pregnancy test Blood pressure measurement Serum creatinine and estimated glomerular filtration rate (eGFR) or starting TDF <sup>e</sup> Alanine aminotransferase for NVP <sup>f</sup> Baseline CD4 cell count
Receiving ART	HIV viral load (at 6 months and 12 months after initiating ART and every 12 months thereafter) CD4 cell count every 6 months until patients are stable on ART	Serum creatinine and eGFR for TDF <sup>e</sup> Pregnancy test, especially for women of childbearing age not receiving family planning and on treatment with DTG or low-dose EFV
Suspected treatment failure	Serum creatinine and eGFR for TDFc Pregnancy test, especially for women of childbearing age not receiving family planning and on treatment with DTG or low-dose EFV	HBV (HBsAg) serology <sup>a,g</sup> (before switching ART regimen if this testing was not done or if the result was negative at baseline and the patient was not vaccinated thereafter)

<sup>a</sup> If feasible, HBsAg testing should be performed at baseline to identify people with HIV and HBV coinfection and who should therefore initiate TDF-containing ART.

<sup>b</sup> Can be considered in settings with a high prevalence of cryptococcal antigenaemia (>3%).

<sup>c</sup> Consider assessing for the presence of chronic conditions that can influence ART management, such as hypertension and other cardiovascular diseases, diabetes and TB according to the WHO Package of Essential NCD interventions (PEN), mental health Gap Action Programme (mhGAP) or national standard protocols. Monitoring may include a range of tests, including serum creatinine and estimated glomerular filtration rate (eGFR), serum phosphate and urine dipsticks for proteinuria and glycosuria.

<sup>d</sup> Among children and adults with a high risk of adverse events associated with AZT (low CD4 or low BMI).

<sup>e</sup> Among people with a high risk of adverse events associated with TDF: underlying renal disease, older age group, low body mass index (BMI), diabetes, hypertension and concomitant use of a boosted PI or potential nephrotoxic drugs.

<sup>f</sup> Among people with a high risk of adverse events associated with NVP, such as being ART-naïve, women with HIV with a CD4 count >250 cells/mm<sup>3</sup> and hepatitis C virus (HCV) coinfection. However, liver enzymes have low predictive value for monitoring NVP toxicity.



<sup>9</sup> For HIV/HBV coinfecting individuals who are already using TDF-containing regimens and develop ART failure, this NRTI should be maintained regardless of the selected second-line regimen.  
ART antiretroviral therapy, AZT zidovudine, DTG dolutegravir, EFV efavirenz, eGFR estimated glomerular filtration rate, EID early infant diagnosis, HBV hepatitis B virus, HBsAg hepatitis B surface antigen, HCV hepatitis C virus, STI sexually transmitted infection, TDF tenofovir.  
Source: WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. Second edition. 2016

## Adherence monitoring

Greater than 95% adherence to the drug regimen will ensure a good virological response and prevent the emergence of viral resistance. For a child taking medication twice daily, omitting more than one dose in 10 days implies < 95%, or suboptimal, adherence.

A good partnership between the healthcare providers (i.e. counsellors, nurses, and doctors) and the caregiver helps to optimise adherence. Ideally, the same primary healthcare provider should continue to treat the patient so that a long-term relationship can develop with the family.

Regular education and support during each clinic visit enhances and maintains good adherence. You may monitor adherence using diary cards, pill counts, alarm clocks, and other improvised measures.

The health worker should look out for children at risk of poor adherence, for example:

- Children with multiple caregivers
- Adolescents
- Children in boarding school.

## Differentiated care (WHO 2016)

UNAIDS estimated that 95% of HIV service delivery in 2014 was facility based. In nearly all countries, the delivery of HIV care in the initial phase of rapid scale-up has been based on a clinic-based model, largely undifferentiated for individual needs. As national guidelines evolve towards initiating ART for all people living with HIV regardless of clinical and immunological status, as recommended by WHO, HIV programmes will be challenged to manage an increasingly diverse set of patient needs. There is now a growing cohort of patients who have been on treatment for several years. At the same time, there is a

need to expand timely access to ART for those who have yet to start. While implementation of the recommendations in these guidelines will mean that more people will start earlier, programmes must also retain the capacity to respond to the needs of patients who present with advanced disease, and are at heightened risk of morbidity and mortality.

Broadly, WHO has defined four groups of patients with specific needs, namely:

- 1 People who present when well, potentially with higher CD4 cell counts, may require additional and targeted adherence and retention support in order to commit to lifelong ART.
- 2 People presenting to care with advanced disease require a fast-tracked clinical and care package to initiate ART and prevent death and reduce ill health.
- 3 Those who are already on ART but need careful monitoring to ensure timely action as required; this may include clinical care, additional adherence support and timely switch to second-line ART regimens in the case of treatment failure.
- 4 Stable individuals are likely to represent the majority of people on ART and they can safely reduce the frequency of clinic visits, potentially receiving ART in community settings.

It is believed that such an approach can relieve overburdened healthcare settings and enable more attention to be paid to patients with more complex conditions who require prompt diagnosis and treatment of opportunistic infections, enhanced adherence support, viral load testing and potential changes of regimen, HIV drug resistance testing or other specialized care. Receiving care closer to their home can also reduce direct and indirect costs related to transport and long facility waiting time for patients and their families. While these four groups have distinct needs, patients may move between the groups over the course of their lifetime in care.

The care package elements for each group of patients are shown in [Table 8.9](#).

**Table 8.9** Diversity of care needs for people living with HIV (WHO 2016)

People living with HIV	Care package elements
People presenting when well	Adherence and retention support
People with advanced disease	Clinical package to reduce mortality and morbidity
Stable individuals	Reduced frequency of clinic visits and community ART delivery models
Unstable individuals	Adherence support, viral load testing, switch to second- or third-line ART if indicated, monitoring for HIV drug resistance (HIV-DR)

## Long-term management

The long-term sustainability of ART depends on social, educational, and emotional support for the family, which may include involving the community and providing social assistance.

The long-term success of ART for children can be achieved only if the health and well-being of the entire family is ensured. This includes providing appropriate ARV drugs for infected adults. Long-term success also depends on well-trained health professionals who provide care based on the best available clinical and scientific evidence.

## Indications for changing therapy

The indications for changing therapy include:

- Adverse events
- Treatment failure
- Drug-drug interactions.

Several factors lead to treatment failure including poor adherence, low drug levels, pre-existing drug resistance and suboptimal potency of the ART regimen. Treatment failure manifests with certain clinical, immunological, and virological criteria that might indicate the need to change to second-line therapy. Virological criteria are the most sensitive indicators of treatment failure and viral load monitoring is increasingly becoming available even in resource-limited settings.

ARVs, like other drugs, have adverse events, some of which are life-threatening; for such adverse events the drugs need to be changed.

ARVs may be given with other drugs for co-morbidities, and there may be drug-drug interactions between the ARVs and these drugs. Appropriate adjustments need to be made in such cases.

The changes to ART regimens for adverse events and drug interactions are normally single drug substitutions.

### Clinical criteria of treatment failure

- Treatment failure should be considered when new or recurrent clinical stage 3 or 4 events develop in a child adherent to therapy (Table 8.10).
- Do not regard short intercurrent episodes of pneumonia, lower respiratory tract infection, and gastroenteritis as clinical failure.
- Clinical disease progression should also be distinguished from immune reconstitution inflammatory syndrome (IRIS) (see below).
- If the child presents with growth failure, ensure that nutritional intake is adequate and that intercurrent infections have been fully treated before diagnosing treatment failure.

**Table 8.10** Approach to new or recurrent stage 3 or 4 clinical events (WHO 2016)

<b>New stage 3 or 4 events</b>	Treat and manage staging event and monitor response <sup>a</sup> Check if on ART for 24 weeks or longer Assess and offer adherence support Assess nutritional status and offer support Check CD4 where available <sup>b</sup> Measure Viral load if available Institute more frequent follow-up Consider regimen switch
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<sup>a</sup> The presence of pulmonary TB or TB lymphadenitis (stage 3 conditions) may not be an indication of treatment failure

<sup>b</sup> CD4 count should be performed once the acute phase of the presenting illness has resolved

### Immunological criteria of treatment failure (WHO 2016)

Immunological treatment failure can be identified by assessing the immunological response to ART in relation to baseline CD4. Treatment

failure is characterized by a drop in the CD4 to values at or below the age-dependent values (see below), or a failure of the CD4 count to rise above these threshold values. Recognition of treatment failure on the basis of immunological values relies on comparison with previous CD4 values, and underscores the need for CD4 measurement at the start of ART. It is not advisable to switch ART based on a single CD4 value.

Immunological failure is recognized as developing or returning to the following age-related immunological thresholds after at least 24 weeks on ART, in a fully treatment-adherent child, as:

- CD4 count of  $< 200$  cells/mm<sup>3</sup> or CD4%  $< 10\%$  for a child more than 2 years to less than 5 years of age
- CD4 count of  $< 100$  cells/mm<sup>3</sup> for a child 5 years of age or older.

These cut-offs were designed to identify children with a more than 10% risk of dying in the following 12-month period. These cut-offs have been shown to be poor for predicting virological failure.

Do *not* measure CD4 count/percentage during a concurrent infection. Measure it preferably one month or more post-resolution. If there is a modest decline in CD4% ( $< 5\%$ ) and if there is no failure to thrive, do not change medication, but maintain close monitoring.

### Virological conditions

Viral load monitoring is not widely available in resource-limited settings, although several countries are setting up reference laboratories for this and other specialized tests. Where available the following criteria may be used to define treatment failure. Virological failure is diagnosed in a fully adherent child,  $\geq 24$  weeks from initiation of ART, if the viral load is persistently above 1 000 copies/ml (Table 8.11). In the presence of virological failure a change to second-line therapy may be considered. However, poor adherence is a major cause of incomplete virological suppression or viral load rebound and must be excluded before the patient is switched to second line therapy.

**Table 8.11** Definitions of virological failure (WHO 2016)

Virological failure
<b>Definition:</b> Plasma viral load above 1 000 copies/ml based on 2 consecutive viral load measurements after 3 months, with adherence support
<b>Comments:</b> An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed. Assessment of viral load monitoring using DBS and point-of-care technologies should use a higher threshold

The viral load should *not* be measured during a concurrent infection; preferably, measure it one month (or more) post-resolution.

In situations where viral load measurement is not on site, efforts should be made to send samples to the appropriate laboratories given the usefulness of viral load monitoring in determining ART treatment failure.

### Second-line therapy

Issues to consider when introducing second-line therapy are as follows:

**Do not** rush into second-line therapy.

- When changing therapy, determine whether poor adherence was responsible for the failure; if it is not possible to improve adherence, attempt directly observed therapy (DOT) with a healthcare worker, a family member, or friend.
- If the patient is adherent, assume that treatment failure has caused viral resistance and change therapy. The new regimen should include at least 2 new drugs.
- When changing therapy, review all other medications for possible drug interactions.
- When changing therapy, consider the patient's quality of life.

## Medications for second-line therapy

Adhere to national guidelines. Where these are not available consider the options in **Table 8.12**.

**Table 8.12** Second-line ARV drug regimens for infants, children and adolescents, as well as adults and pregnant or breastfeeding women (WHO 2016)

Population		Failing first-line regimen	Preferred second-line regimen	Alternative second-line regimens
Adults and adolescents		2 NRTIs + EFV (or NVP) 2 NRTIs + DTG	2 NRTIs <sup>b</sup> + ATV/r or LPV/r	2 NRTIs <sup>b</sup> + DRV/r <sup>c</sup>
Pregnant or breastfeeding women		2 NRTIs + EFV (or NVP)	2 NRTIs <sup>b</sup> + ATV/r or LPV/r	2 NRTIs <sup>b</sup> + DRV/r
Children	Less than 3 years	2 NRTIs + LPV/r	2 NRTIs <sup>b</sup> + RAL	Maintain the failing LPV/r-based regimen and switch to 2 NRTIs <sup>b</sup> + EFV at 3 years of age
		2 NRTIs + NVP	2 NRTIs <sup>b</sup> + LPV/r	2 NRTIs <sup>b</sup> + RAL <sup>d</sup>
	3 years to less than 10 years	2 NRTIs + LPV/r <sup>a</sup>	2 NRTIs <sup>b</sup> + EFV	2 NRTIs <sup>b</sup> + RAL <sup>d</sup>
		2 NRTIs + EFV (or NVP)	2 NRTIs <sup>b</sup> + LPV/r	2 NRTIs <sup>b</sup> + ATV/r <sup>d</sup>

<sup>a</sup> ATV/r can be used as an alternative PI for children older than 3 months of age.

<sup>b</sup> If ABC+ 3TC or TDF + 3TC (or FTC) was used in the first-line failing regimen, AZT + 3TC should be used in second-line and vice versa.

<sup>c</sup> RAL + LPV/r can be used as an alternative second-line regimen in adults and adolescents.

<sup>d</sup> DRV/r can be used as an alternative PI option in special situations.

3TC lamivudine, ABC abacavir, ATV atazanavir, AZT zidovudine, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, LPV lopinavir, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r or RTV ritonavir, RAL raltegravir.

Source: WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. Second edition. Population 2016

## Further therapeutic revisions

- Beyond second-line therapy, treatment strategies are expensive. Ideally, further revisions in therapy should be guided by viral resistance testing.
- In formulating third-line or salvage regimens, second generation NNRTIs, e.g. etravirine and rilpivirine, newer PIs, e.g. tripranavir

and duranavir, and newer classes of agents such as the CCR5 antagonist maraviroc and the integrase inhibitors raltegravir and elvitegravir should be considered. Knowledge about the optimal paediatric dosing for these newer agents is rapidly increasing.

- Newer drugs should be used in combination with at least one, and ideally two other active agents. It may be possible to reintroduce previously prescribed drugs. In addition, continuation of **lamivudine**, despite the presence of lamivudine-resistance mutations may contribute to virological **suppression**.
- Empiric multi-drug regimens (including up to three PIs and/or two NNRTIs) have been promoted by some experts. Cost considerations, regimen complexity and potential drug-drug interactions may limit the use of this approach.
- In future, it may be possible to design first-, second- and third-line regimens with little or no overlapping resistance, reducing the need for viral resistance testing. At present many of the newer treatment options have limited application in resource-limited settings because of prohibitive cost.
- Experienced providers at referral centres should assist with decisions about second-line and advanced treatment regimens.
- Where third-line regimens are included in national guidelines, these should be used. If they are not included, the WHO recommendations in **Table 8.13** can be considered. These show the sequencing from 1st, to 2nd and then to 3rd line regimens.

### Discontinuation of therapy

Under exceptional circumstances it may be necessary to discontinue ART. Such circumstances include extremely poor adherence and cases where the administration of medication is repeatedly interrupted. Continuing suboptimal ART is not useful because it will lead to the emergence of viral resistance. Consider discontinuation only after exploring all potentially corrective measures, including intensive counselling, additional caregiver education, and family support.



Antiretroviral therapy may be re-started when the caregiver status improves.

**Table 8.13** Summary of sequencing options for first-, second-, and third-line ART regimens for children, adolescents, adults and pregnant women (WHO 2016)

Population	First-line regimens	Second-line regimens	Third-line regimens
<b>Adults and adolescents (&gt;10 years)</b>	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r <sup>a</sup> 2 NRTI + DRV/r <sup>b</sup>	DRV/r <sup>b</sup> + DTG <sup>c</sup> (or RAL) ± 1–2 NRTIs
	2 NRTIs + DTG	2 NRTIs + ATV/r or LPV/r 2 NRTI + DRV/r	DRV/r <sup>b</sup> + 2 NRTIs ± NNRTI Optimize regimen using genotype profile
<b>Pregnant or breastfeeding women</b>	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r <sup>a</sup> 2 NRTIs + DRV/r <sup>b</sup>	DRV/r <sup>b</sup> + DTG <sup>c</sup> (or RAL) ± 1–2 NRTIs
<b>Children (0–10 years)</b>	2 NRTI + LPV/r	If less than 3 years: 2 NRTIs + RAL <sup>d</sup>	RAL (or DTG) <sup>f</sup> + 2 NRTIs
		If older than 3 years: 2 NRTIs + EFV or RAL	DRV/r <sup>g</sup> + 2 NRTIs DRV/r <sup>g</sup> + RAL (or DTG) <sup>f</sup>
	2 NRTI + EFV	2 NRTIs + ATV/r <sup>e</sup> or LPV/r	± 1–2 NRTIs

<sup>a</sup> RAL + LPV/r can be used as an alternative second-line regimen in adults and adolescents.

<sup>b</sup> In PI-experienced patients, the recommended DRV/r dose should be 600 mg/100 mg twice daily.

<sup>c</sup> Safety and efficacy data on the use of DTG in adolescents younger than 12 years and pregnant women are not yet available.

<sup>d</sup> If RAL is not available, no change is recommended unless in the presence of advanced clinical disease progression or lack of adherence, specifically because of poor palatability of LPV/r. In this case, switching to a second-line NVP-based regimen should be considered. Based on approval of the use of EFV in children less than 3 years of age, an EFV-based regimen could be considered as an alternative. However, more data are needed to inform how best to use EFV in this population.

<sup>e</sup> ATV/r can be used as an alternative to LPV/r in children older than 3 months of age. However, the limited availability of suitable formulations for children younger than 6 years of age, the lack of an FDC and the need for separate administration of RTV booster should be considered when choosing this regimen.

<sup>f</sup> RAL can be used in children failing PI-based second-line treatment when DTG is not available and when RAL has not been used in a previous regimen. DTG is currently approved only for children 12 years and older; however, studies are ongoing to determine dosing in younger children, and approval for lower age groups is expected in the near future.

<sup>g</sup> DRV/r should not be used in children younger than 3 years of age.

ATV atazanavir, DRV darunavir, DTG dolutegravir, EFV efavirenz, LPV lopinavir, NNRTI non-nucleoside reverse-transcriptase inhibitor, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r ritonavir, RAL raltegravir.

Source: WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. Second edition. Population 2016

**Table 8.14** Clinical signs, symptoms, monitoring, and management of symptoms of serious adverse effects of ART that require drug discontinuation

Adverse effect/possible offending drug(s)	Clinical signs/symptoms	Management
<p><b>Acute hepatitis</b> Nevirapine (NVP); EFV less common; more uncommon with zidovudine (ZDV), didanosine (ddI), stavudine (d4T) (&lt;1%), and protease inhibitors (PI); most frequently with ritonavir (RTV)</p>	<p>Jaundice, liver enlargement, gastrointestinal symptoms, fatigue, anorexia; NVP-associated hepatitis may have hypersensitivity component (drug rash, fever, systemic symptoms, eosinophilia); may have associated lactic acidosis if caused by NRTI</p>	<ul style="list-style-type: none"> <li>• If possible, monitor serum transaminases, bilirubin</li> <li>• All ARV should be stopped until symptoms resolve</li> <li>• NVP should be permanently discontinued.</li> <li>• Once symptoms resolve, restart ART with altered regimen</li> </ul>
<p><b>Acute pancreatitis</b> ddI; d4T; less frequently 3TC</p>	<p>Nausea, vomiting, and severe abdominal pain; may be accompanied by lactic acidosis</p>	<ul style="list-style-type: none"> <li>• If possible, monitor serum pancreatic amylase, lipase.</li> <li>• All ART should be stopped until symptoms resolve</li> <li>• Restart ART and substitute with different NRTI, preferably one without pancreatic toxicity (e.g. ZDV, ABC)</li> </ul>

**Table 8.14** Clinical signs, symptoms, monitoring, and management of symptoms of serious adverse effects of ART that require drug discontinuation (continued)

Adverse effect/possible offending drug(s)	Clinical signs/symptoms	Management
<p><b>Lactic acidosis</b> All nucleoside analogue reverse transcriptase inhibitors (NRTIs), especially d4T</p>	<p>Initial symptoms are variable: a clinical prodromal syndrome may include generalized fatigue and weakness, gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia, and/or sudden unexplained weight loss), hepatitis or pancreatitis may be present; respiratory symptoms (tachypnea and dyspnea) or neurologic symptoms (including motor weakness)</p>	<ul style="list-style-type: none"> <li>• Discontinue all ARV; symptoms may continue or worsen after discontinuation of ART</li> <li>• Supportive therapy</li> <li>• Once symptoms resolve, restart ART using an alternative NRTI with lower risk for mitochondrial toxicity</li> </ul>
<p><b>Hypersensitivity reaction</b> Abacavir (ABC); nevirapine (NVP)</p>	<p>ABC: Constellation of acute onset of symptoms including: fever, fatigue, myalgia, nausea, vomiting, diarrhoea, abdominal pain, pharyngitis, cough, dyspnoea, rash usually mild). While these symptoms overlap those of common infectious illness, the combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC is more typical of a hypersensitivity reaction. Onset is usually within 6–8 weeks of starting ABC NVP: Systemic symptoms of fever, myalgia, arthralgia, hepatitis, eosinophilia with or without rash</p>	<ul style="list-style-type: none"> <li>• Discontinue all ARVs until symptoms resolve</li> <li>• The reaction progressively worsens with drug administration and can be fatal.</li> <li>• Administer supportive therapy</li> <li>• Do not rechallenge with ABC (or NVP), as anaphylactic reactions and death have been reported</li> <li>• Once symptoms resolve, restart ARVs with change to different NRTI if ABC-associated, or to PI- or NRTI-based regimen if NVP-associated</li> </ul>

**Table 8.14** Clinical signs, symptoms, monitoring, and management of symptoms of serious adverse effects of ART that require drug discontinuation (continued)

Adverse effect/possible offending drug(s)	Clinical signs/symptoms	Management
<p><b>Severe rash/Steven-Johnson syndrome</b> Non-nucleoside reverse transcriptase inhibitors (NNRTIs); particularly NVP; EFV (less commonly)</p>	<p>Rash usually occurs during the first 6–8 weeks of treatment</p> <p><i>Mild or moderate rash</i>: usually erythematous, maculopapular, confluent, most prominent on the body and arms, may be pruritic, without systemic symptoms</p> <p><i>Severe rash</i>: extensive rash with moist desquamation, angio-oedema or serum-sickness reaction; or rash with constitutional features: fever, oral lesions, blistering, facial oedema, or conjunctivitis</p> <p>Life-threatening Stevens-Johnson syndrome or toxic epidermal necrolysis</p>	<ul style="list-style-type: none"> <li>• If rash is mild or moderate, ART can be continued without interruption until rash resolves. Close observation is needed</li> <li>• For severe or life-threatening rash discontinue all ARVs until symptoms resolve</li> <li>• Do not readminister NVP to patients with severe or life-threatening manifestations</li> <li>• Once resolved, switch ART regimen to different ARV class (e.g., 3 NRTIs or 2 NRTIs and PI)</li> </ul>
<p><b>Severe life-threatening anaemia</b> AZT</p>	<p>Severe pallor, tachycardia, significant fatigue, congestive cardiac failure Low haemoglobin</p>	<ul style="list-style-type: none"> <li>• Symptomatic treatment, e.g. transfusion</li> <li>• Discontinue AZT only and substitute with another NRTI, e.g. ABC</li> </ul>
<p><b>Severe neutropenia</b> AZT</p>	<p>Manifests with infection or sepsis</p>	<ul style="list-style-type: none"> <li>• If refractory to symptomatic treatment, discontinue AZT and substitute with an alternative NRTI, e.g. ABC</li> </ul>
<p><b>Severe peripheral neuropathy</b> ddI; d4T; less commonly 3TC</p>	<p>Pain, tingling, numbness of hands or feet; refusal to walk; distal sensory loss, mild muscle weakness, and are flexia can occur.</p>	<ul style="list-style-type: none"> <li>• Stop suspect NRTI and switch to different NRTI that does not have neurotoxicity (e.g. ZDV, ABC)</li> <li>• Symptoms usually resolve in 2–3 weeks</li> </ul>

## Adverse events

Adverse events are gross clinical and/or biochemical abnormalities that may arise from infections, ART, or other drugs and treatment. The following principles are used to manage such adverse events. (See [Table 8.14](#) for management and [Appendix G](#) for grading of adverse events):

- Establish whether the adverse event is due to ARV agents or to other medication.
- Because not all problems that arise during treatment result from ARV drugs, consider other disease processes (e.g. consider viral hepatitis in a child who develops jaundice on ARV drugs).
- Continue ART if there are Grade 1 or Grade 2 (mild) reactions; single-drug substitution may occasionally be necessary, for example, in a child with nausea/vomiting due to lopinavir/ritonavir co-formulation.
- Consider terminating treatment if there are Grade 3 reactions, and discontinue treatment if Grade 4 reactions occur. When discontinuing antiretroviral therapy, it is strongly recommended that all antiretroviral agents be stopped. Manage the medical event, then reintroduce ARV drugs using a modified regimen.

## Lipodystrophy

HIV-associated lipodystrophy includes fat loss and/or fat accumulation in distinct regions of the body. Increased fat around the abdomen, back of the neck (buffalo hump), breast (breast hypertrophy), and fat loss (lipoatrophy) from limbs, buttocks, and face occurs to a variable extent.

Other manifestations include insulin resistance, hyperglycaemia, hypertriglyceridaemia, hypercholesterolaemia, and low HDL levels. There is an increased risk of diabetes mellitus and coronary artery disease.

Lipodystrophy is more common in individuals who are taking NRTIs or protease inhibitors; lipoatrophy is commonly associated with stavudine administration.

Managing lipodystrophy:

- The risk of lipodystrophy can be reduced by using ABC instead of d4T or AZT during first-line ART.

There are no satisfactory methods for treating established lipodystrophy.

- Encourage exercise to reduce fat accumulation.
- Some patients improve if switched from a protease inhibitor to an NNRTI.
- Manage lipid and glucose derangements.

### Lipid abnormalities

- Hypercholesterolaemia and/or hypertriglyceridaemia may develop during the course of ART, either in association with lipodystrophy or as independent manifestations.
- Both NNRTI- and PI-containing regimens have been implicated in the pathogenesis of lipid disorders.
- General preventative measures include control of dietary fat intake (total fat < 30% of calories, saturated fat < 10% of calories, cholesterol < 300 mg/day, avoidance of trans fats) and promotion of physical exercise.
- Switching strategies may improve the lipid profile of patients with persistently raised cholesterol and/or triglycerides, e.g. switching from a PI to an NNRTI, ABC or a newer PI such as atazanavir.
- Persistently elevated cholesterol concentration may require intervention with a statin.
- In the presence of markedly elevated triglyceride concentration (> 500 mg/dL) consider treating with a fibrate or niacin.

The grading of the various adverse events and their management is the tables in [Appendix G](#).

## Guiding principles for monitoring adverse events (WHO 2016)

- The availability of laboratory monitoring is not required for initiating ART.
- Symptom-directed laboratory monitoring for safety and toxicity can be used for those receiving ART.
- There are no adverse drug reactions requiring regular or routine monitoring.

### Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) is characterized by a paradoxical clinical deterioration after starting ART. This results from rapid restoration of pathogen-specific immunity to opportunistic infections and causes deterioration of an existing infection (paradoxical IRIS) or new clinical manifestations of a previously unrecognized subclinical infection (unmasking IRIS) during the early stages of ART.

Although a wide range of pathogens has been associated with IRIS, including *Mycobacterium tuberculosis* (MTB), *Mycobacterium avium complex* (MAC), *Mycobacterium bovis* BCG, *Cryptococcus neoformans*, *Aspergillus* spp., *Candida albicans*, *Pneumocystis jirovecii*, cytomegalovirus, herpes simplex virus types 1 and 2, and hepatitis B virus, mycobacterial pathogens are most commonly associated with IRIS.

The median time from start of ART to the development of IRIS is 4 weeks (range: 2–31 weeks). Clinical presentations vary and depend on the causative organism and the affected organ system. For example, IRIS caused by MTB may present with high fever, lymphadenopathy, worsening of the original TB lesion, and/or deteriorating chest radiographic manifestations, including the development of a miliary pattern or pleural effusion.

A study in Uganda found the prevalence of IRIS in children starting ART to be 38%, with the majority of the events unmasking IRIS events. Most occurred in the first month on ART, and TB IRIS was the

most frequent presentation. A pre-ART CD4% < 15% was a risk factor for development of IRIS.

Managing IRIS includes specific antimicrobial therapy (e.g. TB treatment for IRIS caused by MTB). In severe reactions, glucocorticosteroids and/or surgical debulking, and/or temporarily discontinuing ART may help.

## Use of cotrimoxazole in HIV-infected children on antiretroviral therapy

All HIV-infected children should be on cotrimoxazole prophylaxis before start of ART, given the benefits demonstrated in the CHAP trial in Zambia (2004). In the ARROW trial in Uganda and Zimbabwe, continuing cotrimoxazole prophylaxis after 96 weeks of ART was beneficial compared to stopping prophylaxis with fewer hospitalizations for both malaria and infection not related to malaria.

Therefore HIV-infected children should continue to receive cotrimoxazole prophylaxis even when stable on ART.

## Knowledge gaps

- Improved paediatric drug formulations
- Inexpensive and simplified viral load monitoring technology
- Pharmacokinetic and dosing profiles, and efficacy of newer ARV drugs
- The role of newer antiretroviral agents in first-line, second-line and salvage regimens for children.



## Additional and recommended reading

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# Chapter 9

## Adolescents and HIV infection

### Summary

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- Adolescence (ages 10 to 19 years) is a critical period in a person's life, in which rapid changes in physical, emotional, cognitive, and social characteristics take place.
- Adolescents are not a homogeneous group. Some are out of school, some have become parents themselves, and some are orphaned and heading households. Some have not yet been tested for HIV, while others have been tested but have not been informed that they are HIV-infected. Healthcare service providers must take into account the special circumstances of each individual when caring for adolescents who are infected or affected by HIV.
- In 2014, an estimated 12% of all new HIV cases in people aged 15 and older were found among adolescents aged 10–19 years. In 2014, a total of 2.0 million adolescents living with HIV in low- and middle-income countries; 1.6 million of whom were in sub-Saharan Africa.
- There are two groups of HIV infected adolescents: those who acquired HIV through vertical transmission and those who acquired HIV through horizontal transmission (largely sexual). As many as 5% of children with vertical transmission live to adolescence even without ART and many more with ART.
- Implementing comprehensive, effective, integrated HIV prevention, care, support and treatment programmes for adolescents and young people is key to mitigating the impact of the epidemic in developing countries, specifically in sub-Saharan Africa.
- There is a need to provide specific programmes for adolescents living with HIV and this should be guided by data in this age group.
- The transition from adolescent care to adult care needs to be planned with multidisciplinary teams.

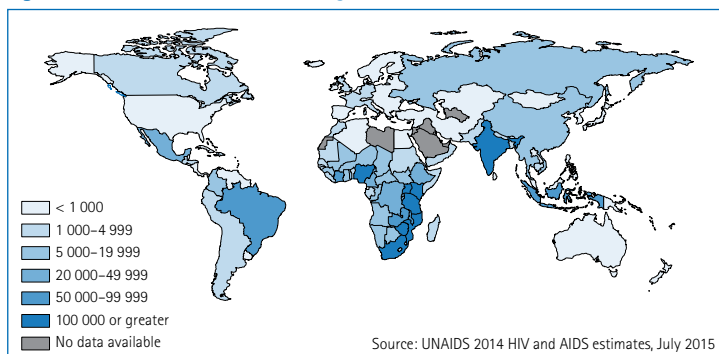


## Introduction

In 2014, about 2.0 million adolescents between the ages of 10 and 19 were living with HIV worldwide. Adolescents account for about 5% of all people living with HIV and about 12% of new adult HIV infections. Regions with the highest numbers of HIV-positive adolescents are sub-Saharan Africa and South Asia. Of the 2.0 million adolescents living with HIV, about 1.6 million (82%) live in sub-Saharan Africa.

**Figure 9.1** shows the number of adolescents who were living with HIV in the year 2014.

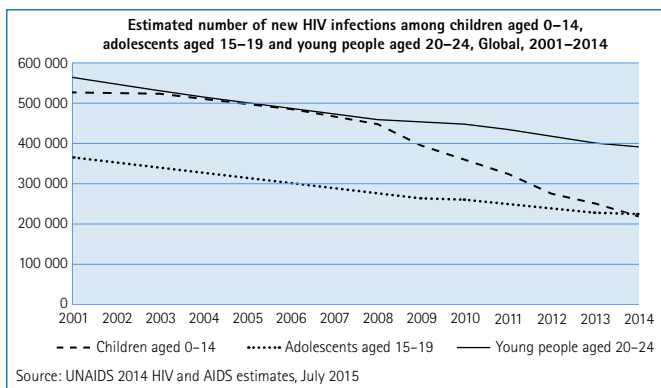
**Figure 9.1** Number of adolescents living with HIV – 2014



Significant gains have been made in reducing HIV prevalence since the year 2000 but countries that have reported a decline in HIV prevalence have recorded the biggest changes in behaviour and prevalence among younger age groups as shown in **Figure 9.2**.

The international community has committed that by 2020, 90% of all people living with HIV will know their HIV status. By 2020, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy. By 2020, 90% of all people receiving antiretroviral therapy will have viral suppression (UNAIDS).

**Figure 9.2** New infection trends.



## Adolescent characteristics and development

WHO defines adolescents as individuals aged 10–19 years and young people as those aged 15–24 years. As the transition between childhood and adulthood, adolescence is recognised in many communities and cultures and is often marked with traditional rites of passage. During this process, adolescents learn about expectations of their communities and, in a sense, receive the mandate to engage in adult roles.

Adolescence is characterized by major physical, emotional and cognitive changes as well as significant changes in the relationship between the adolescent and their family and peers. At the same time, the adolescent is going through a process of acquiring knowledge and skills to enable them live independently. **Table 9.1** summarizes the changes that adolescents experience during the different stages of development. It is worth noting that physical and sexual maturity does not always mean that the adolescent has the emotional and cognitive maturity to anticipate the undesirable effects of sexual activity such as pregnancy and sexually transmitted infections (STIs).

**Table 9.1** General characteristics of adolescent development

<b>Area of development</b>	<b>Early: 10–13 years</b>	<b>Middle: 14–16 years</b>	<b>Late: 17 years and older</b>
Physical	Pubertal changes	End of pubertal changes	Mature physical development
Emotional	Wide mood swings Low impulse control Role exploration	Sense of invulnerability Risk-taking behaviour peaks	Increasing sense of vulnerability Able to consider others and suppress one's needs Less risk-taking
Cognitive	Concrete thinking Little ability to anticipate long-term consequences of one's actions Literal interpretation of ideas	Able to conceptualise abstract ideas such as love, justice, truth, and spirituality	Formal operational thinking Able to understand and set limits Understands thoughts and feelings of others
Relation to family	Estranged Need for privacy	Peak of parental conflict Rejection of parental values	Improved communication Accepts parental values
Peers	Increased importance and intensity of same sex relationships	Peak of peer conformity Increase in relationships with the opposite sex	Peers decrease in importance Mutually supportive, mature, intimate relationships

## Risk factors for HIV infection among adolescents

Determinants of risk-taking behaviour in adolescents include their stage in development, biologic and physiologic characteristics, individual attributes, and the environment in which they live. A number of high-risk behaviours, such as alcohol and drug abuse, often lead to sexual risk taking. Studies among adolescents have shown that young people with a high sense of self-esteem and direction are less likely to be involved in risk-taking behaviour such as sexual experimentation or substance abuse.

Adolescents are an important economic force and have therefore become the target of aggressive advertising by the media, which often portray lifestyles that are at variance with societal norms and good health. An example is the aggressive marketing of sex, cigarettes and alcohol to youth in Africa.

Studies have demonstrated that many adolescents and youth lack in-depth knowledge about HIV. They do not internalise the biological explanation of disease causation. As a result, many revert to traditional models to explain the cause of disease, and to the prevalent belief that the 'power of God' and traditional medicine are effective cures for HIV. The dichotomy of belief systems presents challenges in conveying prevention messages and ensuring that the messages translate into reduced high risk behaviours.

Adolescents tend to have a poor perception of their own risk of HIV, and their perception of risk differs from that of adults. Behavioural factors, particularly sexual activity, increase the risk of HIV transmission among adolescents. Many young people in the region do not have the basic knowledge and skills to prevent themselves from becoming infected with HIV. Young people continue to have insufficient access to information, counselling, testing, condoms, harm-reduction strategies and treatment and care for sexually transmitted infections.

There is ample evidence that adolescents are engaging in sexual risk taking:



- On average one-third of first-born babies in the sub-Saharan African region are born to adolescent women.
- Half the women seeking abortion-care services in public hospitals are adolescent girls.
- Many girls continue to drop out of school because of unwanted pregnancies.

While boys tend to initiate sex earlier than girls, and rural youth are more likely to be sexually active than urban youth, girls are more vulnerable to heterosexual transmission of HIV than boys. Biological factors that put young women at risk include the immaturity of the cervix in adolescence. The single layer of columnar cells in the cervix is believed to be more vulnerable to the transmission of STIs, including HIV, than the multiple layers of squamous epithelial cells in the mature cervix. This, along with the gender imbalance that results in the inability to negotiate for safer sex practices, makes adolescent girls up to six times more vulnerable to HIV infection than their male counterparts in some communities.

Homosexuality is highly stigmatised and largely not acknowledged in sub-Saharan Africa; therefore, the extent to which it contributes to HIV infection among adolescents is largely unknown.

Adolescents involved in sex work, migrants and refugees, adolescents living on city streets or in war situations and adolescents who are marginalised and discriminated against are all especially vulnerable to HIV infection. Children orphaned by AIDS (of whom a large proportion is adolescents) are also more vulnerable, particularly to sexual exploitation, which is a significant risk factor for HIV transmission.

Cultural practices and expectations also put young people at risk of HIV. For example, in many African settings, a girl's status is recognised when she has a sexual relationship and demonstrates the ability to have a baby, and trans-generational sex is often an acceptable practice.

### Summary: Factors that increase vulnerability of adolescents to high-risk behaviours

- Personal factors, such as the lack of knowledge and skills required to protect oneself and others, early sexual debut, teenage pregnancy
- Factors pertaining to the quality and coverage of services, such as inaccessibility of services because of distance, cost and other factors
- Societal factors such as social and cultural norms, practices, beliefs and laws that stigmatise and disempower certain populations and act as barriers to essential HIV-prevention messages, e.g. early marriage.

These factors, alone or in combination, may create or exacerbate individual vulnerability and, as a result, collective vulnerability to HIV.

Source: Inter-Agency Task Team (IATT) on HIV and Young People (2008) Global Guidance Brief on HIV interventions for Most-at-risk Young People.

## HIV/AIDS services for young people

### HIV prevention services

No single strategy works best to prevent HIV transmission among young people. The best programmes have been built on multiple interventions. Interventions must target youth wherever they happen to be and at multiple levels: through policy, community (including schools, health services), and the media. They should aim at providing young people with youth-friendly information, counselling, life skills, commodities, and services for prevention and treatment of sexually transmitted infections (STIs) and HIV. Both formal and non-formal education curricula should contain non-stigmatizing information for both HIV-infected and non-infected adolescents.

HIV prevention efforts among sexually active youth should encourage youth to limit the number of sexual partners and promote secondary abstinence. Those who are sexually active need sexual and reproductive health services that include screening, treatment, and prevention of STIs as well as the use of PrEP where feasible. They should receive counselling, as well as guidance on the use of and a supply of condoms and contraceptives. They should get information about where they can access these services.

School-based interventions rely heavily on teachers – the trusted *gatekeepers* of information. Teachers are often expected to provide sexual and reproductive health education for their students, and they should be well equipped to undertake this task effectively, through a well designed and integrated programme for schools. Recent prevention research suggests that didactic, school-based interventions are effective at providing information but not at changing behaviour. A growing literature supports peer mentoring as an effective approach to health behavior change. Peer mentoring allows for the incorporation of skill-building activities; reinforcement of self-regulation activities; engagement in individual and group activities; and social support to meet personal health goals. Complete sexual abstinence is the most effective means of protection against both pregnancy and STIs including HIV infection. Messages of abstinence are particularly appropriate for younger youth who are not yet sexually active. Youth who want to defer sexual activity should get support to do so and be reassured that abstinence is a healthy life-style choice. They should learn how to overcome the pressure to become sexually active from their peers and mentors. Secondary sexual abstinence should also be encouraged in adolescents reporting sexual activity.

A study among young people perinatally infected with HIV in Uganda showed that most were either sexually active or anticipated being so in the near future. Programmes need to provide young people living with HIV (both sexually active and non-sexually active) information and services on prevention of unwanted pregnancies and about vertical transmission risk, as well as on how to use condoms, and how to avoid infecting their sexual partners with HIV and re-infecting themselves. These young people need to be counselled on when and how to disclose their HIV status to their partner before becoming sexually active.

For a number of years now, there has been growing evidence of the benefits of HIV treatment as a prevention (TasP) method. In 2011 a landmark study, HPTN 052, showed early initiation of antiretroviral treatment in people living with HIV with a CD4 count between 350 and 550, reduced HIV transmission to HIV-negative partners by 96%.

A number of follow-up studies since have also reported significant reductions in HIV transmission, with new infections averted as a result.

With the above evidence WHO now recommends that all HIV-infected people including adolescents be started on lifelong ART.

Pre-exposure prophylaxis (PrEP) uses antiretroviral drugs to protect HIV-negative people from HIV before potential exposure. Trials have shown that when taken consistently and correctly, PrEP is very effective.

PrEP, like TasP, potentially has population-wide benefits. However, if not taken routinely and consistently, PrEP is much less effective. It is important that PrEP is offered as part of a combination package of prevention initiatives, and does not replace other, more effective methods like condoms.

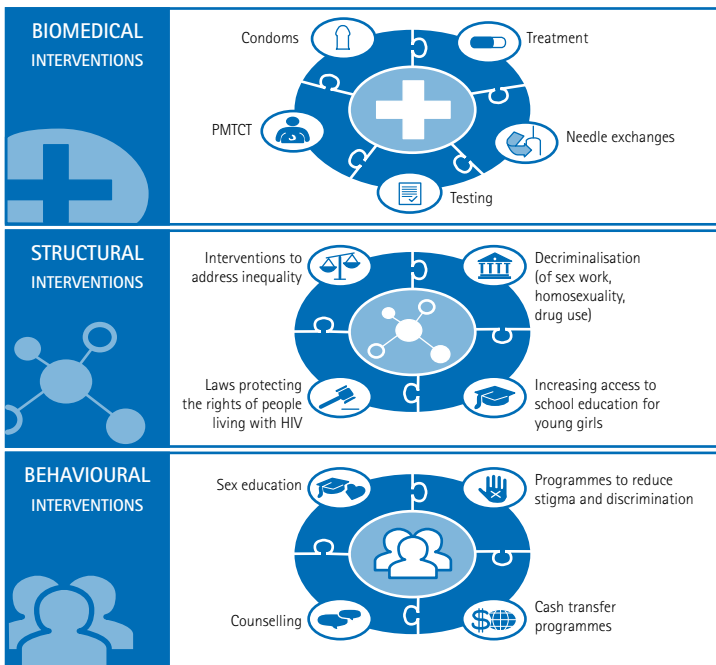
In 2015, the World Health Organization released new guidelines and a policy brief recommending that PrEP should be offered as a choice to people who are at substantial risk of HIV infection (see [Figure 9.3](#)).

### **Sexual and reproductive health (SRH) services**

A comprehensive *essential* package of sexual and reproductive health services for adolescents and young people at all primary healthcare facilities and other youth care service points includes:

- Information, education, and counselling on sexual and reproductive health
- Information on STIs, including information on the effective prevention of STIs, HIV diagnosis and syndromic management of STIs, as well as the importance of partner notification
- HIV/AIDS information, pre- and post-test counselling, and appropriate referral for voluntary testing, if services are not available on site
- Contraceptive information and counselling; provision of methods, including condoms, oral contraceptive pills, emergency contraception, and injectables

**Figure 9.3** Combination prevention strategies



- Information, counselling, and appropriate referral for violence/abuse and mental health problems
- Pregnancy testing and counselling; antenatal and postnatal care
- Referral for post-abortion care and post-abortion contraceptive counselling.

### *HIV counselling and testing for adolescents*

HIV counselling and testing services for adolescents must take into account the special needs of adolescents. In addition to knowing the legal requirements in the community, services should understand that the adolescent may be anxious and feel shy about being in the clinic,

embarrassed to be seeking services and worried that someone they know will see them.

Important characteristics for adolescent-friendly facilities include:

- **Privacy:** a space where counselling can take place without being seen or overheard and where the interaction is free from interruptions
- **Confidentiality:** the provider needs to reassure the client that all matters pertaining to the visit will not be shared with others
- **Respect:** the counsellor needs to recognize the dignity of the adolescent, their need to be treated as capable of making good decisions and their right to a professional response to any question they may ask.

Despite the desire of many adolescents to know their HIV status, some programmes and published guidelines discourage testing for this group. This is mainly associated with lack of policy on age of consent for testing adolescents which ranges from 12 to 18 years in different countries. The current models of voluntary counselling and testing (VCT) sites (free-standing, integrated, mobile/outreach, community, located in a youth centre) may not be appropriate for adolescents, especially the younger ones, whose cognitive development has yet to reach the point of linking current activities to future outcomes. Younger adolescents may not appreciate the seriousness of HIV disease and therefore may not go for care and treatment in a timely manner.

Counselling and testing services offered in the context of pregnancy care (as part of PMTCT) should extend to adolescents and their partners. This includes screening for STIs and HIV/STI prevention counselling. Young women are more likely to present for antenatal care later in pregnancy and less likely to deliver at a health facility or have a skilled birth attendant at delivery.

### Disclosing an HIV diagnosis to an adolescent

Disclosure of HIV status to adolescents presents challenges. It is preferable that a young person attending a sexual health service will have the support of a parent or of a guardian. Often, however, young people do not want their parents or caregivers to know about the medical consultation or its outcome.

An adolescent girl faced with a diagnosis of HIV during pregnancy may find it difficult to disclose her status to her partner (especially if he is older) or to her own parents or guardians.

It is important for health workers to discuss the value of parental or other support with the young person; at the same time, they should respect the young person's wishes, views, and confidentiality, should he or she not want parental involvement. Adolescents who are parents should be treated as adults.

Where there is possible child abuse, disclosure presents a greater challenge. If sexual abuse is suspected or ascertained, the clinician must support the young person and respect his/her views on disclosure.

Parents of vertically infected children may already know the child's HIV status. Frequently these children's caregivers may be too afraid to disclose this diagnosis to the adolescent for fear of being blamed or even rejected. Health workers should emphasise that disclosure is advantageous because it enables adolescents to begin to face and comprehend the issues surrounding their illness and care.

There is controversy about the age of disclosure, with some people advocating for disclosure as early as the age of 5–7 years, assuming that older adolescents may not be able to deal with it. Disclosure is a continuing process (not a one-time event) and is different for each family. A good cue for beginning the process is questions from the adolescent, although one should not necessarily wait for these. Providers should be alert to reactions or comments that may signal that the young person is not ready to hear the information. Typically the health worker's role is a supportive one, but in the absence of an

appropriate family member or at the request of the family, the health worker may have to assume the primary role.

When a health worker is required to take the lead role in disclosure, the following exploratory questions may launch the process:

- Why do you think you are coming to see the doctor?
- What is the blood test for?
- Why do you think you take medication?
- Do you have any questions you would like to ask me?

It is critical never to make any assumptions about what a child or adolescent does or does not know.

## Services for HIV-infected adolescents

HIV-infected adolescents need a variety of services, including clinical, psychological and social. **Table 9.2** shows the WHO-recommended minimum services that should be available to young people.

The setting and organization of services for HIV-infected adolescents needs to take into account the social context in which the youth are living and their stage of development. Chronically ill children who have growth and developmental delay of adolescence may feel comfortable receiving follow-up in a paediatric clinic setting. On the other hand, those who are already undergoing the changes of adolescence may feel they do not fit into the children's clinic even though they are not able to cope with the settings of the adult clinics.

HIV-infected youth are frequently marginalised and also have escalating health needs. Their survival will depend largely on their ability to communicate their needs and negotiate for services. Training in communication and negotiation will empower them to access services.

Ultimately, one of the most critical life skills will be their ability to take responsibility for their own health and HIV treatment. The health worker can help the adolescents achieve this objective by providing information about their treatment, communicating clearly about



follow-up, providing the opportunity for drop-in services between visits as and when desired, and developing a warm relationship with the adolescents that supports communication and disclosure of sensitive problems.

#### Fostering good communication with an adolescent

- Accept responsibility for leading the discussion of and reflection on any issues.
- Avoid giving advice or magic formulas.
- Respect the adolescent and encourage him/her in their ability to take responsibility for decisions.
- Consider each adolescent as an individual and take the time to understand him or her.
- Help the adolescent to examine his or her behaviour and to come up with the changes that he or she thinks are necessary.
- Accept the adolescent and avoid being judgemental.

Source: Adapted from Pathfinder, 2004

In most countries HIV-infected adolescents are now able to access ART. As such, many live longer and are well enough to begin engaging in intimate sexual relationships. Sexual health services should be broadened to include this group of adolescents, with added discussion of how HIV infection modifies such life choices as whether to get married or have a baby. WHO recommends a minimum package of care for adolescents and youth living with HIV ([Table 9.2](#)).

**Table 9.2** WHO Recommended minimum package of services for young client

#### Minimum package of services

##### HIV testing and counselling

##### Treatment for:

- OIs, including PCP, TB, and candidiasis
- Diarrhoea (ORS)
- Malaria
- Deworming

**Prophylaxis (primary/secondary) for:**

- OIs, including PCP and cryptococcus
- Malaria (IPT, mosquito nets), TB

**ARVs (first and second line)****PMTCT and antenatal care****Complete history and clinical examination**

- Including weight and height, Turner staging and neurodevelopment
- Look for STI signs and symptoms

**Sexual and reproductive health**

- Condoms/family planning including emergency contraception
- Pregnancy options and support
- Sex education

**Prevention with/for positives**

- Counselling for prevention
- Positive (healthy) living
- Family testing
- PEP and PrEP for negative partners
- Condoms

**Psychosocial counselling**

- Mental health screening and referral
- Adherence counselling
- Disclosure counselling
- Clinic-based peer support group
- Substance abuse counselling

**Nutrition counselling****Laboratory**

- Pregnancy
- Haemoglobin
- Syphilis
- Sputum/gene expert
- Blood slide for malaria
- CD4 lymphocyte count/ML test

### **IEC materials**

- Prevention
- Treatment literacy
- Disease literacy
- Living positively
- Existing legal rights (as they apply locally)

### **Effective referral system with follow-ups**

- Linkages with family, community, NGO services
- Linkages with other youth services
- Connections with legal institutions

### **Immunizations**

- Tetanus toxoid, human papilloma virus (HPV)

## **Prevention and management of OIs and antiretroviral treatment**

Adolescents diagnosed with HIV/AIDS need to receive the same care that is increasingly available to adults – including antiretroviral treatment. Clinicians should calculate the drug dosage for adolescents who have not yet achieved Tanner stage II (see [Appendix F](#)) as per the paediatric schedule; otherwise, they should be treated as adults.

Doses for drugs such as cotrimoxazole, and other antibiotics for the treatment of opportunistic infections (OIs), should be on a per/kg basis, until the adolescent is over 60 kg, when they would typically graduate to adult dosing guidelines.

All HIV infected adolescents should be started on ART irrespective of clinical or immunological stage of the disease.

### **Drug adherence**

Adherence to long-term therapy poses a special challenge in adolescents. This age group tends to have thoughts ranging from immortality to self-destruction. A multidisciplinary team could include clinicians, counsellors, nurses, social workers, and psychologists to address the needs of adolescents.

Among the factors affecting drug adherence among adolescents and that need attention are:

- **Peer pressure.** The desire to fit in with their HIV-uninfected peers, fear of accidental disclosure and having to explain medications and clinic visits may prevent adolescents from taking their medications and keeping up with visits.
- **Family and community related factors.** If the adolescents do not get adequate support for adherence from their families, they are unlikely to adhere well to their medications. Stigma from the community, including school, may also have an impact on drug adherence.
- **Becoming sexually mature.** Learning to manage sexual feelings is even more difficult for an HIV-infected adolescent. The temptation to stop medications may be especially strong when becoming sexually involved. It is critical for the health worker to discuss issues of disclosure to a potential partner and how to engage safely in sexual activity.
- **Active substance abuse** (alcohol, cocaine, heroin, etc.) makes it difficult to adhere to treatment. Alcohol use also increases the likelihood of serious side effects from some antiretroviral drugs. Clinic staff should screen and counsel youth on substance use and create an atmosphere that encourages disclosure of drug use.
- All adolescents should be screened for alcohol and drug use using the following three questions:
  - During the past 12 months, did you drink any alcohol (more than a few sips)?
  - During the past 12 months, did you smoke any marijuana?
  - During the past 12 months, did you use anything else to get high?Patients who answer yes to any of the questions above should undergo further assessment and management by a health provider experienced with managing alcohol and drug use disorders.
- **Depression.** Individuals who are depressed have little motivation for life's activities, including taking prescribed medications. All

ALHIV should receive a basic screening for depression using the following two questions:

- During the past month have you often been bothered by feeling down, depressed, or hopeless?
- During the past month have you often been bothered by little interest or pleasure in doing things?

Patients who answer yes to either of the questions should undergo further assessment and management by a health provider experienced with managing mental health problems.

Some strategies may improve adherence among adolescents:

- Help them to believe that they can take drugs as prescribed. This is the first step to successful antiretroviral drug adherence. It also improves adherence when they believe HIV medications will fit into their life-style. Help the adolescent adopt a positive attitude towards the medication.
- Before starting ARVs, help the adolescent to practice drug adherence by first ensuring that they take vitamin pills and cotrimoxazole prophylaxis well. Adherence with previous medication is well correlated with adherence to current medication. Encourage the adolescent to keep a diary and to note the reasons for not taking the drugs.
- Let the adolescents know that they should continue taking the drugs even if they are feeling well. Remind them that HIV is a chronic disease, that antiretroviral drugs (ARVs) are not a cure and that in order to continue to feel well they need to take the ARVs every day, as prescribed.
- Develop a good relationship with the adolescents and let them know you are their partner in striving for good health. A good relationship increases the likelihood that they will be adherent to prescribed drugs.
- Peer support groups. The support adolescents give each other when they meet regularly has been found to enhance adherence to ART. This prevents the adolescents from feeling isolated and gives them a chance to participate in interesting activities without fear of

discrimination or rejection, such as music, dance and drama, sports, art and crafts.

- Training in life skills. High self-esteem (self-confidence), communication, assertiveness and negotiation, using one's head before acting, dealing with emotions, and others, are life skills that help adolescents to cope with the tumultuous period of adolescence as well as coping with the demands of living with HIV/AIDS, including adhering to their ART. More details are outlined in the sections following.

### **Ongoing counselling and psychosocial care**

By the time they reach adolescence, many perinatally-infected children have the stigmata of chronic illness, including stunted growth and delayed development, as well as poor school performance because of frequent absences. They may be orphaned or live in a household with chronically ill parents. The delay in adolescent development often leads to poor self-esteem and a great sense of inadequacy.

Communities may ostracize adolescents orphaned by AIDS. Some of these sick youth are heads of households and have to fend for themselves and their younger siblings, as well as deal with issues of having to mature socially too soon. They face complex physical and psychosocial problems.

Effective counselling for adolescents should be culturally sensitive, tailored to their developmental needs, and in accordance with local values and laws.

Psychosocial care should revolve around disclosure of HIV status, family or partner notification, and understanding the disease and treatment modalities. Adolescents must be helped to cope with illness and death – their own as well as that of their parents.

### **Training in life skills**

Having life skills helps adolescents be confident, knowledgeable, and able to take responsibility for their lives.

As a first step, HIV-infected adolescents should be given information about their own bodies and the process of development, including why their growth might be slow and what can be expected with ARV therapy. The process should also include one-on-one or peer group discussions that help them to develop self-awareness, self-appreciation, and self-respect.

As family members die, the ability to build friendships and support networks will sustain adolescents. Spiritual development helps to build resilience for coping with difficult major life events, such as loss of family members.

Adolescents also need the skills to earn a living. Services should make every effort to keep the young person in school and to provide vocational training.

Health workers are not necessarily the best people to provide this training to HIV-infected children. By providing a meeting space in the clinic and inviting skilled individuals, healthcare workers can help facilitate the process and foster the formation of a forum where adolescents can get together and through which they can develop some of these skills.

## **The transition of adolescents from paediatric to adult care clinics**

In many parts of Africa, adolescents are cared for in paediatric care clinics or where child and adult care are integrated and they tend to be treated the way children are treated in those clinics. However, a time comes when they grow into adults and would therefore need to be cared for by adult physicians or to be seen in adult care settings.

The transition from paediatric to adult care is often not smooth and is ill defined. The following is recommended to make the transition less problematic:

- Ideally adolescents should be seen in an adolescent-specific clinic with services tailored to their needs.

- Where separate adolescent clinics are not possible, adolescent clinic days should be established and on these days the services are specific to their needs.
- Use participatory management, i.e. involve adolescents in planning for their services.
- Provide for and support adolescents in participating in peer support group activities
- Sexual and reproductive health services should be provided.
- Adolescent information should include the fact that at some point in their care they will move to adult care clinics.
- The adolescents should be empowered to take care of themselves rather than to rely on a caregiver.
- As the transition occurs, specific staff in the adult care clinics should be identified and assigned to handle the adolescents in transition.
- The adolescents who have successfully moved to adult clinics can offer peer support to the others in the process.

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# Chapter 10

## Communication, counselling and psychosocial support for HIV-infected children and their families

### Summary

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- Counselling aims to help the child and family cope with the many emotions that are caused by the presence of HIV/AIDS in the family.
- Various behavioural problems occur if the psychosocial needs of the child are not adequately and appropriately met.
- Communicating with children requires understanding their thoughts and feelings and responding in a way that is helpful.
- Children cope with disclosure of HIV test results as effectively as, if not better than, adults.
- Disclosure can start as early as 5–7 years of age, but it must be done gradually, in a culturally sensitive manner, and with the consent and participation of the child's parents or caregivers.
- Make every effort to link health care facility-based psychological care and counselling interventions with other social and spiritual support services outside the healthcare system.



## Introduction

A diagnosis of HIV infection in a child usually implies that other family members too may be living with HIV, although family members who have not yet been tested for HIV may not be aware of their status. A diagnosis of HIV may disrupt family balance by placing a 'dark cloud' over the family's future.

Many families affected by HIV are already burdened with poverty and other social issues. HIV can overwhelm a family's already weak coping capacity and push them into complete disorganization and crisis. More than one family member may be ill with HIV-related complications at the same time. This places added strain on the family; depleting economic reserves and increasing vulnerability to psychological stress and depression.

For the reasons outlined above, the HIV-infected child cannot be treated in isolation; care of the HIV-infected child must be family-centred and child-focused. A family-centred approach is crucial to strengthening the family's ability to cope with the child's illness and its consequences, and this necessitates delivery of comprehensive care to the family by a multidisciplinary team.

Counselling, psychological and social support are integral components of the holistic approach to caring for an HIV-infected child. This is a continuous process that usually begins at the first point of contact in the healthcare delivery system and continues through non-medical sector support services. Psycho-social issues must be addressed from the perspectives of the child, the caregiver and family, the healthcare provider, as well as other systems around the child that include schools. Psychological and social support for a child and his/her family allows them to build on their inner strengths and capacities to adopt a positive outlook in the presence of HIV infection and disease.

## Periods of psychosocial vulnerability

Psychological stresses are heightened at the time of initial diagnosis of HIV infection, during episodes of illness and during terminal illness.

### **At the time of diagnosis of HIV infection**

The family's response to the diagnosis of HIV infection in a child includes shock, fear, guilt, disbelief, anger and sadness. Due to the implications of the diagnosis and a wish to reverse the outcome, it is not unusual for parents to request repetition of diagnostic tests or to 'shop around' different healthcare services hoping to get a different diagnosis. Once the HIV status is accepted, families experience grief reactions as they mourn the loss of their hopes and dreams for the future, and some family members may develop depression that requires intervention.

### **During episodes of illness**

When a child living with HIV gets episodes of illness, parents struggle with feelings of helplessness, sadness and anger. It is during these episodes that the implications of the disease become an emotional reality and need for psychosocial support is paramount to address the loss reactions.

### **During terminal illness**

Dealing with terminal illness is one of the most challenging tasks in the care of HIV-infected children, and poses a real challenge to families, who have to watch a young loved one face the finality of death. During this time parents need assistance to ensure that their child receives dignified end-of-life care, either in a healthcare facility or at home. Even for healthcare workers, accepting the hard fact that a young life is coming to a premature end is a heart-breaking experience. While hospice care is fairly well understood and documented for adults, the same cannot be said for children, in whom this field is just beginning to unfold. For details on the care of the terminally ill child including psychosocial support, see **Chapter 12**.

### **Psychosocial assessment**

Psychosocial assessments that identify each family's strengths, coping abilities and vulnerabilities are an essential component of a comprehensive care package of services for an HIV-infected child. Such assessments help healthcare service provider teams to plan for

appropriate psychological and social interventions. An example of an assessment tool is provided in **Table 10.1**.

**Table 10.1** Psychosocial assessment for anticipated family adaptation

• The child and family's knowledge and reactions to the disease
• Beliefs, attitudes, and expectations regarding treatment and outcome
• Coping ability during previous crises
• History of depression and/or non-prescribed drug and alcohol use
• Nature and stability of residential and occupational arrangements
• Quality of relationships between family members and extended family members
• Who is aware of the diagnosis and what was their reaction?
• Socio-economic status of the family
• Socio-cultural factors or religious beliefs that might affect treatment decisions and adaptation
• History of previous losses
• Sources of emotional and financial support; availability of medical insurance, where applicable
• Health status of all family members

Source: Wiener L, Septimus A. Psychosocial consideration and support for the child and family. In: *Pediatric AIDS: the challenges of HIV infection in infants and children, and adolescents*. Pizzo PA, and Wilfert CM, (eds.) Williams and Wilkins. 1991.

### **Clinical presentation of a child with psychosocial problems**

A child at risk of developing psychosocial problems will present with the following:

- Emotional disorders, e.g. anxiety, depression, personality changes that may include mood swings, poor interpersonal relationships and poor impulse control
- Behavioural disorders, e.g. delinquency, disobedience
- Psychological disorders, e.g. depression, schizophrenia, and other forms of mental illness.

## Issues to address in providing psychological and social support to children affected by HIV

### Issues from an infected or affected child's perspective

HIV-infected children, and uninfected children from families where a member or members are HIV-infected, have to deal with many psychosocial issues, including:

- Dealing with the child's own chronic ill health, pain and discomfort
- Being different from other children
- Watching a parent battle chronic and/or terminal illness, and sometimes even assuming a care-giver role for sick parents
- Bereavement and its consequences, such as separation from close family members or change in socio-economic circumstances (having to leave school, having to do without basic necessities, having to get a job to make a living, having to look after younger siblings, or being homeless)
- Asking questions that are not adequately answered or getting evasive answers
- Having to take drugs daily.

### Issues from the caregiver's perspective

Regardless of how a child became infected, parents experience some degree of guilt. In sub-Saharan Africa where mother-to-child transmission is the main mode of HIV transmission in children, the mother, who is invariably the primary caregiver, is also HIV-infected. However, the primary caregiver may be someone other than the mother of the child. Psychological issues that caregivers will need to deal with include:

- Dealing with his or her own HIV diagnosis (in cases where the caregiver is one or both parents of the child)
- Dealing with the child's illness and the related feelings of guilt, anger, and hopelessness



- Deciding whether and/or what to share with the spouse, child, relatives, neighbours, or school authorities
- Fear of disclosure and the need to lie to others
- Reproductive desires and decisions in the face of HIV infection
- Time away from work (for frequent visits to health care facilities) and implications for job security and family earnings
- Concern about who will take care of the children in case of the caregiver's death
- Fear of his or her own death.

### Issues from the healthcare service provider's perspective

Healthcare service providers for HIV-infected children often find it challenging to address the children's psychological needs. Challenges include:

- Inadequate knowledge and skills to communicate effectively with, and provide appropriate counselling and psychological support to children and their families
- Inadequate knowledge of information that is appropriate for children at different developmental ages
- Lack of enough time to develop and nurture a relationship designed to make a child 'open up' and share his/her feelings
- Unavailability or lack of knowledge of referral options.
- Limited resource materials to guide health care providers, parents and teachers on offering psychosocial support to children and adolescents.
- Cultural and traditional factors of 'talking to' children but 'not with' children
- Limited knowledge of the needs of children.

## **Psychosocial needs of children**

All children need care, attention, security, love, nurturing, play, acceptance, a supportive home environment, and specific help to overcome their individual problems.

When children lose someone they love, they need simple and age-appropriate information about what has happened. They need to be listened to by someone who is prepared to answer the same questions several times. Most importantly, they need reassurance that they will be taken care of and loved.

## **Problems that can occur in HIV-infected/affected children**

Affected children may become aggressive, disruptive, and/or restless. Other common problems are bed-wetting, sleep disturbance, truancy, refusal to go to school, and bodily complaints with causes that may be difficult to ascertain (psychosomatic disorders). Depression and withdrawal are common and may often go unnoticed and/or untreated yet they pose long-term psychological effects on the lives of children.

## **Communicating with children**

Effective communication with children involves creative attempts at understanding the child's thoughts, feelings, concerns and responding to the child in a way that is helpful. There is a need to understand the cultural environment the child lives in because every culture has distinct ways of communicating, expressing feelings, and dealing with difficult circumstances – part of a child's social knowledge. Communication styles also vary according to social class, the environment in which the child has been brought up (urban versus rural), and the chronological and developmental age of the child.

Communicating effectively with children requires skills in listening, observing, and understanding their messages and responding appropriately. At least one person who is familiar with and normally cares for the child should be present. This is true for all children, especially young ones who often find it difficult to trust and communicate with someone they do not know well, or are not familiar with.

The different ways (media) of communicating with children include:

- Make-believe play
- Using stories and asking children to tell their stories
- Drawing pictures
- Music, dance and drama
- The children writing about their own experiences.

Children have many ways of communicating. They express themselves through play, drawing (sometimes even on the ground – soil/sand), making toys, and acting out situations through music, singing, dancing, and sometimes writing.

Play therapy is a powerful tool for young children to create a structure in which they can express and address feelings of fear, isolation, separation and abandonment. Playing while allowing children to talk freely can help build up their confidence.

Common themes that usually emerge through therapy include:

- Fear of others finding out their HIV status
- Fear of rejection (by family members, friends and peers)
- Concern about their parents' health
- Difficulties with talking openly with their parents about dying.
- Fear of death after HIV diagnosis
- Stigma and discrimination at family level and school
- Feelings of hopelessness for the future.

It is important to let children feel free to express themselves, using any methods or media that they may wish. Healthcare service providers and caregivers should be careful to avoid criticizing children about using any of these methods, for criticism may inhibit free expression. Acceptance attitude and treating each as an individual is very important while communicating and working with children. All children will continue to ask questions about a topic even after

explanations have been given to them; this holds for questions about disease as well. They deserve to be given correct answers, appropriate to their ability to understand and comprehend. A general rule is never to tell lies to children as this may lead to loss of trust when the child eventually finds out the truth.

### **Difficulties communicating with children**

There are many reasons why it is sometimes difficult for us to communicate effectively with children. One reason is that we do not encourage them to talk about themselves. For example, in a healthcare setting or even during home visits, we often get information about children through third parties, usually caregivers, even when the child is present and able to provide the same information. Another reason is that a child who does not know the caregiver well (a relative, for example) may find it quite difficult to talk about his or her own feelings. Cultural and traditional factors may also contribute to this difficulty in communicating. A girl who was raped, for example, may feel comfortable talking about this only to her grandmother or, in her absence, to an older woman, and not necessarily to the healthcare worker.

Other factors that tend to block communication with a child include: talking too much, being critical or judgmental, aggressiveness or bullying, laughing at or humiliating a child, getting upset or arguing, being uncomfortable or embarrassed when a child is upset, or not respecting the child's beliefs. A healthcare worker who behaves in this way may make it difficult for the child to trust him/her. The child may subsequently become suspicious, angry or hostile and more often than not fail to open up.

### **Issues regarding HIV testing for children**

HIV testing for children should follow national HIV testing and counselling guidelines, where these are available. Where national guidelines are not available, WHO guidelines can be used and will usually suffice. It is important to ensure that children's rights are respected as much as possible. Testing symptomatic children in order to provide appropriate care should be done on contact and in

consultation with the caregiver. Test results may not be disclosed to the child until such time as the child is old enough and ready to understand their meaning.

Always seek consent for testing from the parent or caregiver. But older children (about 10–12 years of age and above) should also give their consent (technically assent since are under 18 years and cannot consent), and then undergo pre-test counselling. They should know who will be involved in the testing process and who will receive the results. Sexually active children and adolescents who require (or request) HIV testing may withhold their consent for disclosure of test results to their parents or caregiver. However they should be counselled on the need to involve an important other person for support.

### **Disclosure of HIV status**

Studies from Uganda indicate that children who are informed of their HIV status cope with disclosure as effectively, if not better, than adults. Experience with counselling children about conditions not related to HIV indicates that children cope better when told of these conditions at an early rather than later age. It has been shown, for example (mainly in developed countries) that children who are told at an early age that they are living with foster parents develop fewer psychological problems than those who are told later and who grow up believing they were living with their biological parents. The age of disclosure of the diagnosis HIV infection to the child is dependent on the child's age and understanding. Messages about the diagnosis should be tailored to and given at different stages, ensuring that the messages are appropriate for age (critical to the ability of the child to understand the message). Disclosure of a child's HIV status can begin as early as 5–7 years of age, and is a process rather than a one-point exercise. This process may last varying periods of time depending on how ready the child and family are for complete disclosure. Disclosure should not be hurried; otherwise it may result in more harm than good.

## Who should disclose to children?

There are two approaches:

- Parents/guardians disclosing
- Healthcare provider disclosing.

Ideally, parents or caregivers should be the ones to disclose HIV test results to their children. However, most parents do not know how to go about this and how to handle the emotional reactions associated with disclosure. As such, healthcare workers need to support parents and empower them to disclose HIV test results to their children. Parents need to be helped to first come to terms with their own or the child's HIV status, before they are able to effectively and appropriately carry out the disclosure process.

Healthcare providers can also disclose to children but involvement of the parent/guardian is still important because they are expected to give continued support. This may be necessary because some children may feel that parents/guardians disclose in stories instead of telling them the truth and both children and parents/guardians may feel that disclosure of HIV status is a healthcare provider role because they are the ones who test. When this approach is taken it is still important for the healthcare worker to obtain a supportive role of the parents and care takers.

## Sharing results with others

Many parents worry about other family members or the public knowing the HIV status of their child, and will need support to help them understand the benefits of informing specific, selected people (close relatives or school teachers), who may be in a position to help the child or family in the absence of the parent/primary caregiver or in crisis situations.

## Child counselling

Counselling is intended to help the child and family cope with the emotions and challenges they experience as a result of HIV infection in the family. Such counselling helps HIV-infected patients, including children, adopt a positive-living attitude. This, in turn, can help them

prolong their life, improve their quality of life, and adhere better to ART and other related interventions.

### **Which child requires counselling?**

Basically, all HIV-infected/affected children require counselling. Methods for communicating with children vary with age, understanding/mental development and socio-economic circumstances. For example, a child who has never attended school may not be able to draw pictures as easily as a child who has attended school. Likewise, the younger the child is, the more likely he or she is to require presence of a mother or caregiver during counselling sessions.

### **The counselling process**

The counsellor should be familiar with the basic principles of counselling. These may be available in the form of national operational guidelines. The counselling process begins with the first contact with the child. This may be in a clinic setting when the child is brought in sick, at home during home visiting, or at school. It is common for a child to be accompanied by a parent or other family member. As a general rule, interaction with the child should take place in the presence of a parent and, when appropriate, with other family members or siblings, until the counsellor has gained the confidence and trust of both the child and the caregivers.

Another reason for having more than one family member present is that it enables the counsellor to observe the reactions and interactions of both child and family members. Older children can be counselled alone or with a family member present, whichever the child prefers.

Parents/caregivers should be continually informed and should participate in decision-making for, and planning of, appropriate care for their child, including where the child should be treated.

The counsellor must be sure to address the social needs of the child by arranging for and making appropriate referrals for socioeconomic and spiritual support.

### **At what age should counselling begin?**

There is limited evidence-based data on the appropriate age when child counselling should begin. However the information and support given to each child should be age-appropriate.

It is usual to begin the process of informing children about their HIV status when they are between 5 and 7 years old, depending on the child's ability to understand and on the parents' consent. This should be done gradually. Many parents may be afraid to disclose the HIV diagnosis to their child. It is therefore often necessary to counsel the parents first, to help them understand the importance of having the child know his or her status. See the section on disclosure above.

Carrying out discussions with children in the presence of parents or guardians ensures that the messages the children receive from counsellors and parents are consistent. Service providers should always endeavour to take the caregiver/parents' viewpoints into account, even when they do not necessarily match those of the providers, or child.

### **Steps for counselling HIV-infected children**

There are certain steps that can be followed as a basis for counselling HIV-infected children. These steps vary with the situation.

#### *A child with unknown HIV status presenting with clinical signs of HIV infection and/or risk factors such as mother or sibling living with HIV*

- Ascertain the child's and/or the mother's or the caregiver's understanding of HIV infection in general and, more specifically, of MTCT.
- Discuss the presumptive diagnosis of HIV infection in the light of existing signs, symptoms, and risk factors.
- Explain the benefits of early awareness of HIV infection in the child's life and for the family.
- Request permission for an HIV test to be performed on the child.
- If parents do not allow the child to be tested or they decide to postpone the HIV test, accept their decision and reassure them



that their refusal will not compromise the management of the child's current illness. However, impress upon the parents that this places the child at increased risk because appropriate treatment cannot be started without establishing a correct diagnosis. Ongoing counselling and support should be given because parents may later understand the need for the child to have an HIV test.

#### *A child known to be HIV-infected and already in care*

- Inform and support the child about living with HIV infection.
- Explain the benefits of seeking care, including antiretroviral therapy, and the fact that, with appropriate care, the child can live and grow into adulthood.
- Advise the child to follow instructions given by his or her service provider.

#### *Child known to be HIV-infected, on ART and responding poorly to treatment (see also Chapter 8 and Chapter 9)*

- Discuss the management of current problems and possible reasons for poor response to treatment.
- Discuss the dangers of poor adherence to treatment.
- Address any concerns with adherence.
- Refer the child for further investigations and/or community-based or home-based care programme, or a peer support group as necessary.
- Provide continuing psychosocial support and assist the family in coping with a chronic illness such as HIV.

#### *A child known to be HIV-infected and responding well to treatment*

- Discuss follow-up, care, and risk factors for future illnesses.
- Discuss shared confidentiality and the social well-being of the child and the family.

- Encourage continued adherence to treatment and ways of maintaining good adherence, e.g. having treatment buddies, joining a peer support group, and others.

## **On-going psychosocial support for HIV-infected children in care**

HIV-infected children need support to remain in care. The support may take the form of:

- Attending peer support group activities, where children share their experiences and support each other in coping with living with HIV. This is usually done through music, dance and drama, sports, testimonies and other activities carried out in support group meetings. Vocational training and skills building can be provided in these groups, especially to adolescents out of school.
- Building life skills: Children can be trained in life skills, such as developing self awareness and having high self esteem, coping with emotions, communication, assertiveness and negotiation, and appropriate decision making.
- Utilizing mobile phone technology to aid communication with children: Where possible important messages can be passed on to the children through short message services (SMS) e.g. reminders to take their medications, reminders about clinic appointments, and others.

## **Supporting HIV-negative siblings**

Non-infected children are certainly going to be affected by their sibling's or parent's HIV status and will become anxious about the former's illness or death. Parents may also forget and neglect non-infected siblings as they become absorbed in providing care to their infected child. Health workers should watch carefully for and help to relieve anxiety, depression, and/or school difficulties in non-infected siblings. The latter also need to be supported to develop life-skills, focusing on their reproductive health needs, including reducing risks of HIV infection as they grow up into adulthood.

## Bereavement counselling

When children lose a family member, attention must be paid to helping them and their families to move through this time with the least amount of suffering and as much support and dignity as possible. Open communication about what is happening should be encouraged among the children themselves, their parents, and health workers. All children in a family require continued counselling and psychological support after the death of a loved one. Parents and caregivers also need support for their emotional reaction toward a dying child. Using a specific medium like a 'Memory Book' is often useful for facilitating discussion about the child's family history and preparing for the future in the event of death of a close family member.

## Children whose parents are terminally ill

Children whose parents are terminally ill are affected in many ways and have a wide range of problems and needs:

- Psychological distress
- Anxiety about their security and safety
- Lack of parental nurturing
- Lack of basic social needs
- Loss of inheritance
- Need to work
- Less education and skills
- Mental health needs
- Emergency and long-term child care
- Bereavement and grief counselling.

Responding to a dying parent's needs will also address many of the child's immediate concerns, including reassurance that the child will receive care when the parent is no longer available. To appropriately respond to the needs of a child whose parent is dying, it is important

to understand how child developmental stages affect children's perception of death and dying (see [Table 10.2](#)).

**Table 10.2** Children's perceptions of death and possible interventions

Age	Perception of death	How to help the child
1–3 years	Equate death with sleeping and expect people who have died to eventually wake up. Fear separation from parent/caregiver	Keep the child's daily routine as unchanged as possible. Make time each day to hold, talk to, and comfort the child
3–4 years	Children this age do not accept death as final and think of it as a temporary separation. Children may believe that they are in some way responsible for the death because of powerful imaginations (magical thinking). Some may believe that perhaps, if they 'wish hard enough, the dead person will come back'	Explain clearly why the person died: 'died because she was not well. It had nothing to do with you, with something that you did or didn't do'
5–8 years	Begin to accept death as final and view it as separation from loved ones. They have a great fear of a sick parent dying, and of being abandoned. They worry about their own death	Reassure the child that minor illnesses and injuries can be treated Reassure the child that it is okay to cry, to feel angry, sad, or frightened when someone dies. Reassure them that they are not responsible for the death
8–10 years	Children learn that all living things must die; they begin to feel sorrow and loss. Interest in the mystery of death grows	Answer questions as fully as possible. Do not discourage normal curiosity about death. Acknowledge the child's feelings. Allow the child to cry and talk about the loss
9–11 years	React strongly to death. Interested in what happens after death Death is accepted as a part of life	Answer questions fully Acknowledge and explore the child's feelings Interventions may include: talking about memories; writing a daily journal; drawing pictures of how he or she feels; prayer; compiling a picture album of the loved one

*Adapted from: Manual. Maternal-Child HIV Training Course. AIDS Research and Family Care Clinic. Coast Province General Hospital, Mombasa, Kenya. August, 2001.*

Although the above observations are based largely on what is known about the child development in industrialized countries, there is every reason to assume that African children have comparable perceptions of death at the same ages.

The uninfected sibling of an HIV-infected and sick child may, similarly, have unmet psychosocial needs, as a result of the continuous attention demanded by the sick child. Secrecy and lack of communication may deter the child from asking questions. Resentment may occur because of feelings of deprivation and exclusion.

It is important for the family to set time aside for this sibling or siblings and to communicate what is happening, within the limit of each individual child's developmental stage and understanding.

### Knowledge gaps

- Age and culturally appropriate counselling approaches
- The short- and long-term effects of disclosure of HIV infection status to children at different ages.

### Recommended reading

Consult your national guidelines on counselling HIV-infected adults.

*Psychosocial Care and Counselling for HIV-infected Children and Adolescents – A Training Curriculum*. ANECCA. 2008.  
Available at [www.rcqhc.org](http://www.rcqhc.org) and [www.anecca.org](http://www.anecca.org)



# Chapter 11

## Nutrition and HIV

### Summary

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- Malnutrition is a significant cause of morbidity among children less than 5 years of age in Africa, and underlies 35% of childhood deaths.
- Breastfeeding increases the survival of HIV-infected children independently of whether they are on ART.
- In resource-constrained settings, early weaning to prevent late postnatal breastmilk transmission has been shown to be dangerous, associated with increased diarrhoea morbidity and mortality.
- New infant feeding guidelines protect breastfeeding for the HIV-exposed child and thus increase HIV-free survival through provision of antiretroviral drug treatment and/or prophylaxis for the mother or the infant throughout the breastfeeding period.
- HIV-exposed and -infected children have an increased vulnerability to malnutrition.
- Growth is a sensitive indicator of HIV disease and HIV disease progression in children.
- HIV infected children have energy requirements that are 10% above normal daily requirements, 30–40% if they have an opportunistic infection and 50–100% during periods of catch-up growth associated with nutritional recovery and ART initiation.
- Caregivers should ensure adequate nutrient intake based on locally available foods, provide universal (vitamin A) or targeted (iron, folate, zinc) micronutrient and mineral supplementation at the recommended daily allowance (RDA).
- Malnutrition in a child with HIV/AIDS is a multifaceted problem, requiring multiple interventions.





## Introduction

Failure to thrive is commonly the first indication of HIV infection. HIV-infected children in developing countries show a decline in length- and weight-for-age z-scores within the first months of life, and eventually show a picture of chronic malnutrition. High viral load in children is associated with increased risk of failure to thrive, while infections such as pneumonia, diarrhoea, and TB further exacerbate growth failure. Even in developed countries, where there is adequate food security, HIV-infected children show progressive loss of lean body mass, with relative preservation of subcutaneous fat tissues.

This chapter reviews the factors associated with increased vulnerability to malnutrition in HIV-exposed and -infected children and discusses strategies to prevent malnutrition, reduce postnatal transmission of HIV through breastmilk, and promote child growth, development, and survival in the context of HIV.

## Risk factors for malnutrition in HIV-exposed and -infected children

Childhood malnutrition is prevalent worldwide. In sub-Saharan Africa, approximately 1 in every 3 children less than 5 years of age is undernourished. Malnutrition increases a child's vulnerability to infection. It is estimated that malnutrition underlies 60% of all infectious disease morbidity. The case fatality rates for common childhood illnesses such as acute lower respiratory infection and diarrhoea are significantly higher in malnourished children. The co-existence of malnutrition and HIV further increases the risk of death from common childhood infections.

Factors that significantly increase the risk of malnutrition during childhood include low birth weight (LBW), household food insecurity, inappropriate feeding practices, repeated infections, and inadequate time set aside for infant feeding and child care. HIV-exposed and -infected children face many additional risks of malnutrition:

- **Increased basal requirements:** Infections and chronic illness are characterized by increased basal metabolic needs. Cytokine mediators of inflammation such as tumour necrosis factor (TNF)

alpha and cachetin alter metabolism and appetite, leading to weight loss. For children in Africa who are not on ART, the norm is frequent febrile episodes and back-to-back infections with high energy demands for repair, in addition to the normal requirements for growth and development.

- **Decreased intake due to oral disease or lack of appetite:** Repeated episodes of infection, oral candidiasis, dental problems, and medication contribute to loss of appetite and difficulty in eating.
- **Maternal malnutrition:** HIV-infected women have a higher prevalence of malnutrition compared to sero-negative women and therefore have an increased likelihood of delivering a low-birth-weight (LBW) baby.
- **Repeated infections:** Infants of women with advanced HIV disease receive reduced amounts of passive antibodies from their mothers during pregnancy, resulting in frequent episodes of infections that make them more vulnerable to malnutrition, even if the child is not HIV-infected.
- **Increased losses of nutrients:** HIV-infected children have an increased loss of nutrients when they experience episodes of vomiting, diarrhoea, and gastrointestinal bleeding secondary to mucosal ulcerations.
- **Malabsorption:** Changes in the integrity of the intestinal mucosal membrane may lead to malabsorption of macro- and micronutrients
- **Inappropriate or suboptimal infant feeding practices:** Abrupt weaning as well as poor quality and inappropriate replacement and complementary feeds provide fewer calories and poor nutritional value. In poor households, scarcity of nutritious foods also contributes to malnutrition.
- **Psychosocial factors:** In nearly all instances, paediatric HIV is a family diagnosis that exerts social, psychological, and economic stress on the family. Psychosocial problems contribute to suboptimal nutrition of HIV-infected patients. An unstable

family situation with inadequate emotional and social support is associated with poor growth in HIV-infected and -uninfected children, particularly orphans. Furthermore, the parents/guardians may be ill themselves and therefore unable to grow the food or unable to work and get funds to buy the food.

## Infant feeding practices in the context of HIV

Breastmilk is the ideal food for all infants from birth to 6 months of age and remains a major source of energy and nutrients beyond the first 6 months; it contains the correct balance of fat, protein, carbohydrates and water for optimal infant nutrition. Breastmilk also contains antibodies and other anti-infective factors. The protection provided by breastmilk against infections continues as long as the child is breastfed. Higher mortality, as well as a higher incidence of diarrhoea, has been found in infants who are not breastfed.

Breastfeeding, in the absence of ART, increases the incidence of HIV infection among exposed infants. There is a higher risk of HIV transmission through breastfeeding when women are newly infected with HIV during lactation (refer to [Chapter 3](#)).

Recent studies have shown that breastmilk transmission of HIV can be virtually eliminated by the use of antiretroviral drugs (ARVs) throughout the period of breastfeeding. Previously the only way to completely eliminate breastmilk transmission of HIV was to feed the infant from birth with suitable replacements for breastmilk, such as commercial infant formula. Recent evidence suggests that breastfeeding and effective ARV treatment or prophylaxis (NVP prophylaxis for the infant or triple ARVT for the mother) increases HIV-free survival of the infant. Further, early weaning to prevent late postnatal infection is not safe and is associated with the increased risk of mortality from diarrhoeal disease.

Infant feeding should be discussed at each clinic visit and appropriate counselling provided to the mother or caregiver to address her concerns and ensure that the child is getting adequate nutrition.

### Hygienic food preparation

Whatever feeding method is chosen, mothers and families should be counselled on proper food hygiene, including:

- Washing hands with soap and water before preparing food
- Washing the feeding and mixing utensils thoroughly or boiling them to sterilise them before preparing the food and feeding the infant
- Boiling water for preparing the child's food or drinks
- Avoiding storing milk or cooked food, or, if this is not possible, storing it in a refrigerator or a cool place and reheating thoroughly (until it bubbles) before giving it to the infant or using fermented milks such as sour milk, yoghurt and sour porridge
- Storing food and water in clean, covered container and protecting it from rodents, insects and other animals
- Keeping food preparation surfaces clean
- Washing fruits and vegetables with water that has been boiled, peeling them if possible and blanching them in hot water (to preserve nutrients).

### Safer breastfeeding

Efforts in the last few years have found several ways to make breastfeeding safer for HIV infected women:

- ART for all breastfeeding women: treatment reduces the viral load in breast milk and can reduce the risk of transmission to nearly zero.
- Exclusive breastfeeding for the first 6 months of life: giving only breastmilk and prescribed medicine (including CTX) but no water, other liquids or food to the infants for the first 6 months of life, WITH ARV prophylaxis for infant and ART for the mother (ARV interventions) during breastfeeding. WHO now recommends that a breastfeeding infant receive extended NVP prophylaxis or that the mother receive a three-drug ART regimen until one week after all breastfeeding has stopped (see Chapter 3).
- Good breastfeeding techniques, especially appropriate attachment for the infant, are important. Breastfeeding problems (cracked and sore nipples, mastitis, and breast abscesses) significantly increase the risk of transmitting HIV through the breastmilk.

## Infant feeding from 0–6 months

### Exclusive breastfeeding

Given the need to minimise the risk of HIV transmission to infants while at the same time avoiding increasing their risk of morbidity and mortality from other causes, WHO recommends either exclusive breastfeeding (EBF) with ARV prophylaxis for the infant and combination ART for the mother (ARV interventions) or avoidance of all breastfeeding.

Mixed feeding has been shown to be more risky for HIV transmission than exclusive breastfeeding, possibly because breast engorgement, which is more likely to occur with mixed feeding, causes subclinical mastitis, a condition that increases the viral load in breastmilk.

EBF is recommended during the 6 months of life and should then be complemented with supplementary foods. The 2010 WHO recommendations stated that *'breastfeeding should then only stop once a nutritionally adequate and safe diet without breastmilk can be provided'*. The WHO 2016 guidelines emphasize this and also add that breastfeeding could continue beyond 12 months as long as the mother is on ART. This is in circumstances where nutritionally adequate and safe supplementary feeds cannot be obtained.

### Replacement feeding

In the past replacement feeding has been offered as an option for the HIV-exposed child.

Recent studies have shown that infants of women with high CD4 count ( $CD4 > 350/mm^3$ ) have an increased risk of death, infections and hospitalization if they are not breastfed and HIV-free survival is further enhanced when the infant or the mother is on ARV prophylaxis.

Infants of women with advanced HIV disease ( $CD4 < 350/mm^3$ ) are at the highest risk of infection, with > 80% of all MTCT transmission of HIV taking place in this group of infants. Even when HIV-infected women with advanced disease initiate ARV treatment, replacement feeding is associated with an at least six-fold increased risk of death from diarrhoea and other infectious diseases.

Conditions that have been identified as necessary for safe replacement feeds are:

- Safe water and sanitation are assured at the household level and in the community, **and**
- The mother, or other caregiver can reliably provide sufficient infant formula milk to support normal growth and development of the infant, **and**
- The mother or caregiver can prepare replacement infant milk feeds cleanly and frequently enough so that these feeds are safe and carry a low risk of diarrhoea and malnutrition, **and**
- The mother or caregiver can, in the first 6 months, exclusively give infant formula milk, **and**
- The family is supportive of this practice, **and**
- The mother or caregiver can access healthcare that offers comprehensive child health services.

From 0–6 months, milk in some form is essential for an infant. A baby who is not breastfeeding will need about 150 ml of milk per kg of body weight per day. *Commercial infant formula* is an option for HIV-positive women when the family has reliable access to sufficient formula for at least six months. Feeding an infant for 6 months requires an average of 40 × 500 g tins (or 44 × 450 g tins) of formula. The family must also have the resources – water, fuel, utensils, skills, and time – to prepare formula correctly and hygienically.

The best way to give replacement feeding is to cup-feed. Replacement feeding is often a new way for a mother to feed a baby, and it should not be assumed that mothers know how to do it. Particular attention must be paid to hygiene, correct mixing, and the feeding method. Even in the best situation, feeding newborn babies with any food other than breastmilk increases the frequency of diarrhoeal disease and the family must make an effort to minimise this risk.

### Expressed then heat-treated breastmilk

This technique is recommended only as an interim feeding strategy to be used in conditions such as maternal or infant illness, and temporary interruption of maternal ARV because of the rebound viraemia. It requires expressing the milk from the breasts manually or with a pump, then heating it to kill HIV. While correct implementation of this strategy inactivates the HIV, it is often not a feasible solution for mothers. Cup-feeding is also recommended when using expressed and heat-treated breast milk.

### Infant feeding after 6 months of age

After the age of 6 months, breast milk and other forms of milk alone are not adequate to meet a baby's nutritional requirements. Thereafter, for both breastfed and replacement-fed infants, complementary foods, should be introduced.

Milk should continue to be an important component of the diet, providing up to one-half or more of the nutritional requirements between the ages of 6 and 12 months and up to a one-third of the requirements between the ages of 12 and 24 months.

In addition, complementary foods made from appropriately prepared and nutrient-enriched family foods should be given three times per day up to the age of 9 months; between 9 and 12 months, four feeds should be given daily; thereafter, five feeds per day.

If there is animal protein in the diet the baby will need at least 250 ml of milk per day and if there is no animal protein, the infant needs 500 ml of milk per day. Thus, continued breastfeeding is key to ensuring continuing good health of the infant.

The HIV-exposed but uninfected child can be weaned after one year, once they are assured adequate nutritional intake from the family pot. If a nutritious diet is not assured the mother should be supported to continue breastfeeding under cover of a triple ART regimen (see **Chapters 3** and **8**). Weaning should be done gradually over a one month period.

## Growth monitoring, dietary assessment and nutritional supplementation

Growth and development monitoring and promotion are critical child survival strategies in resource-poor settings. Growth is a sensitive indicator of HIV disease and disease progression in children. Poor growth has been shown to precede CD4 decline and the development of OIs.

HIV-infected children have higher energy requirements than non-infected children: an additional 10% for asymptomatic children, 30–50% for symptomatic children, and up to 100% for symptomatic children experiencing weight loss or having severe malnutrition.

### Growth monitoring

Health workers can provide support for families through careful growth monitoring and regular nutritional assessments. All health facilities should have equipment to accurately monitor growth. A discussion with the caregiver of how to use the available tools and a discussion of the child's weight and height measurements are critical components of every visit. A simple growth chart is an excellent tool for the primary care worker. All health workers must be carefully trained in the importance of, and the techniques for, accurate measurement of height/length, weight, and head circumference and the interpretation of these measurements. All health facilities should have an infant scale and workers should carefully plot measurements on the growth monitoring child health card. See [Appendix E](#) for instructions on weighing infants and children.

Growth monitoring begins with measuring and carefully charting weight, length, and head circumference on child health cards. WHO has introduced growth standards and tools for monitoring child growth (available at [www.who.int/childgrowth/training/en](http://www.who.int/childgrowth/training/en)). At the community level, the simple-to-use mid-upper-arm circumference (MUAC) tape method can be used.



Subsequent measurements include weight, height, head circumference, triceps skin-fold thickness (SFT), and mid-upper arm circumference (MUAC). However, weight is the optimal nutritional indicator because it is a composite measure of the different nutritional changes.

The growth charts (**Figure 11.1**) show typical patterns of weight gain and growth faltering that may be seen using the child health cards.

**Figure 11.1** A weight for age growth chart

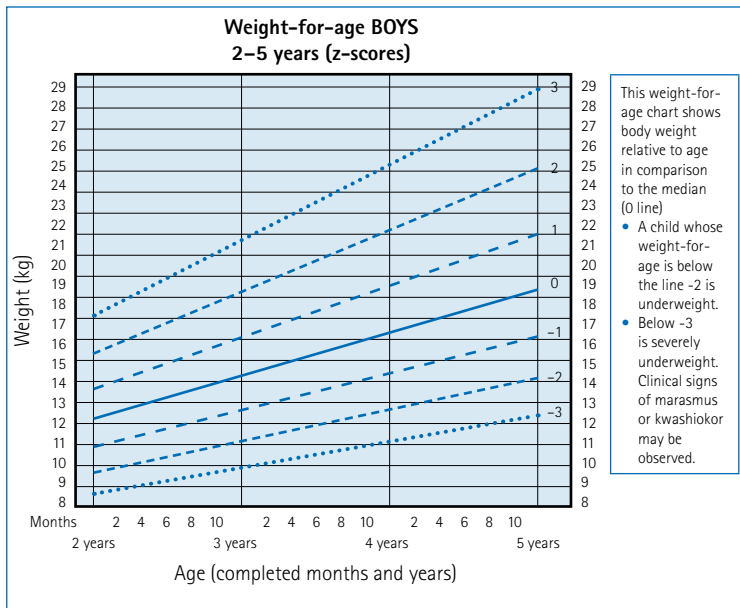
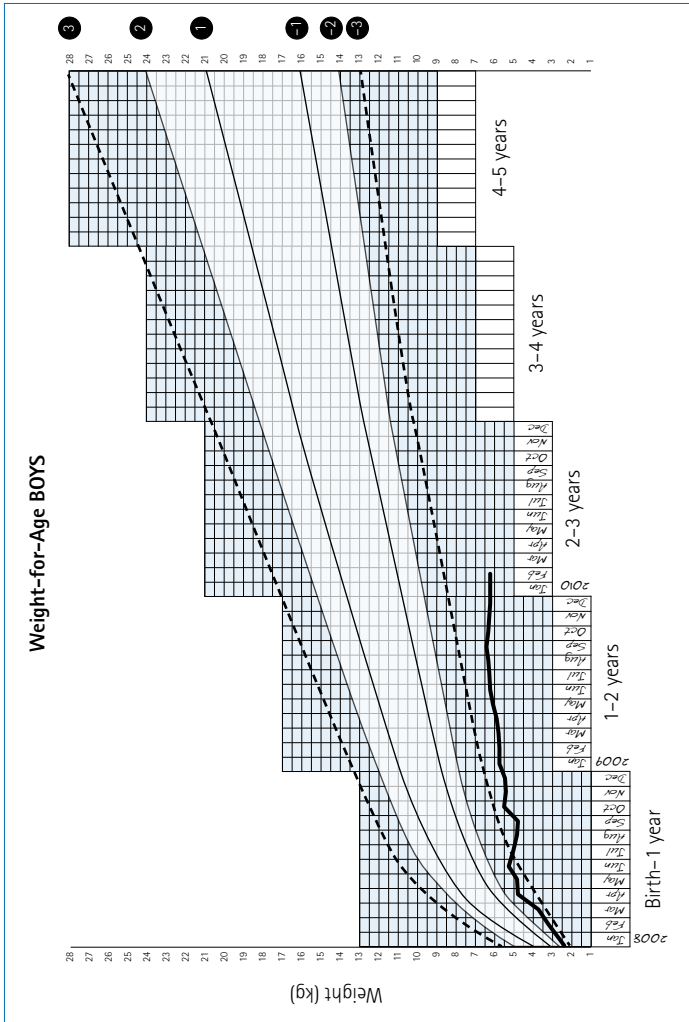


Figure 11.2 Growth chart showing growth faltering



### Nutritional support strategies to promote good nutrition and prevent malnutrition

- Provide accurate information and skilled support to mothers and caregivers for feeding infants and young children.
- Ensure the good health of the mother and other caregivers.
- Ensure adequate nutrient intake based on locally available foods.
- Provide vitamin A supplementation according to national guidelines.
- Emphasize good hygienic practices.

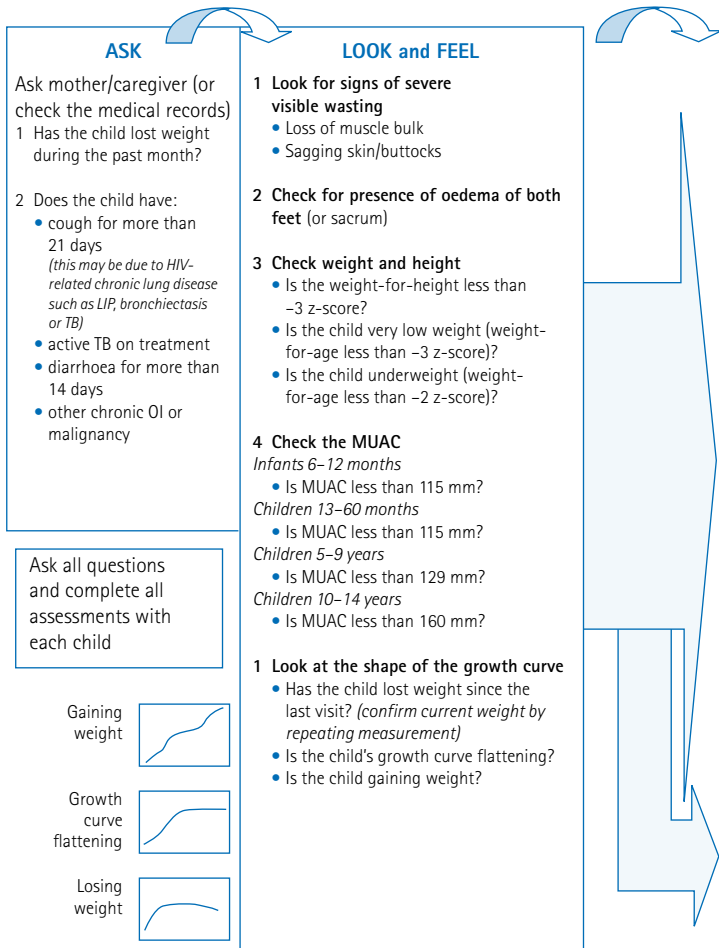
### Nutritional assessment

During an infant's first year, nutritional assessments should be carried out every month in keeping with recommendations for all children. Thereafter, nutritional assessments should be carried out every 3 months (or monthly if there is altered nutritional status). Dietary history and feeding practices should be carefully elicited, including other nutrition-related problems (poor appetite, chewing, swallowing, intolerance or aversion, food taboos, and history of nutritional supplementation). **Figures 11.1** and **11.2** show anthropometric cut offs that reflect good nutritional status and different levels of malnutrition.

### Nutritional supplementation

Children require energy for growth, physical activity, basal metabolism and heat production. The energy requirements vary depending on the age and activity of the child (See **Table 11.1**). The average requirement for the first year is about 80–120 kcal/kg and decreases in the subsequent years with increasing requirements during adolescence.

Figure 11.3 Nutritional assessment of an HIV-infected child



SIGNS	CLASSIFY AS	TREAT
Signs of severe visible wasting, or oedema present in both feet, or weight-for-height less than $-3$ z-score, or MUAC less than: <ul style="list-style-type: none"> <li>• 115 mm in infants <i>6–12 months</i></li> <li>• 115 mm in children <i>13–60 months</i></li> <li>• 129 mm in children <i>5–9 years</i></li> <li>• 160 mm in children <i>10–14 years</i></li> </ul>	SEVERE MALNUTRITION	NUTRITION CARE PLAN C
Reported weight loss, or very low weight (weight-for-age less than $-3$ z-score), or underweight (weight-for-age less than $-2$ z-score), or confirmed weight loss ( $> 5\%$ ) since the last visit, or growth curve flattening	POOR WEIGHT GAIN	NUTRITION CARE PLAN B
Child is gaining weight	GROWING APPROPRIATELY	NUTRITION CARE PLAN A
Chronic lung disease, or TB, or persistent diarrhoea, or other chronic OI or malignancy	CONDITION WITH INCREASED NUTRITIONAL NEEDS	NUTRITION CARE PLAN B

**Table 11.1** Recommended food helpings for adults and children

	Adults and adolescents*	6–11 years
Grain group	5–11 servings	6 servings
Vegetables	3–5 servings	3 servings
Fruits	2–4 servings	2 servings
Meat, beans, fish, peas, nuts, and seed	2–3 servings	2 servings
Milk, yoghurt and cheese group	3–5 servings	2 servings
Fats and oils, sweets/sugar	Use sparingly	Use to increase energy content of diet

NB: 1 serving = 1 whole fruit, 125 ml of juice, 1 egg, 30 g of meat, 150 g of fish, 1 cup (200 ml) of cooked rice or ugali, 1 chapatti, 1 slice of bread, 1 medium potato, 1 medium glass of milk, 1 cup leafy green vegetables, ½ cup cooked vegetables, ½ cup cooked legumes (peas, beans), 2 tablespoonfuls of nuts, etc.

\*200 ml cup/glass

Ideally these meals should be packaged into three main meals and two snacks.

HIV-infected children have often been shown to be deficient in two essential micronutrients, vitamin A and zinc. Caregivers should ensure adequate nutrient intake based on locally available foods and provide universal (vitamin A) or targeted (iron, folate, zinc) micronutrient and mineral supplementation.

Early nutritional supplementation in HIV-infected children and adults helps to preserve lean body mass (LBM) and slows disease progression. Healthcare providers should not wait until there are signs of malnutrition to support nutrition in HIV-infected children. Multivitamin supplements that include zinc are recommended daily. Give vitamin A according to national guidelines or following the International Vitamin A Consultative Group recommendation of three 50 000 IU doses of vitamin A, to be given at the same time as infant vaccines during the first 6 months of life. WHO also recommends iron supplements for HIV-infected children.

## Other nutritional interventions

- Presumptive de-worming of the child every 6 months starting at 6–9 months of age.
- An extra meal per day after episodes of illness to allow for catch-up growth (see WHO Integrated Management of Childhood illness (IMCI) guidelines).
- All households should use iodized salt.

## Nutritional management and rehabilitation

When growth curves begin to slow or the potential for malnourishment is recognized, health workers should take immediate action, particularly for HIV-exposed or infected children. Malnutrition in an infected child can hasten CD4 decline. The question, ‘Has anyone in your household involuntarily missed a meal in the past week?’, is a very sensitive indicator of household food security.

Strategies for preventing malnutrition in HIV-exposed and -infected children require an integrated approach that addresses maternal and child health and prevention and care (see [Table 11.2](#)).

**Table 11.2** Strategies to prevent and treat malnutrition in HIV-exposed and HIV-infected children

Strategy	Action
<b>Prevent low birth weight</b>	<ul style="list-style-type: none"><li>• Prevent maternal ill health and malnutrition</li><li>• Provide nutrition counselling to improve food intake</li><li>• Monitor maternal weight gain during pregnancy</li><li>• Screen for maternal anaemia, provide antihelminthic treatment</li><li>• Provide micronutrient (iron and folate) and multivitamin supplements</li><li>• Prevent and promptly treat infections in pregnant women, malaria, urinary tract infections, STIs, PCP, TB)</li><li>• Manage complications of pregnancy (hypertension and diabetes)</li></ul>
<b>Prevent mother-to-child transmission of HIV</b>	<ul style="list-style-type: none"><li>• Adopt a comprehensive approach to PMTCT, including integrating PMTCT services into maternal and child health services for HIV-infected mothers who are already pregnant (see <a href="#">Chapter 3</a>)</li></ul>

Strategy	Action
<b>Institute appropriate infant feeding practices</b>	<ul style="list-style-type: none"> <li>• Counsel mothers on the benefits of exclusive breastfeeding for 6 months and introducing complementary feeding thereafter</li> <li>• Support mothers in their choice of feeding</li> <li>• Support timely institution of appropriate complementary food</li> </ul>
<b>Prevent common childhood infections</b>	<ul style="list-style-type: none"> <li>• Immunize against common childhood infections</li> <li>• Institute CTX prophylaxis to prevent invasive bacterial infections</li> <li>• Provide health education and counselling on hygiene practices at household level</li> <li>• Provide vitamin A supplementation according to the national schedule</li> <li>• Ensure safe water supply, hygiene and sanitation in the household</li> </ul>
<b>Ensure prompt and appropriate treatment of infections</b>	<ul style="list-style-type: none"> <li>• Empower families by training them to recognise illness in the baby and improving their health-seeking behaviour</li> <li>• Teach mothers to increase frequency of feeding after episodes of illness to allow for catch-up growth</li> <li>• Train primary-level health workers to manage common childhood infections (IMCI) and to suspect and manage HIV-related conditions</li> </ul>
<b>Monitor growth</b>	<ul style="list-style-type: none"> <li>• Weigh the child regularly and plot the weight on a growth chart</li> <li>• Detect and address early growth faltering</li> </ul>
<b>Provide micronutrient and food supplementation</b>	<ul style="list-style-type: none"> <li>• Provide vitamin A supplementation according to national guidelines</li> <li>• Provide multivitamin and iron supplementation if no contraindications</li> </ul>
<b>Encourage family planning and child spacing</b>	<ul style="list-style-type: none"> <li>• Promote family planning and child spacing to ensure maternal nutritional recovery between births and optimal child care practices</li> </ul>
<b>Provide antiretroviral treatment (ART)</b>	<ul style="list-style-type: none"> <li>• Advocate, promote, and implement ART for children. Strategies to facilitate equitable ART access for children include early diagnosis, subsidies, family models of care, children-dedicated clinics (hours, space, and/or personnel), and training of health workers to demystify paediatric ART</li> </ul>



If there is evidence of malnutrition, evaluate the following:

- Ongoing losses
- Nutrient intake
- Physical examination to look for evidence of thrush or oral ulcers, gastrointestinal bleeding, oedema, and signs of systemic infections
- Laboratory investigations that include a complete blood count, liver function tests, stools and urine microscopy, as well as culture and sensitivity, and chest X-ray to look for evidence of TB. In more sophisticated centres, clinicians may perform pancreatic enzyme levels, upper GI series, and endoscopy.

For children with moderate and severe forms of malnutrition, nutritional rehabilitation is necessary (see [Tables 11.3](#) and [11.4](#) and also [Chapter 6](#)).

**Table 11.3** Nutritional management for children with and without evidence of malnutrition

Nutrition management of child with <i>no</i> evidence of malnutrition	Nutrition management of child with evidence of malnutrition
<ul style="list-style-type: none"><li>• Provide nutritional counselling and education, with an emphasis on the increasing nutrient needs with growth and chronic illness</li><li>• Care providers should give advice based on locally available and affordable foods</li><li>• Encourage families to maintain kitchen gardens to supplement the family's needs</li></ul>	<ul style="list-style-type: none"><li>• As a general rule, early nutritional interventions are more effective than later interventions.</li><li>• Initially try oral nutrition therapies</li><li>• Increase caloric density of foods that are familiar to the child by adding a high-fat supplement (cooking oil, butter, or margarine)</li><li>• Treat underlying infection</li><li>• Initiate nutritional counselling and care and more intensive follow-up (initially 2-weekly and then monthly)</li></ul>

**Table 11.4** Examples of food portions that can be used to increase energy content of diet for children of different ages.

	HIV-infected child who is growing well	HIV-infected child who is growing poorly or has conditions that increase nutrient requirements
Additional nutritional requirement on top of normal requirements	10% increased energy requirement	30–40% increased energy requirement
6–11 months	1–2 spoonfuls of margarine or 1–2 spoonfuls sugar added to porridge (once a day)	2 spoonfuls margarine/oil and 1–2 spoonfuls sugar to porridge. Aim to add 3 times daily
12–23 months	1–2 spoonfuls of margarine or 1–2 spoonfuls sugar added to porridge (once a day)	Extra cup of full cream milk or cheese/peanut butter sandwich (1 slice)
2–5 years	Extra cup of full cream milk/fermented milk in addition to the normal diet	Extra cup of enriched milk or cheese/peanut butter sandwich (4 slices)
6–11 years	Extra cup of full cream milk/fermented milk in addition to the normal diet	Extra cup of enriched milk or cheese/peanut butter sandwich (6 slices)
12–14 years	Extra cup of fruit yoghurt or cheese/peanut butter sandwich in addition to the normal diet	3 cheese/peanut butter/egg sandwiches (6 slices)

### Antiretroviral treatment and nutrition in children

Access to antiretroviral treatment (ART) for African children has increased rapidly since 2004. A full nutritional assessment should be done before ART is initiated (see [Chapter 8](#)). ART sometimes causes nausea and vomiting, which can subside in a few weeks. ART also can increase appetite, so counselling of the caretaker should include a review of food availability and good nutrition. The use of ready-to-use-foods (RUTF), such as PlumpyNut® or others should be considered,

where available, to improve ART effectiveness and adherence. Older children and adolescents may not tolerate PlumpyNut® and other forms of highly nutritious foods should be considered.

## **Psychosocial and mental healthcare for depression and emotional problems**

Although all HIV-infected children are susceptible to severe forms of malnutrition, studies have found a differentially greater impact on orphans who also often suffer poverty, have psychological and emotional problems, and suffer from inadequate childcare practices that contribute to the malnutrition. Make appropriate links with social welfare services and to community-based groups for the continued support of OVC (see [Chapter 10](#)).

It is important to identify children who have mental health problem, such as depression, and who need specific mental health care. When there is doubt as to the mental well-being of a child, the child should be referred to the most experienced person on the team or to the closest mental health service, whichever is easier.

## **Long-term solutions needed for vulnerable communities**

Malnutrition in a person with HIV/AIDS is a multifaceted problem requiring multiple interventions—both short-term and long-term—applied simultaneously, to break the vicious cycle of malnutrition: depressed immunity, infections, and malnutrition. In particular, links to community and social services are required to address household food insecurity and other issues.

## **Knowledge gaps**

- Little is known about the impact of micronutrient deficiencies on the natural history of HIV/AIDS among children.
- What are the daily RDA macro- and micro-requirements of HIV-infected children?
- What is the role of commercial food supplements in resource-poor settings (as these are currently diverting meagre resources from desperate families)?

- What is the impact of ARV treatment on the growth of HIV infected children? Will they have catch-up growth? What do they need to ensure that they grow well?

## Recommended and additional reading

Miller T. Nutritional aspects of pediatric HIV infection. In: Walker WA, and JB Watkins. *Nutrition in Pediatrics*. London: BC Decker Inc. Second edition, 1997.

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# Chapter 12

## Long-term care for children infected with HIV/AIDS and their families

### Summary

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- Advances in HIV care, and availability of antiretroviral therapy have improved survival among HIV-infected children.
- HIV/AIDS is a chronic illness and health providers need to be familiar with the principles of long term management.
- Essential holistic care for HIV-infected children includes palliative care encompassing control of pain and other symptoms and care of the terminally ill child.



## Introduction

Antiretroviral therapy has already revolutionized paediatric HIV care, resulting in improved survival of infected children, even in resource-limited settings. Chronic disease management has therefore become as necessary for these children as it is for adults. HIV is now a chronic illness whose outcome depends on efficient long term care. Management of chronic illness differs from management of acute illness in many ways. Not only does chronic illness require ongoing treatment and support, but it also requires far more engagement and participation of clients and community. In this chapter the essential elements of good chronic illness care are introduced.

When identified early and started on ART, HIV-infected children will live a normal life largely free of HIV-associated symptoms. However, health workers may from time to time encounter symptomatic HIV-infected children, probably because they have been identified late or they are failing on treatment or have side effects of ARVs. These children need symptomatic relief. The most effective way to manage symptoms is to treat the cause. However, symptom management has a major role in ensuring quality of life. In any case, not all symptoms have clear treatable causes.

HIV still has no cure and health workers need to be able to provide end-of-life care for children who are terminally ill. Palliative care, including both symptom management and end-of-life care is discussed in this chapter.

## Long-term care

All chronic illnesses need appropriate long-term care. Critical factors in effective long-term management of HIV-infected children include leadership and governance, knowledgeable personnel, a functional health infrastructure, access to essential drugs and supplies, early and active communication and involvement with parents/guardians, community-level support structures, and ongoing efforts to support caregivers.

## **National programmes**

National programmes need to be responsible for planning and coordination of the HIV response through strategic policy frameworks and structures to ensure effective oversight.

Policies and guidelines need to facilitate quality long-term care and treatment.

## **Personnel**

Adequate numbers of health workers are required, who are knowledgeable and skilled in a range of HIV-care needs, including terminal care and symptom relief, and who understand the basic principles of managing chronic disease, are critical for effective long-term care planning.

## **A functional health infrastructure**

Basic HIV diagnostics and clinical care requires functional health systems with communication channels and referral relationships among care providers, hospital departments, other agencies and communities.

## **A functional information management system**

Written information is essential for tracking the patient through different services and monitoring and documenting disease progression: registers, patient files, treatment notes, hand-carried patient cards with identifying number, and a treatment plan. To ensure data accuracy and quality, capacity-building and supporting use of data for decision-making need to be prioritized. Technological advances provide an opportunity for improving data access, quality and use. National programmes need to expand the use of electronic medical records and other technologies such as mobile technologies for patient follow-up, data analysis and management

## **Access to essential drugs and supplies**

This is required for providing comprehensive care and services for children and their families. Commodities that support diagnosis,



treatment and monitoring of treatment outcomes are required in adequate quantities, desired quality and in a timely manner.

### **Early and active communication and involvement with parents/guardians**

Communication with the child and parents or guardians is a critical component of care. It should include making care plans that include the preferred place of care, including terminal care, where appropriate. This is a long-term process and it varies with the child's developmental age. Supporting structures need to be in place including age, population and culturally appropriate information, communication and education materials

### **Community-level support structures**

Structures such as self-help groups are important in long-term care. Examples of skills building and services provided by such groups include:

- Community feeding centres for vulnerable children
- Community revolving funds for economic empowerment activities.
- Building memories through deliberately planned activities with the child and family; these are important for a dying child and family members
- Other options are documenting family experiences through diaries, albums, video footage – within the family's resources (for example, the memory book/box and the HIV/AIDS quilt).

### **Support for caregivers**

There must be continuing efforts to support caregivers by providing them with information, education, counselling, referrals and skills building through community/home-based care providers, outreach workers, and institution-based counsellors and clinical care providers.

### **The clinician's role in long-term care planning**

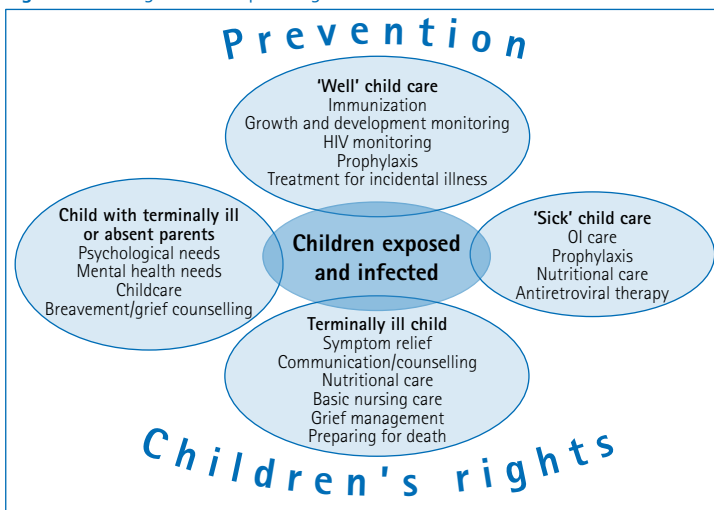
The clinician's role in long-term care planning includes being a:

- Facilitator/catalyst of the process by mobilising a care team (in many settings this team is limited in skills, skill sets, and number)

- Team leader, a monitor of the care plan
- Advocate for the child's rights
- Person to mobilise community and external resources to improve paediatric HIV care
- Liaison between child and parents and facility and community based healthcare workers, and other service providers

Figure 12.1 shows a framework for long term planning for HIV exposed and infected children.

Figure 12.1 Long-term care planning for children with HIV



This handbook covers many of the needs highlighted above in detail in other chapters.

## Palliative care

The earlier definition of palliative care stressed its relevance to patients not responsive to curative therapy. Over time this has changed and the principles of palliative care should be applied early

in any chronic disease since the problems at the end of life have their origins early in the disease. Palliative care also goes beyond the patient and includes considerations for the well being of family members. Relief of symptoms in the child undoubtedly relieves a lot of stress to the mother and other family members. The WHO definition of palliative care appropriate for children and their families is as follows:

- Palliative care for children is the active total care of the child's body, mind and spirit and also involves giving support to the family.
- It begins when illness is diagnosed and continues regardless of whether or not a child receives treatment directed at the disease.
- Health providers must evaluate and alleviate a child's physical, psychological and social distress.
- Effective palliative care requires a broad multidisciplinary approach that includes the family and makes use of available community resources; it can be successfully implemented even if resources are limited.
- It can be provided in terminal care facilities, in community health centres and even in children's homes.

### Symptom relief

Symptoms are a major cause of discomfort and poor quality of life during the course of HIV infection and AIDS in children. Pain management is a major focus of palliative care. Unfortunately, many health workers treat children (especially young ones) as if they do not suffer from pain. Chronic cough and severe pruritic and disfiguring skin disorders are particularly problematic for older children who are attending school because the symptoms are highly visible and both teachers and pupils are concerned about contagion. Many of these HIV-related symptoms can be prevented, treated, or controlled with basic medications and therapies. Symptoms should be managed during acute and chronic illness.

Non-pharmacological methods are an important adjuvant to symptom management with medications (or can be used alone). They include

distraction methods, massage, aromatherapy, and more traditional therapies, which vary from place to place.

It is important to try to identify the cause of symptoms, to the extent possible, without adversely affecting the quality of the child's life and within the limits of available resources, especially if the causes might alter management. However, empiric and symptomatic treatment should not be withheld while doing a diagnostic workup or in situations where the underlying diagnosis cannot be established. Also, health workers should try to anticipate and prevent symptoms, when possible (e.g. pressure sores).

### **Pain management**

Pain as a symptom takes on special significance in children because it is very common and is often under-diagnosed and under-treated, even when effective and inexpensive medications are available. A rational approach to pain management includes the following:

- Assessment (history and physical examination to elicit potential causes and type of pain)
- Classification (is the pain mild, moderate, or severe?)
- Treatment (depending on likely cause, type, and severity of pain)
- Reassessment to ensure that optimal pain management is achieved and maintained.

### **Assessment**

Assessment and classification of pain in children is different from that in adults and depends on the age of the child and the stage of development. There are several ways to assess pain in children:

- Interviewing the older children
- Interviewing the caregiver. (Younger children in particular need adults to recognise and respond to their pain.)
- Observation.

By using a combination of these methods, observe and document the following:

- Listlessness/lack of interest
- Irritability, crying, wincing
- Not wanting to move (pseudoparesis)
- Changes in mood
- Change in sleep pattern
- Poor appetite
- Loss/lack of concentration
- Loss/lack of interest (for example, in play).

Other common symptoms of HIV disease in children and their management are summarized in **Table 12.1**.

**Table 12.1** Some common symptoms of HIV disease in children and their management

	Medical treatment	Home care
Nausea and vomiting	<i>Treat cause</i> Give antiemetic, e.g. metochlorpromide if intractable. Be aware of complications antiemetic drugs	<ul style="list-style-type: none"> <li>• Small frequent feeds</li> <li>• Fluids given between meals</li> <li>• Offer cold foods</li> <li>• Eat before taking medications,</li> <li>• Prefer dry foods,</li> <li>• Avoid sweet, fatty salty, or spicy foods</li> </ul>
Sore mouth	<i>Treat cause</i> Oral anesthetics may be helpful. Smelly mouth with sores use metronidazole or tetracycline mouth wash	<ul style="list-style-type: none"> <li>• Keep mouth clean</li> <li>• Clean with soft cloth or gauze in clean salt water. Give clear water after each feed</li> <li>• Avoid acidic drinks and hot food</li> <li>• Give sour milk or porridge, soft and mashed, ice cream or yoghurt</li> <li>• Ice cubes may help</li> </ul>

	Medical treatment	Home care
Chronic diarrhoea	<i>Treat cause</i> If intractable consider oral morphine/codeine or constipating medications. Give zinc supplement Micronutrient supplements	<ul style="list-style-type: none"> <li>• Rehydration with small frequent feeds such as rice soup, porridge ORS. Avoid sweet drinks</li> <li>• Offer yogurt instead of fresh milk,</li> <li>• Avoid high fiber foods</li> </ul>
Cough or difficult breathing	<i>Treat cause/screen for and treat TB</i> Nebulised bronchodilators or steroids for wheezing child Bothersome dry cough, use codeine or oral morphine	<ul style="list-style-type: none"> <li>• Soothing remedies such as honey and lemon, steam with eucalyptus or neem leaves</li> <li>• Sit in the best position</li> <li>• Open windows for air circulation</li> <li>• Avoid overcrowding, cooking or smoking in the room</li> </ul>
Severe dermatitis	<i>Treat cause</i> Antihistamines, steroids Emollients/antiseptics	<ul style="list-style-type: none"> <li>• Hygiene.</li> <li>• Keep nails short to minimize trauma and secondary infection from scratching</li> </ul>
Convulsions	<i>Treat cause</i> Anticonvulsants	<ul style="list-style-type: none"> <li>• If child has fever, expose, tepid sponge and give paracetamol</li> <li>• Protect the child from harm; fire, fall from height, drowning etc</li> <li>• Take the child to hospital, Convulsion is a danger sign</li> </ul>
Wounds	<i>Treat cause</i> Infections, pressure, malnutrition	<ul style="list-style-type: none"> <li>• Wound dressing</li> <li>• Metronidazole powder to control odour, honey applications on clean wounds</li> </ul>

### ***Causes of acute pain in HIV/AIDS***

- Oral cavity pain: aphthous ulcers, oral infections due to candida (white patches or red sores), herpes (cold sores), and cytomegalovirus may cause dysphagia, and pain which can be located on the tongue, gums, lips or roof of the mouth.

- Abdominal pain can be caused by intestinal infections, urinary tract infection, pancreatitis, hepatitis, colitis and sepsis. Diarrhoea and vomiting are commonly associated with abdominal pain. Cramping or episodic pain is often seen in settings where there is intestinal infection or bowel obstruction
- Headache can be due to sinusitis, meningitis or encephalitis. Children with HIV can also experience noninfectious causes of headache such as tension headache and migraine. Infections of the central nervous system may give rise to fever, epileptic seizures as well as variability in consciousness along with pain.
- Neurological and neuromuscular pain is common in the setting of static and progressive encephalopathy, especially when there is hypertonicity, spasticity and muscular spasms. Myopathy and herpes zoster are other important causes of neurological or neuromuscular pain.
- Ear pain can occur due to infections of the middle ear (otitis media) or of the ear canal (otitis externa).
- Skin pain caused by sores and rashes can occur due to infections (viral, bacterial or fungal). It can be both acute and chronic.
- Chest pain: pneumonia and pulmonary tuberculosis accompanied by severe respiratory distress and coughing may cause both pain and distress.
- Generalized pain: some children with HIV complain about generalized pain without any localizing site. Usually this type of pain is seen in very sick children.
- Side-effects of antiretroviral therapy (ART) such as diarrhoea may induce painful complications such as diaper dermatitis. Medicine-specific side-effects include muscle pain (zidovudine), headache (efavirenz) and abdominal pain (stavudine).

### *Causes of persisting pain in HIV/AIDS*

- Neuropathic pain: peripheral neuropathy due to damage to the nerves by HIV and the adverse effects of ART described as

discomfort, burning or numbness. In particular, nucleoside reverse transcriptase inhibitors – especially stavudine and didanosine – are associated with neuropathy. Herpes zoster infection may cause severe pain after the sores have healed, due to neuropathy (post-herpetic neuralgia).

- Wasting syndrome can be associated with chronic diarrhoea (contributing to buttock ulceration and cramping), mouth and throat ulceration, fatigue, fever and weakness (enhancing any pain experience), depression, musculoskeletal pain, abdominal pain, and neuropathy secondary to nutritional deficiencies.

If you identify the cause of the pain, proceed with pain management along with specific treatment of the underlying cause, especially if this is reversible and the treatment does not compromise the child's quality of life. For example, it is not advisable to offer aggressive chemotherapy for Kaposi's sarcoma in a child who is terminally ill.

### *Classification*

In addition, different tools can be used to grade the intensity of the pain, depending on the age of the child:

For children aged 3 years and older, the Wong-Baker Faces Scale is used (see [Figure 12.2](#)).

### **Treatment**

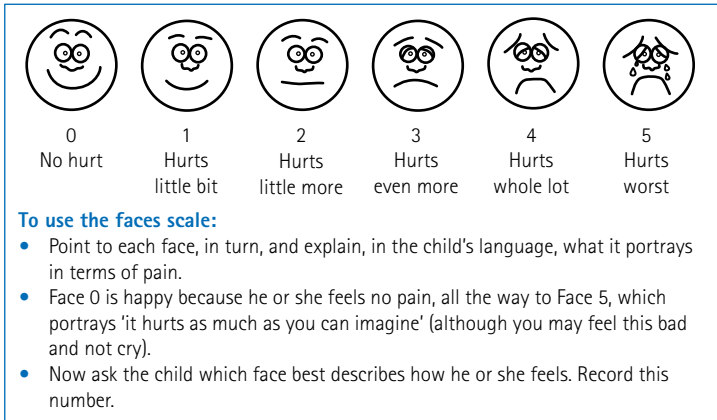
#### *Principles for the pharmacological management of pain*

Correct use of analgesic medicines will relieve pain in most children with persisting pain due to medical illness and relies on the following key concepts:

- Using a two-step strategy
- Dosing at regular intervals
- Using the appropriate route of administration
- Adapting treatment to the individual child.



**Figure 12.2** The Wong-Baker Faces scale



The latter three principles were introduced by WHO as 'by the clock', 'by the mouth' and 'by the individual' in 1986, together with the introduction of the three step-ladder of pain relief. This three-step ladder has been abandoned now for children in favour of a two-step approach

### *Treating pain using a two-step strategy*

**The first step: mild pain:**

Paracetamol and ibuprofen are the medicines of choice in the first step (mild pain).

In children above 3 months of age who can take oral medication and whose pain is assessed as being mild, paracetamol and ibuprofen are the medicines of choice. For children below 3 months of age, the only option is paracetamol.

**The second step: moderate to severe pain:**

If pain severity associated with a medical illness is assessed as moderate or severe, the administration of a strong opioid is necessary. Morphine is the medicine of choice for the second step, although other

strong opioids should be considered and made available to ensure an alternative to morphine in case of intolerable side-effects.

The decision to prescribe and administer opioid analgesics, bypassing the first step, should be based on a clinical judgement of the severity of a child's pain, on careful considerations of the disability caused by pain, on the cause of the pain, and expected prognosis and other aspects.

### **Treating pain at regular intervals**

#### *The principle*

When pain is constantly present, analgesics should be administered, while monitoring side-effects, at regular intervals ('by the clock' and not on an 'as needed' basis).

Medication should be administered on a regular schedule for persisting pain, rather than on an 'as required basis', unless pain episodes are truly intermittent and unpredictable. Children should, therefore, receive analgesics at regular intervals, with the addition of 'rescue doses' for intermittent and breakthrough pain.

### **Treating pain by the appropriate route**

Medicines should be administered to children by the simplest, most effective, and least painful route, making oral formulations the most convenient and the least expensive route of administration. The choice of alternative routes of administration, such as intravenous (IV), subcutaneous (SC), rectal or transdermal when the oral route is not available should be based on clinical judgement, availability and patient preference.

### **Tailoring pain treatment to the individual child**

The treatment should be tailored to the individual child and opioid analgesics should be titrated on an individual basis.

Opioid analgesics should be titrated on an individual basis, so the dose should be adapted in steps until the correct dosage has been found, based on the patient's reaction to the medicine. There is no specific or maximum dose of opioids that can be predicted in any individual

case. The correct dose should be determined in collaboration with the patient to achieve the best possible pain relief with side-effects acceptable to the patient.

### *Formulations of morphine listed in the WHO model list of essential medicines for children, 2010*

- Injection: 10 mg in 1 ml ampoule (morphine hydrochloride or morphine sulfate)
- Granules (prolonged-release) (to mix with water): 20 mg, 30 mg, 60 mg, 100 mg, 200 mg (morphine sulfate)
- Oral liquid: 10 mg/5 ml (morphine hydrochloride or morphine sulfate)
- Tablet (immediate-release): 10 mg (morphine sulfate).
- Tablet (prolonged-release): 10 mg, 30 mg, 60 mg, 100 mg, 200 mg (morphine sulfate).

Adapted from: Guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. WHO, 2012.

### **End-of-life-care**

Terminal care for children with life-threatening illnesses, including AIDS, is a major challenge globally, and especially in resource-poor settings. In these settings, there is a paucity of experience and culturally acceptable and replicable models of both institutional and community-based planned terminal care.

An HIV/AIDS diagnosis in a child creates difficulties beyond the physical sickness, because of the associated guilt and the possibility or likelihood that more family members are infected, sick, or dying.

The child and parents are often ill-prepared for the coming death from HIV/AIDS related complications, the reluctance or ill equipped health workers to discuss death with patients, the unpredictability of the disease progression, and denial.

Where parents and/or caregivers are aware of or suspect a child's imminent death, they may react by withdrawing emotionally. This contrasts sharply with needs at the end of life: for physical comfort, physical touching, emotional closeness, and spiritual health, all of which can have a major positive impact on the quality of remaining life.

In the African setting, as in most cultures, there are complex belief systems and rituals surrounding death and dying, and these systems may be different for a child and an adult.

Terminal care preparation for children and their families is a long-term process that requires continuity in both care providers and services. This is often not guaranteed in many resource-poor settings, and needs to be planned for to make it happen. Terminally ill children are often placed in acute care facilities, but they may receive inappropriate care in these facilities because they must compete for resources with patients who are more acutely ill.

### **What can be done to improve terminal care for children?**

Orientation and training of healthcare workers in terminal care is essential to enable them to recognise terminal illness, prepare the child and family, manage multiple symptoms optimally, and recruit needed support from members of the team.

Alternatives to acute care facilities, including hospice-care institutions and homes, should be considered and discussed with the family.

Training the primary care givers on basic nursing care and help with activities of daily living (ADL) are central to good terminal care in particular, because failure to manage symptoms appropriately (see [below](#)) can directly affect the quality of dying and may even hasten death.

The frontline health worker in terminal care is the family caregiver and, increasingly, home care teams should receive instruction and training to optimise care in the home setting focusing on the needs of the child and family. The training should include the following:

- Relieving distress and ensuring comfort, to the extent possible (managing symptoms, attending to positioning and mobilising, maintaining hydration and, at a minimum, keeping the mouth moistened, keeping skin dry, etc.). Avoiding the temptation to provide care in a dark closed environment.
- Assisting with activities of daily living.
- Limiting hospital admissions if the family can provide care at home. Reviewing admission options if the family is not comfortable providing care at home.
- Providing emotional support to the dying child and grieving family.
- Encouraging recruitment of more family members to participate in the care of the child.
- Helping the family to plan ahead.
- Communicating with the child and family and other caregivers; this is central to the success of terminal care. Answering questions as they come up; it is acceptable not to know the answer. Listening carefully. For children, giving information appropriate to their age. Providing spiritual support: Prayer with the child and or care giver is important. Connecting the family with a spiritual counselor.
- Providing physical presence: A family with a dying child needs compassion from significant others. Someone to listen, hold and talk to, as well as physical contact by light touch or holding a hand can be powerful
- Providing comfort measures as these are the most important thing near the end of life. Reassuring that eating less or nothing is okay; only give absolutely essential medication to relieve suffering.
- Avoiding bedsores; keeping the child dry and clean. Turning regularly.

## Knowledge and operational gaps

- Terminal care needs and current practices in sub-Saharan Africa, particularly about culturally acceptable models of care. For example, is institutional hospice care an acceptable option for terminally ill children?
- Integration of palliative care and paediatric HIV care into maternal and child healthcare systems in Africa.
- Optimizing paediatric palliative care by understanding beliefs and practices around the death of a child and how these differ from those around adults.
- How to strengthen community and facility based health systems to support paediatric palliative care. The cost of providing quality paediatric palliative care in SSA.

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# Chapter 13

## Programming for quality comprehensive paediatric HIV prevention, care and treatment services

### Summary

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- There is now global consensus that paediatric AIDS can be virtually eliminated and the international community as well as national governments are gearing up to attain the goal of virtual elimination.
- Frontline service providers can play an active role in strengthening programming; increasing access to services, improving the quality of services and improving monitoring and evaluation, including impact evaluation.
- Programming for comprehensive quality HIV services for women, children and families is built on a framework of integrated maternal, newborn and child health (MNCH) and sexual and reproductive health (SRH) as the main delivery platforms.
- Periodic assessments are used to increase understanding of the context within which the services are provided and the gaps that need to be closed to reach desired results.
- The starting point for planning is to agree on desired goals or results. Once these are agreed upon, it is important to work through the constraints and bottlenecks identified by the assessment, define and agree on strategies to address those constraints.
- Planning should include a time frame for carrying out the activities, the responsible person or office, and a means of verifying

that the activity has been carried out. It should also include a budget, and the source of funding.

- Strategies to improve quality will aim at ensuring that services are provided according to international and national guidelines and that mothers and children receive comprehensive services in a continuum from and within facilities and the community.
- The components of comprehensive services need to be clearly defined and known by service providers at all levels and integration and linkages strengthened in order to reach the desired outcomes efficiently.
- Lack of good quality data is a common constraint to good planning and to programme measurement.
- Sustained high quality health services depend on strong and functioning health systems, including leadership and management, technical capacity building including supportive supervision and mentorship, financial management skills, supply chain management, infrastructural improvements and health information management systems.



## Background

There is now global consensus that paediatric AIDS can be virtually eliminated and the international community as well as national governments are gearing up to meet the goal of virtual elimination. Elimination of paediatric AIDS entails universal access to quality comprehensive PMTCT services and thus will require intense efforts from service providers, programme managers and government ministries. This chapter will review critical pieces of the programme management cycle to assist health providers and managers to improve their systems and processes to meet the goal of elimination of paediatric AIDS and provide quality services to children and families living with HIV.

Too often the work of programming is left only to policy makers, public health specialists, planners and administrators with little or no involvement of service providers, who are the major producers of programme results. In order to achieve elimination of paediatric HIV and provide quality services to children and families living with HIV, programmes must be strengthened and the knowledge and skills of frontline service providers be constantly updated, not only for service delivery but for programme management as well.

Frontline service providers can play an active role in strengthening programming for HIV prevention, care and treatment in children the goals of which are to:

- Increase access to services for prevention of HIV in children and for comprehensive care and treatment for the children already infected: Universal access means that ALL women and children who need services are able to receive them and that the barriers that hinder access are removed. Such barriers include distance (far away facilities), cost (e.g. user fees), poor quality (e.g. stock outs and negative health worker attitudes), or low demand and utilization (e.g. communities are not aware or not accepting the services).
- Improve the quality of services for children and their families: High quality services are client-centred, providing all components of a comprehensive package of services to meet the needs of the

individual and the family at each point of contact with the health system.

- Improve the monitoring and evaluation: Regular monitoring and evaluation is critical in helping us understand how well programmes are meeting their goals. The process of data gathering, analysis and use for programme improvement and evaluation is a constant cycle.

## Programming for comprehensive quality HIV services

Programming for comprehensive quality HIV services for women, children and families as discussed in this chapter assumes a framework of integrated maternal, newborn and child health (MNCH) and sexual and reproductive health (SRH) as the main delivery platform for such services (see [Chapters 3](#) and [4](#) for components of comprehensive services).

Good HIV programming is guided by a broad set of principles, including:

- Public health approach
- Comprehensive, client-centred continuum of care
- Involvement of community members and people living with HIV

### The public health approach

The public health approach (described by the World Health Organization with the Ottawa Charter for Health Promotion in 1986) seeks to find the maximum feasible benefit for the greatest number of people and entails:

- Selecting interventions based on the best available evidence and the burden of disease
- Optimizing the use of the available human resources and facilitating the provision of care by more types of health care workers
- Implementing standardized treatment protocols, using simplified clinical monitoring and decision making

- Using strategies that prioritize effectiveness while minimizing costs, including the use of generic medicines and alternative laboratory technologies.

### **Continuum of care**

The concept of ‘continuum of care’, as traditionally used in the context of integrated MNCH service, emphasizes the connections and linkages of services for both the mother and the child in terms of time and place, and the interdependency of the health of the mother and that of her infant and young child. The goal is to optimize client- (and family-) centred outcomes, recognizing that not all components of comprehensive services may be provided at the same time or same place. Good programming therefore clearly plans for service delivery in terms of what (component of the package), where (within or outside a health facility) and by whom (cadre of service provider). This also strengthens another element of the continuum – that of prevention of new infections, diagnosing those new HIV infections that occur, and provision of care and treatment for women and children during pregnancy, labour and delivery and the post-delivery period. Continuum of care improves retention and follow-up for those with chronic diseases such as HIV, which is especially vital for successful outcomes.

### **Involving community members and people living with HIV**

An important process that is often overlooked, especially by front-line service providers at facility level, is meaningful stakeholder (including community) involvement throughout the entire programming process. Well-intentioned programmes can fail to achieve their intended outcomes if the programmes are not linked to and working with the communities they serve, and if other stakeholders (e.g. administrators, NGOs) are not involved in programming. As with all chronic diseases, the individual patient, family and community have a central role in managing illness in addition to being the overall owners and customers of services at a population level. People living with HIV (PLWHIV) have unique knowledge and perspectives to contribute to programming for HIV and can form a critical bridge between health service providers and HIV infected clients and families.

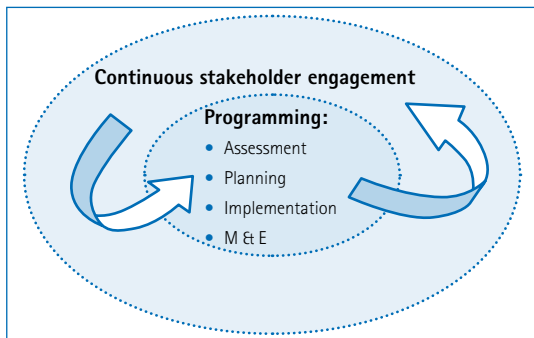
## The programme management cycle

Programme management involves all of the components that enable a health system to function:

- Service delivery: The number and type of facilities offering services and how services are linked or integrated to ensure a continuum of care
- Health work force: Service providers at all levels and their level of training, including the non-traditional ones such as lay counsellors
- Health information systems: Tools such as registers and reports
- Health commodities: Equipment, medicines and laboratory supplies, logistics management systems
- Effective financing: User fees, subsidies, services affordable for end user
- Leadership and governance: Policies, functioning oversight system, regulations for quality assurance for medical products and laboratories

The steps in programming include: assessment, planning, implementation, and monitoring and evaluation. At each step, involvement of stakeholders, including healthcare providers, clients, and the community, should be assured.

Figure 13.1 Programming management cycle



## Assessment

Assessments are used to increase understanding of the context within which the services are provided. A good assessment can provide clear documentation of the status of the health system: identify the major factors impeding service delivery and expansion; identify the quality gaps that have an impact on access and uptake by the population in need; and determine the necessary actions and opportunities to address the shortcomings in light of the goals of universal access.

Assessment could be done at the beginning (baseline assessment), in the middle (as part of quality improvement or in mid-term evaluation), or at the end of a programme or funding cycle (as part of programme evaluation). The level of detail of the assessment as well as the tools used for assessment will depend on the programme goal and objectives.

### *Identifying gaps and bottlenecks*

It is important to identify populations that do not access or get into contact with the health system and the reasons for this lack of access, and also equally important to identify gaps that directly affect outcomes for those populations that do get into contact and initiate services but do not continue with the service or do not get the complete service package.

Some of the gaps include:

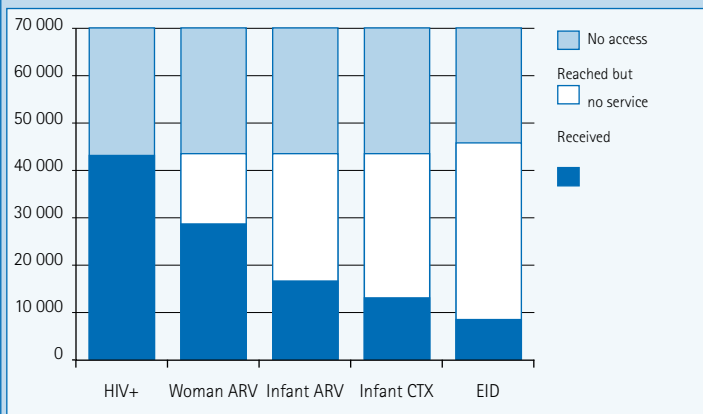
- Missed opportunities to engage women and children already making contact with MNCH services to also obtain HIV services (e.g. high access to ANC but not testing for HIV, or high access to immunizations but HIV exposed infants not getting DBS taken for PCR testing).
- High HIV testing in ANC but low ARV uptake for HIV positive women and their exposed infants.
- ‘Loss to follow up’ (LTFU), an increasingly important barrier in HIV and other chronic care programmes, which describes the failure to retain women and children in care once they have been identified and enrolled in services. The women and children are very much

present in the community, but are ‘lost’ to the narrowly focused and organized care system.

**Figure 13.2** is an illustration of a typical PMTCT cascade common in most PMTCT programmes in Africa

The numbers on the y-axis represent a hypothetical population of 70 000 HIV-infected pregnant women expected to deliver annually. The green colour represents women or children who received the indicated service, the yellow colour those who got in contact with the system but never received the service, and the red colour those who never had access to the service.

**Figure 13.2** Typical PMTCT cascade with missed opportunities



In the example above and using the hypothetical number of 70 000 HIV-infected women in a population expected to deliver annually,

- 71% of them (or 50 000) attend ANC at sites that offer PMTCT, leaving the remainder (20 000) of women (shown in light blue) with no access. Only 90% of those attending ANC sites with PMTCT services are tested for HIV, which is a missed opportunity for services for 10% of them (shown in white) and only 95% of those tested received their results. In the end, only 62% (or 43 400) of the HIV-positive women are identified.

- Of the women identified as HIV positive, the 86% receiving ARVs or ART are shown in dark blue. Those shown in white attended a facility with PMTCT but did not receive ARVs.

In the end only:

- 37 324 of the 70 000 HIV-positive pregnant women ever get any ARVs.
- 37% (or 12 000) of the 70 000 infants of HIV positive mothers are provided with ARVs for PMTCT.
- 17% HIV exposed infants receive cotrimoxazole preventive therapy (CXPT)
- 30% exposed infants receive EID to identify HIV infected infants, and
- A small portion of the infants identified as infected get onto treatment early enough to avert the very high mortality in the first two years of life.

A good assessment will provide answers to the questions – why this pattern, what causes these gaps, and most importantly what are the possible solutions?

Typical findings from assessments of services for HIV-infected children indicate that the following are common constraints:

- HIV-exposed infants and children are not being identified early enough and offered HIV testing
- For those who are tested, results do not get back to the mother or caregiver or get back with significant delays
- Those who get results and are positive are not started on ART early enough resulting in:
  - High attrition for children enrolled in treatment programmes.
  - Death, as a result of late treatment initiation, being a big contributor to the attrition among infants and young children.

## Planning

Planning involves writing down a series of activities to be carried out in order to reach a specific goal and/or specific objectives. It is important to ensure that the listed activities will lead directly to the stated objectives, which in turn will result in expected outcomes.

## Setting objectives and targets

The starting point for planning is to agree on the 'results' or 'objectives' that you want to achieve. It is often helpful to formulate objectives as 'SMART'.

- S – Specific
- M – Measurable
- A – Achievable
- R – Realistic
- T – Time bound

Specific means the objective is concrete, focused and well-defined, emphasizing action and the required outcome. Measurable is in terms of numbers, quantity and comparison; it means that the measurement source is identified and the results of the activities can be tracked. Achievable means as agreed by all stakeholders, after understanding the limitations and constraints, with the available resources and looking at the proposed timeframe. Realistic means there are resources such as people, money, skills, equipment and knowledge to get the job done. Many objectives are achievable, but this may require adjusting priorities given the available resources. Time bound means there is a specified period within which to achieve the objective. Theoretically all objectives are achievable but the critical reflection of time 'by when' changes this perspective.

Examples of *SMART* universal access objectives or results are the following:

*Objective 1.* ALL (or 100%) HIV-positive pregnant women receive ARVs by 2015

*Objective 2.* ALL (or 100%) HIV-infected children aged < 15 years receive ARVs by 2015

However, in order to plan for these objectives in a way that demonstrates whether or not they are met, there is need to know and specify the following:

- The size of the *population in need*



- The number (or proportion) of the population in need *already* receiving services
- The standard that will be used to determine that the services provided meet the desired quality.

### *Strategy formulation*

Once the goals or results are agreed upon, it is important to work through the constraints and bottlenecks identified by the assessment, and to define and agree upon strategies to address those constraints. A set of key strategies and activities to address the gaps in each of the areas of intervention can be found in the relevant chapters of this handbook (see **Chapter 3** for PMTCT and **Chapter 4** for care of HIV-exposed and infected infants).

Some of the strategies to increase access to HIV prevention, care and treatment services include decentralization, integration, and community sensitization and engagement.

Decentralization aims at bringing services closer to the people in need, with most of the planning and budgeting happening at district level. It is an approach that is embraced in most countries. However, there may be some policy and structural bottlenecks that hinder HIV services being delivered at the primary level facilities. Some of these bottlenecks include lack of policy, lack of knowledge and/or lack of supplies that would allow health workers at primary facility level to provide one or more components of a comprehensive package of services.

To have effective decentralized services entails strengthening the mid and lower level health facilities in the areas of:

- Leadership and management
- Technical capacity building through training, mentorship and supportive supervision
- Financing and financial management skills
- Supplies and supply chain management

- Infrastructural improvements (building renovations, supply of essential equipment)
- Health information management systems.

While the above actions (strengthening lower level health systems) is usually a function of national governments, service providers at facility level are important stakeholders and need to be actively involved, especially for strengthening their leadership and management skills.

Like everything else, successful programmes at any level require good leadership at that level. Every effort should be made to identify individuals with leadership skills or train and mentor assigned persons in leadership. For example, successful implementation of PITC in a children's ward is often due to the leadership of a self motivated, dynamic nurse on that ward, who is able to mobilize and lead a team on the ward so that routine testing is carried out throughout the day regardless of which nurse is on duty. Similarly, successful scale up and coverage of PMTCT services in a district is usually a result of a motivated district team. It is rare that comprehensive services for prevention, care and treatment for children can be provided by a single entity or organization; therefore planning should identify partnerships that can be formed for effective and efficient services across a continuum.

## Integration

Integration, defined as the inclusion of elements of one type of service into the regular functioning of another service, is a means of achieving greater access to services while maintaining or enhancing programme effectiveness.

### Factors that facilitate integration of services

- Supportive policies
- Joint planning, budgeting, QI, M&E
- Training service providers
- Physical proximity of clinics
- Shared resources – personnel, equipment, drugs, test kits
- Intergrated supportive supervision.

An important consideration when discrete activities and interventions are being planned is how to ensure that the activities are logically sequenced and linked to so that integration, referrals, community dialogue and partnerships are taken into account. Practical examples of how this can be done include:

- Re-organization of services, client flow, and service protocols and registers to enable provision, recording and tracking of HIV testing and counselling and provision of ART/ARVs as part of routine ANC services.
- Whole-site training, re-training and mentorship to deliver multiple services, making these services more widely and routinely available and accessible. Introducing mechanisms and tools for effective referrals – such as physical escort (usually by support groups), and referral notes filled in triplicate to allow feedback to source of referral.
- Strengthening linkages and referrals focusing both on services within the same facility, as well as services outside the facility in the community. A well functioning referral system ensures that the client receives all components of a comprehensive package and knows where to go to continue receiving ongoing and needed services.

### **Community sensitization and engagement**

Community sensitization aims at increasing community knowledge through information, education and communication on health-related issues. Community engagement on the other hand aims at working with the communities to identify solutions to gaps in service delivery and jointly to carry out community-based and some facility-based activities.

A number of studies have shown that community sensitization and engagement can increase:

- Demand and utilization of services for prevention care and treatment of HIV infected children and their families
- Retention of women, children and families in programmes

- Enhanced adherence to treatment
- Strengthen psychosocial well being of pregnant and lactating women and children enrolled in care and treatment programmes.

The planning process should identify community-based organizations (CBOs) with which to form partnerships for carrying activities for community sensitization and engagement, but service providers have an important role in providing factually correct and evidence-based information to these CBOs and the community in general. Some of the approaches that have proven successful in increasing access to services are community- and home- based testing, especially for couple testing, use of community health workers, traditional birth attendants, and peer support groups.

### Activity formulation and operational plans

In order for service providers to implement plans better, the plans must be broken down to shorter time periods, and focus more concretely on facility and community level activities. This type of plan is commonly known as an 'operational' or action plan, and typically spans one year (or at most two).

The example below brings the two results above down to a one one-year time period (e.g. January-December):

- Fifty (50) additional PHC facilities will offer PMTCT services (bringing the total of PHC services offering PMTCT services to 200 by the end of December).
- All 200 facilities currently offering ART will provide ART services for infants and children by the end of December (currently only 50 of the 200 are offering ART services for both adults and children).

These objectives are specific enough that the next logical consideration is: *what will it take for this to happen?* The answers may include training of health workers at targeted facilities, supplying and equipping those facilities (e.g. with test kits, ARVs, recording and reporting tools and registers, job aids), etc.

Planning should include a time frame for carrying out the activities, the responsible person or office, and a means of verifying that the activity has been carried out. It should also include a budget, and the source of funding. For example, a district implementing PMTCT may have multiple funding sources for the programme – government, community, international agencies – and the plan should indicate which activity is funded through which funding source.

Planning, especially at facility level, should be sufficiently detailed for every service provider at that facility to easily understand what needs to be done to bridge the gaps identified during assessments, or during routine monitoring.

All plans and targets should be anchored to the national plan taking into consideration the unique environment of each region and facility.

## Implementation

Implementation of services for prevention, care and treatment of HIV in children, as much as possible, should be done in an integrated way as outlined in **Chapters 3** and **4** and in accordance with national guidelines.

International and national guidelines are rarely detailed enough to provide specific procedures, and facilities may need to develop site-specific standard operating procedures (SOPs) in each of the service areas and to ensure that all staff know and use the SOPs. Charts showing client flow and the components of a comprehensive package of services need to be prominently displayed or easily accessible to health care workers to act as a constant reminder of what services the women and children should receive. **Table 4.1** (in **Chapter 4**) shows the *ANECCA 10 point package of comprehensive services for HIV exposed and infected children* and **Table 13.1** describes the components of comprehensive services for women in the antenatal and postnatal period (similar to those of other adults).

**Table 13.1** Package of services for women in ANC and in post natal period

Services for pregnant women	Services for other adults
<ul style="list-style-type: none"><li>• HIV testing and counselling for self, partner and family</li><li>• Clinical and immunological staging</li><li>• TB screening and management</li><li>• OI screening and management</li><li>• Nutritional assessment and management of malnutrition</li><li>• Provision of ARVs for treatment</li><li>• Provision of CTX prophylaxis</li><li>• Adherence and psychological support</li><li>• Regular follow up and assessment for ART adherence, Adverse events and possible treatment failure for those on long-term treatment</li><li>• HBC and palliative care</li><li>• Positive prevention</li><li>• Screening and management of non-communicable diseases including mental health problems</li></ul>	<ul style="list-style-type: none"><li>• HIV testing and counselling for self, partner and family</li><li>• Clinical and immunological staging</li><li>• Provision of ART</li><li>• TB screening and management</li><li>• OI screening and management</li><li>• Cancer screening and treatment</li><li>• Sexual and reproductive health education</li><li>• Nutritional assessment and management of malnutrition</li><li>• Provision of CTX prophylaxis</li><li>• Adherence and psychological support</li><li>• Regular follow up and assessment for ART adherence, adverse events and possible treatment failure for those on long-term treatment</li><li>• HBC and palliative care</li><li>• Positive prevention</li><li>• Family planning services</li><li>• Screening and management of non-communicable diseases including mental health problems</li></ul>

Source: Adapted from EGPAF Swaziland

Apart from SOPs and client flow charts described above, implementation also requires readily available tools like patient stationery, registers, and job aids for different groups of service providers.

### Task shifting or sharing

In order to rapidly increase access to services for prevention, care and treatment of HIV in children and their families, it is often necessary to adopt or expand the task shifting approach as one method of

strengthening the health workforce. Task shifting is a process whereby specific tasks are moved, where appropriate, to health workers with shorter training and fewer qualifications.

Depending on what is in the national task shifting policy, facilities should clearly document which tasks can be done by what cadre of staff and to who it is acceptable to delegate. For example, in order to increase access to ART for HIV-infected pregnant women in rural health facilities, it may be necessary to have a well-ART-trained nurse to initiate ART in the ANC. Lay counsellors and people living with HIV play an important role in PMTCT and in care and treatment of children affected by HIV, and are a resource that should be identified and utilized. The 2008 WHO, UNAIDS and PEPFAR recommendations and guidelines on task shifting provide an excellent resource for implementing task shifting. This approach requires a good mentoring and supportive supervision system in order to maintain the quality of services.

### **Mentorship and supportive supervision**

Providing quality comprehensive services for children and their families will in most settings in require constant and regular supportive supervision and mentorship, especially when the services are decentralized to primary level facilities and when task sharing has been an accepted practice.

Mentorship is a process of practical training that promotes ongoing professional development for high quality services. The mentor is usually a senior, trusted, experienced and 'mentorship-skilled' health worker that shares the knowledge, skills and perspectives in a consultative process usually at the mentees place of work. Mentoring should be integrated with and ideally follow initial training and it should be seen as part of continuous medical education.

### **Mentorship versus supportive supervision**

Supportive supervision aims at improving services for HIV/AIDS through joint observation, discussion, and direct problem solving. It focuses more on the conditions required for the proper functioning of the facility and facility staff. For example are the key supplies for HIV prevention and care and treatment available? Supportive supervision

is usually conducted by members of the district health management team, the 'administrators' while mentorship is conducted by the professional clinicians, nurse-midwives, pharmacists or laboratory technicians for professional skills transfer.

Mentorship and supportive supervision are complementary with a great deal of overlap, but ideally should be carried out separately by different teams.

### **Implementing a quality improvement (QI) programme**

The quality of HIV service provision needs to be addressed throughout the programme cycle – during assessment, planning, implementation and monitoring, as it is a key determinant to programme outcomes. The quality of services must be assured to achieve elimination of paediatric HIV and prolong survival of those infected, ensuring good quality of life.

The American Heritage Dictionary describes quality as degree or standard of excellence, and other authorities in quality of health care services use different definitions of quality one of them being doing the right thing at the right time, right away.

All these definitions imply that there must be a standard against which quality is measured and in the simplest terms, means: Are services being provided according to international or national standards and guidelines? The fundamental point however is: Are our programmes producing the desired outcomes – preventing new HIV infections in children, and improving the survival of HIV infected children and their mothers and families?

A quality improvement (QI) programme aims at institutionalizing a culture of quality assessment and quality improvement on all aspects of service delivery, with the major goal of ensuring attainment of intended outcomes.

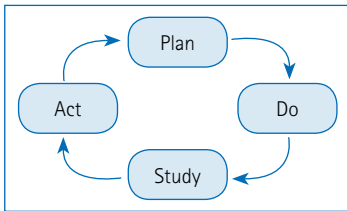
Quality improvement can be implemented at all levels: National, district or facility level, with a dedicated team for coordinating QI activities. It must be emphasized, however, that quality is a responsibility of every service provider. At facility level, and



depending on available staff, a QI team, with a designated leader, may be composed of a clinician, a nurse, a laboratory technician and a pharmacist depending on the available staff and their leadership qualities.

The function of the QI team is to facilitate the implementation of a QI programme, which, at its basic minimum, is a process of identifying specific issues that are considered important and can be improved by the facility staff. The process, a QI cycle (with many names such as: PDSA cycle, Performance Improvement Approach) involves meetings to identify specific issues or gaps that need improvement, determining actions to bridge the gaps, implementing those actions, using data to document and monitor improvements, sharing the improvements with colleagues, and then repeating the process to further improve the programme. That is why it is also sometimes called continuous quality improvement (CQI). **Figure 13.3** illustrates the PDSA cycle.

**Figure 13.3** PDSA cycle for quality improvement



In **Figure 13.3** you will see that during planning you define what needs to be done –objectives, activities, responsible persons, and needed resources. You then DO implement an intervention, then STUDY the outcome of the intervention based on data, and based on the results, ACT by disseminating and re-examining your previous approach and starting another cycle.

At all stages of quality improvement, decisions must be guided by data, whether quantitative or qualitative. Examples of qualitative data include opinions of clients for satisfaction or service providers for barriers; while quantitative data include numbers, such as routine programme statistics or specially conducted data review exercises.

### Sharing best practices

Programmes should support the practice of sharing of best practices among service providers within a facility, between facilities in a district or region, or at national and international level. One such approach would be to have regional or district level workshops during which facilities share their experiences and innovative approaches in implementing HIV prevention, care and treatment programmes for children and their families. During such workshops service providers use programme data to illustrate best practices and to identify gaps and barriers in service delivery. The workshops then provide an avenue for solving problems and for introducing innovative ways to overcome barriers in programme implementation.

### Improving monitoring and evaluation (M&E)

The goals of M&E are to:

- Make informed decisions regarding service delivery and the accompanying programme management.
- Ensure the most effective and efficient use of resources.
- Determine whether a programme is on track so the necessary corrections can be made.
- Determine whether the programme is having the desired impact – for example reduced MTCT, reduced maternal morbidity and mortality, reduced infant and child morbidity and mortality.

### Data quality and data use

A good M&E system uses accurate data in a timely manner. Lack of good quality data is a very common constraint to good planning and to programme measurement. To improve data quality efforts must start with the recording of the data (accurate, clear and readable recording into patients' files, clinic registers, and other record books. Service providers particularly clinicians and nurses are therefore the most important determinants to good data, and they must specifically targeted in efforts to improve data quality. Often because of shortage of staff and work overload, recording into clinic registers is poorly

done and some programmes delegate the role of health information recording to people not trained for this role.

Training service providers in data use also helps in improving data quality. All service providers at facility level should:

- Know what services are provided at their facility, and how these services are recorded (daily, monthly, etc.)
- Know the population targeted by specific HIV services
- Understand that HIV testing is an entry point to follow-up services
- Know how HIV services currently provided by the facility are tracked (or should be tracked) alongside other services (or exceptionally, as stand-alone records, e.g. pharmacy ARV inventory and dispensing logs).

Illustrations using site level data (for example the graphical illustration in the planning section above) should be used to immediately relate the story of missed and current opportunities for expanding service delivery. Simple site level data-driven illustrations are very powerful tools and motivators to regularly review facility data, and using these to make site level adjustments in patient flow and local practices can result in increased uptake of services (see also quality improvement above). At an aggregate level, these simple improvements at one facility are exactly what is needed to improve overall national measurement, tracking, planning, budgeting and re-planning at national level.

Another data-driven site-level illustration is forecasting and quantification of test kits and drugs required by type. For HIV test kits, service statistics are a good starting point. If the policy is to recommend HIV testing for all pregnant women, all TB patients, all malnourished patients, and all hospitalized patients, then HIV test kits should be provided to cover this number at any facility offering these services as a starting point – based on actual service statistics of the last month, quarter, year as the case may be.

These starting points must be complemented with broader short and medium term measures to generate better data, including

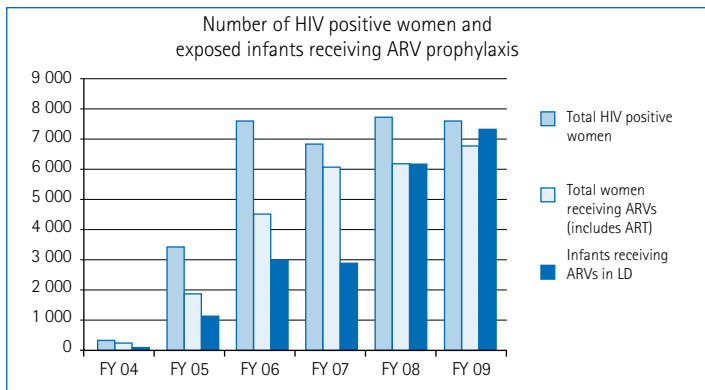
ensuring systemic improvements in the national health management information system, institutional and human capacity, rational introduction of electronic data systems, innovative use of mobile phones and SMS, appropriate financing, etc.

The components of a good M&E system in a comprehensive prevention care and treatment programme include:

- Clear goal, objectives and activities
- Clear, simple and easily usable indicators
- Data collection, analysis, and utilization plan
- Data dissemination plan.

PMTCT monitoring data will show a cascade of services that begin with women and girls of reproductive age. At every contact with a health facility, data are collected about the services provided, following the woman through pregnancy and she and her infant until two years of age. By reviewing the services provided at each step in the cascade, facilities and programme managers can see how well they are performing.

**Figure 13.4** Example of using routine programme data



In the example shown in **Figure 13.4**, routine programme data are used to see uptake of specific PMTCT services over a period of time. This diagram was developed from routine data collected in registers and reported in the monthly summary forms. It provides an excellent overview of the implementation of services. In FY07, for example, uptake of infant prophylaxis was lagging behind. Great improvement was seen in FY08 because the team reviewed programme monitoring data and made changes to the way services were delivered in order to improve performance.

Training, mentorship and regular supportive supervision visits are important ways to assist health workers to improve data collection, use and reporting.

Service providers at facility level should use the knowledge from this chapter to improve the quality of services they provide and to continuously improve programme outcomes.



# Appendices





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## Appendix A: Assessment of risk when exposed to HIV infection

	Low risk	Medium risk	High risk
Type of exposure	Intact skin	Mucous membrane/ non-intact skin	Percutaneous injury
Source	HIV negative	HIV status unknown; clinically well*	HIV positive with advanced disease/acute seroconversion illness. (Consider treatment history)
Material	Saliva, tears, sweat, faeces, urine, sputum, vomit	Semen, vaginal secretions, synovial, pleural, pericardial, peritoneal, amniotic fluids	Blood and bloody bodily fluids, CSF, Viral cultures in labs

## Appendix B: Collection, packaging and dispatch of dry blood spots (DBS)



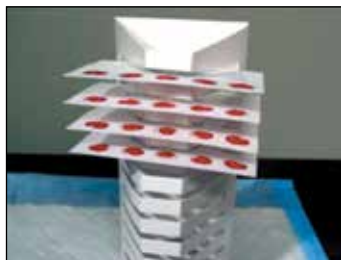
**Figure B1** Collection of DBS



**Figure B2** Valid specimens



**Figure B3** Ensure adequate drying of specimens before packaging



**Figure B4** Packaging into Ziplock bags: bag must be gas-impermeable; other bags are inadequate



**Figure B5** Adding desiccant to bags: 1-2 desiccants per small bag, 5-10 per large bag



**Figure B6** Packing: add humidity card and seal bag

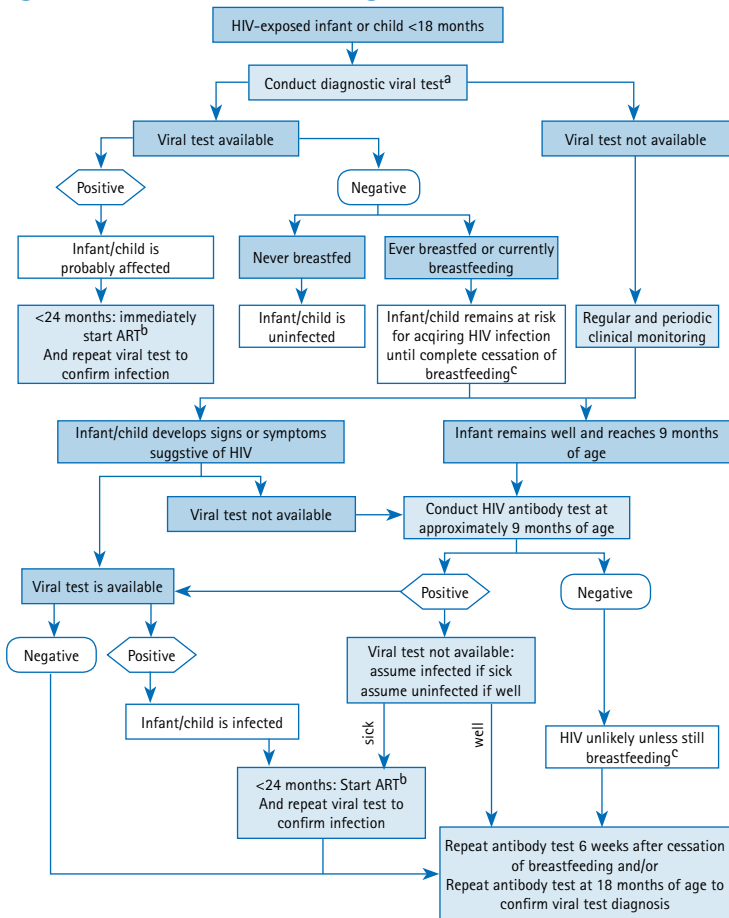


**Figure B7** Storage: keep packaged DBS in sealed plastic bags in cool place until transported to testing lab. Refrigerate if storing for a week or longer. Avoid leaving in vehicle, as sun and heat will cause the DBS to deteriorate



**Figure B8** Packaging DBS for shipping

## Appendix C: Establishing the presence of HIV infection in HIV-exposed infants and children less than 18 months of age in resource-limited settings (WHO 2010)



- a For newborn, test first at or around birth or at first postnatal visit (usually 4–6 weeks)  
 b Start ART, if indicated, without delay. At the same time, retest to confirm infection  
 c The risk of HIV transmission remains as long as the breastfeeding continues

## Appendix D: Management of severe malnutrition (the ten steps of WHO)

### A: Initial treatment

#### *Step 1: Prevent and treat hypoglycaemia*

Treat all children admitted with severe malnutrition presumptively for hypoglycaemia by giving a bolus of intravenous 10% dextrose. Hypoglycaemia is present when the blood sugar is  $<3$  mmol/l. If blood glucose cannot be measured, assume all severely malnourished children are hypoglycaemic.

To prevent hypoglycaemia, feed the child every three hours with a high calorie liquid diet. To treat hypoglycaemia give the first feed of F-75 if it is quickly available and then continue with 2–3 hourly feeds. If the first feed is not quickly available, give 50 ml bolus of 10% glucose or sucrose solution (one rounded teaspoon of sugar in 3.5 tablespoons water), orally or by nasogastric (NG) tube, followed by the first feed as soon as possible. The child should then continue with 2–3 hourly feeds of F-75 day and night at least for the first day. In the initial resuscitative stage, give it orally or by nasogastric tube if the child is taking poorly.

If the child is unconscious, lethargic or convulsing, give IV 10% glucose (5 ml/kg), followed by 50 ml of 10% glucose by NG tube. Then give starter F-75 as above.

During therapy, severely malnourished children should continue to be monitored closely for hypoglycaemia. If the initial blood glucose was low, repeat dextrostix taking blood from finger or heel, after 30 minutes. If blood glucose falls to  $<3$  mmol/l, repeat the 10% glucose or sugar solution, and continue feeding every 30 minutes until stable. If rectal temperature falls to  $<35.5$  °C or if there is deterioration in level of consciousness, repeat blood sugar level estimation using the dextrostix measurement and treat appropriately.

Hypoglycaemia can be prevented by giving two-hourly feeding starting immediately on contact with the health care system. Always give feeds throughout the night.

### *Step 2: Prevent hypothermia*

Hypothermia is defined as when the core body temperature as measured by axillary or rectal temperature are less than equal to 35 °C (<95 °F), or temperature that does not register on a normal thermometer. This should be differentiated from peripheral stocking and glove distribution of cold extremities characteristic of shock. The two entities may co-exist if the child is dehydrated or having overwhelming sepsis. In order to treat hypothermia, the child should be fed immediately. Re-warm the child: either clothe the child (including head), cover with a warmed blanket and place a heater or lamp nearby (do not use a hot water bottle), or put the child on the mother's bare chest (skin to skin) and cover them with a warmed blanket or clothes. The child should also receive appropriate antibiotic therapy.

The body temperature should be checked during re-warming 2 hourly until it rises to >36.5 °C (take half-hourly if heater is used). The child should be kept covered at all times, especially at night. Check for hypoglycaemia whenever hypothermia is found.

Hypoglycaemia is prevented by feeding the child two hourly, starting immediately. Feeds should be given throughout the day and night. The child should be kept covered and away from draughts. The child should be kept dry, change wet nappies, clothes and bedding. The child should not be exposed to cold (e.g. bathing, prolonged medical examinations). Let the child sleep with mother/carer at night for warmth.

### *Step 3: Treat dehydration*

Dehydration is over-diagnosed and its severity overestimated in severely malnourished children as it is difficult to assess hydration status accurately in such children using clinical signs alone. Low blood volume can coexist with oedema. All severely malnourished children with watery diarrhoea should be assumed to have some dehydration.

Do not use the IV route for rehydration except in cases of shock. The standard WHO-ORS solution contains too much sodium and too little

potassium for severely malnourished children. Instead use special Rehydration Solution for Malnutrition (ReSoMal) (see the recipe below or use commercially available ReSoMal).

Give ReSoMal (orally or by nasogastric tube) 5 ml/kg every 30 minutes for two hours, and then continue with 5–10 ml/kg/h for next 4–10 hours. Replace the ReSoMal doses at four, six, eight and 10 hours with F-75 if it still necessary to continue rehydration at these times. Once rehydrated initiate/continue feeding with starter F-75.

If there is shock, for IV rehydration use Ringer's Lactate solution with 5% glucose, half strength normal saline with 5% glucose, or half-strength Darrow's solution with 5% dextrose. Give this as 15 ml/kg over one hour and possibly repeat if there is a good response.

The progress in re-hydration should be monitored half-hourly for two hours, then hourly for the next 6–12 hours, recording pulse rate, respiratory rate, urine frequency, stool/vomit frequency. During re-hydration, rapid respiration and pulse rates should slow down and the child should begin to pass urine. Return of tears, moist mouth, eyes and fontanelle appearing less sunken, and improved skin turgor, are also signs that re-hydration is proceeding. It should be noted that many severely malnourished children will not show these changes even when fully re-hydrated.

Be alert for over-hydration which is very dangerous and may lead to heart failure. Continuing rapid breathing and pulse during re-hydration suggest coexisting infection or over-hydration. Signs of excess fluid (over-hydration) are increasing respiratory rate by 5/min and pulse rate by 15/min, increasing oedema and puffy eyelids. If these signs occur, stop ReSoMal immediately and reassess after one hour.

Prevention of dehydration in a severely malnourished child with continuing watery diarrhoea should be carried out in the following way:

- If the child is breastfed, continue breastfeeding.
- Continue feeding with starter F-75.



- Give ReSoMal between feeds to replace stool losses. As a guide give 50–100 ml after each watery stool.

Recipe for ReSoMal oral rehydration solution	
Ingredient	Amount
Water (boiled and cooled)	2 litres
WHO-ORS	One 1 litre packet
Sugar	50 g
Electrolyte/mineral solution*	40 ml

\* If commercially available electrolyte/mineral solution is not available, use 45 ml of KCl solution.

ReSoMal contains approximately 45 mmol Na, 40 mmol K and 3 mmol Mg per litre.

#### Step 4: Correct electrolyte imbalance

All severely malnourished children have deficiencies of potassium and magnesium which may take at least two weeks to correct. Oedema is partly due to these imbalances. Do NOT treat oedema with a diuretic. Excess body sodium exists even though plasma sodium may be low. Giving high sodium loads could kill the child. Electrolyte imbalance is treated by giving extra potassium (3–4 mmol/kg/day) and magnesium (0.4–0.6 mmol/kg/day). When rehydrating, give low sodium rehydration fluid (e.g. ReSoMal). Prepare food without adding salt. The extra potassium and magnesium can be prepared in a liquid form and added directly to feeds during preparation or to ReSoMal.

#### Step 5: Treat/prevent infection

In severe malnutrition the usual signs of infection, such as fever, are often absent, yet multiple infections are common. Therefore, assume that all malnourished children have an infection on arrival in hospital and start antibiotics immediately. Hypoglycaemia and hypothermia are signs of severe infection.

Give all malnourished children a broad-spectrum antibiotic(s) and measles vaccine if child is more than six months and not immunized (delay if the child is in shock). Antimalarial treatment should be

given if the child has a positive blood film for malaria parasites. Mebendazole 100 mg orally twice a day for three days if there is evidence of worm infestation. In countries where infestation is very prevalent, give mebendazole to all malnourished children after day seven of admission.

If the child appears to have no complications give cotrimoxazole 5 ml paediatric suspension orally twice daily for 5 days (2.5 ml if weight <6 kg). (5 ml is equivalent to 40 mg TMP+200 mg SMX.) If the child is severely ill (apathetic, lethargic) or has complications (hypoglycaemia; hypothermia; broken skin; respiratory tract or urinary tract infection) give ampicillin 50 mg/kg IM/IV six-hourly for two days, then oral amoxicillin 15 mg/kg eight-hourly for five days, or if amoxicillin is not available, continue with ampicillin but give orally 50 mg/kg six-hourly for seven days, AND gentamicin 7.5 mg/kg IM/IV once daily for seven days. If the child fails to improve clinically within 48 hours, ADD chloramphenicol 25 mg/kg IM/IV eight-hourly for five days. Where specific infections are identified, add specific antibiotics as appropriate.

If anorexia persists after five days of antibiotic treatment, complete a full 10-day course of antibiotics. If anorexia still persists, reassess the child fully, checking for sites of infection and potentially resistant organisms, and ensure that vitamin and mineral supplements have been correctly given.

### *Step 6: Correct micronutrient deficiencies*

All severely malnourished children have vitamin and mineral deficiencies. Although anaemia is common, do NOT give iron initially but wait until the child has a good appetite and starts gaining weight (usually by the second week), as giving iron can make infections worse. Give the following daily for at least two weeks: a multivitamin supplement, folic acid (give 5 mg on day one, then 1 mg/day), zinc (2 mg/kg/day), copper (0.3 mg/kg/day) and iron (3 mg/kg/day but only when gaining weight); vitamin A orally on day 1 (for age >12 months, give 200 000 IU; for age 6–12 months, give 100 000 IU; for age 0–5 months, give 50 000 IU). A combined electrolyte/mineral/vitamin mix for severe malnutrition is available commercially. This

can replace the electrolyte/mineral solution and multivitamin and folic acid supplements mentioned in steps 4 and 6, but still give the large single dose of vitamin A and folic acid on day 1, and iron daily after weight gain has started.

## B: Stabilization phase

### *Step 7: Start cautious feeding*

In the stabilisation phase a cautious approach is required because of the child's fragile physiological state. Feeding should be started as soon as possible after admission and should be designed to provide just sufficient energy and protein to maintain basic physiological processes.

The essential features of feeding in the stabilization phase are:

- Small, frequent feeds of low osmolarity and low lactose
- Oral or nasogastric (NG) feeds (never parenteral preparations)
- Energy: 420 kJ/kg/day (100 kcal/kg/day)
- Protein: 1–1.5 g/kg/day
- Fluid: 130 ml/kg/day (100 ml/kg/day if the child has severe oedema)
- If the child is breastfed, encourage to continue breastfeeding but give the prescribed amounts of starter formula to make sure the child's needs are met.

Milk-based formulas such as starter F-75 containing 315 kJ/100 ml (75 kcal/100 ml) and 0.9 g protein/100 ml will be satisfactory for most children. Very weak children may be fed by spoon, dropper or syringe. A recommended schedule in which volume is gradually increased, and feeding frequency gradually decreased is:

Days	Frequency	Vol/kg/feed	Vol/kg/d
1–2	2-hourly	11 ml	130 ml
3–5	3-hourly	16 ml	130 ml
6–7+	4-hourly	22 ml	130 ml

For children with a good appetite and no oedema, this schedule can be completed in 2–3 days. If, after allowing for any vomiting, intake does not reach 335 kJ/kg/day (80 kcal/kg/day = 105 ml starter formula/kg) despite frequent feeds, coaxing and re-offering, give the remaining feed by NG tube. Do not exceed 420 kJ/kg/day (100 kcal/kg/day) in this phase. There should be close monitoring of the amounts of feeds offered and left over, vomiting, stool frequency and consistency and daily body weight.

#### Recipes for starter and catch-up formulas

	F-75 (starter)	F-100 (catch-up)
Dried skim milk (g)*	25	80
Sugar (g)	100	50
Vegetable oil (ml)	30 (or 35 ml)	60 (or 70 ml)
Electrolyte/mineral solution (ml)	20	20
Water: Make up to:	1 000 ml	1 000 ml
Contents per 100 ml:		
Energy (kJ)	315	420
Protein (g)	0.9	2.9
Lactose (g)	1.3	4.2
Potassium (mmol)	4.0	6.3
Sodium (mmol)	0.6	1.9
Magnesium (mmol)	0.43	0.73
Zinc (mg)	2.0	2.3
Copper (mg)	0.25	0.25
% energy from protein	5	12
% energy from fat	36	53
Osmolarity (mOsmol/l)	413	419

#### Preparation:

Using an electric blender, place some of the warm boiled water in the blender. Add the milk powder, sugar, oil and electrolyte/mineral solution. Make up to 1 000 ml and blend at high speed. If there is no electric blender available, mix the milk, sugar, oil and electrolyte/mineral solution to a paste and then slowly add the rest of the warm boiled water and whisk thoroughly with a manual whisk. Store the made up formula in a refrigerator.

### *Step 8: Achieve catch up growth*

Signs that a child has reached this phase are a return of appetite and resolving oedema.

In the rehabilitation phase a vigorous approach to feeding is required to achieve very high intakes and rapid weight gain of >10 g gain/kg/day. Modified porridges or modified family foods can be used provided they have comparable energy and protein concentrations.

Replace starter F-75 with the same amount of catch-up formula F-100 for 48 hours then, increase each successive feed by 10 ml until some feed remains uneaten. The point when some remains unconsumed is likely to occur when intakes reach about 30 ml/kg/feed (200 ml/kg/day). After the gradual transition give frequent feeds (at least 4-hourly) of unlimited amounts with a goal of providing 630–920 kJ/kg/day (150–220 kcal/kg/day) of energy and protein 4–6 g/kg/day. If the child is breastfed, encourage to continue breastfeeding. However breast milk does not have sufficient energy and protein to support rapid catch-up growth, so give F-100 as indicated.

Progress after the transition is monitored by assessing the rate of weight gain. Weigh the child each morning before feeding and plot the weight. Calculate and record the weight gain every three days as g/kg/day. Expected weight gain is 10–15 g/kg/day for children undergoing institutional based nutritional rehabilitation, 10 g/kg/day with F100 and 15 g/kg/day for children using the peanut based RTUF. Children undergoing home management of acute severe malnutrition gain 5 g/kg/day. If weight gain is poor (<5 g/kg/day) the child requires full reassessment. If the weight gain is moderate (5–10 g/kg/day), check whether intake targets are being met, or if infection has been overlooked. If weight gain is good (>10 g/kg/day), continue with the feeding regimen.

The child should be monitored for early signs of heart failure (rapid pulse and fast breathing). If there is increase in both respirations (by five or more breaths/min) and pulse (by 25 or more beats/min) for two successive four-hourly readings reduce the volume fed to 100 ml/kg/day for 24 hours. The feeds should then be increased slowly as follows; 115 ml/kg/day for the next 24 hours, 130 ml/kg/day

for the following 48 hours and then increase each feed by 10 ml as described earlier

***Step 9: Provide sensory stimulation and emotional support***

In severe malnutrition there is delayed mental and behavioural development. Provide tender loving care, a cheerful, stimulating environment, structured play therapy 15–30 min/day and physical activity as soon as the child is well enough. The mother or the primary caregiver should be involved in the care process (e.g. comforting, feeding, bathing, play)

***Step 10: Prepare for follow-up after recovery***

A child who is 90% weight for height (equivalent to  $-1$  SD) can be considered to have recovered. The child is still likely to have a low weight for age because of stunting. Good feeding practices and sensory stimulation should be continued at home. Show parent or carer how to feed frequently with energy- and nutrient-dense foods and to give structured play therapy. Parents should be advised to bring child back for regular follow-up checks, ensure the child receives booster immunizations and 6-monthly vitamins.

## Appendix E: Measuring weight in infants and children

Adapted from the Anthropometric Measurement Guide of the Food and Nutrition Technical Assistance project (FANTA project) ([www.fantaproject.org](http://www.fantaproject.org))

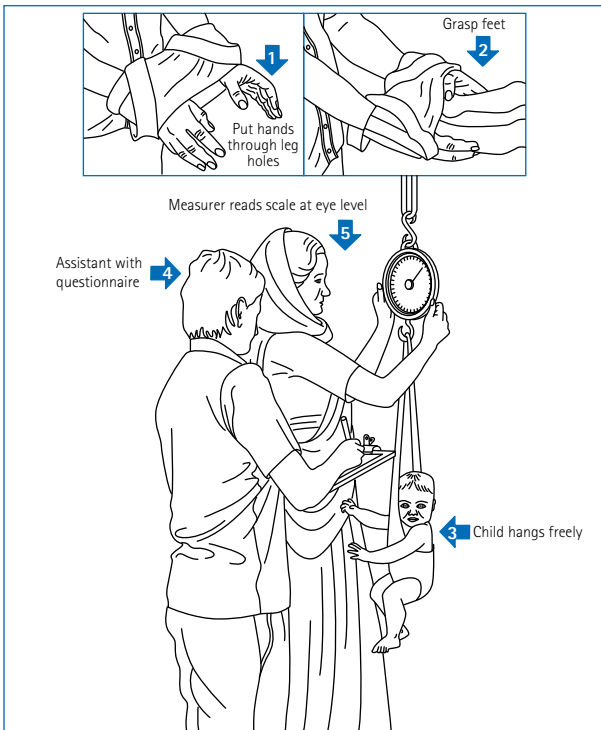
### 1 Measuring weight using the hanging Salter-like scale

(illustrated in [Figure 1](#) on the next page)

- a Measurer or assistant: Hang the scale from a secure place like the ceiling beam. You may need a piece of rope to hang the scale at eye level. Ask the mother to undress the child as much as possible.
- b Measurer: Attach a pair of the empty weighing pants to the hook of the scale and adjust the scale to zero, and then remove from the scale.
- c Measurer: Have the mother hold the child. Put your arms through the leg holes of the pants ([Arrow 1](#)). Grasp the child's feet and pull the legs through the leg holes ([Arrow 2](#)). Make certain the strap of the pants is in front of the child.
- d Measurer: Attach the strap of the pants to the hook of the scale. **DO NOT CARRY THE CHILD BY THE STRAP ONLY.** Gently lower the child and allow the child to hang freely ([Arrow 3](#)).
- e Assistant: Stand behind and to one side of the measurer ready to record the measurement. Have the questionnaire ready ([Arrow 4](#)).
- f Measurer and assistant: Check the child's position. Make sure the child is hanging freely and not touching anything. Repeat any steps as necessary.
- g Measurer: Hold the scale and read the weight to the nearest 0.1 kg ([Arrow 5](#)). Call out the measurement when the child is still and the scale needle is stationary. Even children who are very active, which causes the needle to wobble greatly, will become still long enough to take a reading. **WAIT FOR THE NEEDLE TO STOP MOVING.**

- h** Assistant: Immediately record the measurement and show it to the measurer.
- i** Measurer: As the assistant records the measurement, gently lift the child by the body. **DO NOT LIFT THE CHILD BY THE STRAP OF THE WEIGHING PANTS.** Release the strap from the hook of the scale.
- j** Measurer: Check the recorded measurement on the questionnaire for accuracy and legibility. Instruct the assistant to erase and correct any errors.

**Figure E1** Child weight using the hanging Salter-like scale

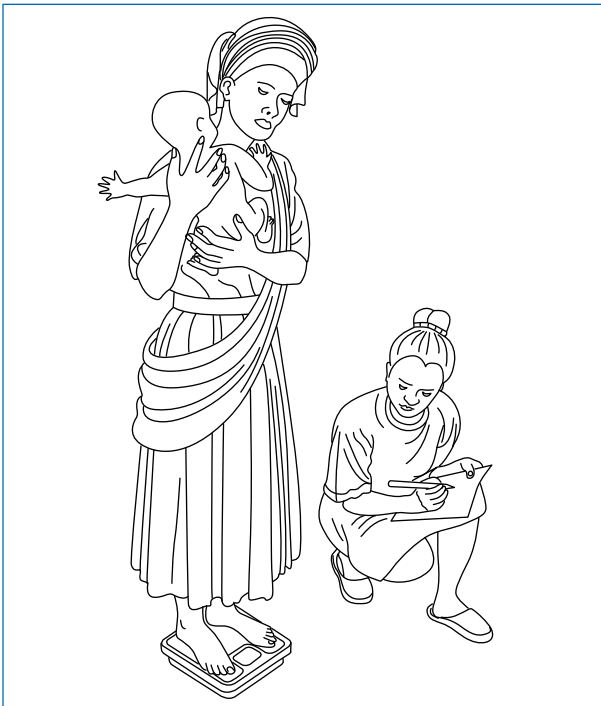




## 2 Child weight using the UNICEF UNISCALE

The UNICEF electronic scale requires the mother and child to be weighed simultaneously. Minimize the clothing on the child. Ensure the scale is not overheated in the sun and is on an even surface enabling the reading to be clear. Ask the mother to stand on the scale. Record the weight and include the reading with one decimal point (e.g. 65.5 kg). Pass the child to a person nearby. Record the second reading with just the mother (e.g. 58.3 kg). The difference (e.g. 7.2 kg) is the weight of the child. Refer to the UNICEF document 'How to Use the UNISCALE' (June, 2000) prepared by the Nutrition Section: Program Division/UNICEF New York. See [Figure 2](#) below.

**Figure E2** Child weight using the UNICEF UNISCALE



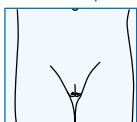
## Appendix F: Tanner staging

Because the onset and progression of puberty are so variable, Tanner has proposed a scale, now uniformly accepted, to describe the onset and progression of pubertal changes. Boys and girls are rated on a 5 point scale. Boys are rated for genital development and pubic hair growth, and girls are rated for breast development and pubic hair growth.

**Figure F1** Tanner staging in females as determined by pubic hair growth and breast development.



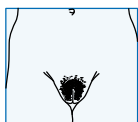
**Pubic hair stage 1**  
Prepubertal. The vellus over the pubis is no further developed than that over the abdominal wall, i.e. no pubic hair.



**Pubic hair stage 2**  
Sparse growth of slightly pigmented, longer but still downy hair, straight or only slightly curled, appearing chiefly along the labia.



**Pubic hair stage 3**  
The hair is considerably darker, coarser and more curled. The hair spreads sparsely over the mons.



**Pubic hair stage 4**  
The hair now resembles adult type. The area covered is still smaller than in the adult, but the hair is beginning to spread across the mons. There is no hair spread to the medial thighs.



**Pubic hair stage 5**  
The hair is adult type and quantity; darker, coarse and curled; and distributed in the classic female triangle. Some individuals may have hair spread to the medial thighs.



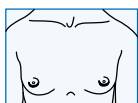
**Breast stage 1**  
There is no development. Only the papilla is elevated.



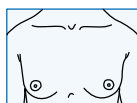
**Breast stage 2**  
The 'breast bud' stage. The areola widens, darkens slightly, and elevates from the rest of the breast as a small mound. A bud of breast tissue is palpable below the nipple.



**Breast stage 3**  
The breast and areola further enlarge and present a rounded contour. There is no separation of contour between the nipple and areola and the rest of the breast. The breast tissue creates a small cone.



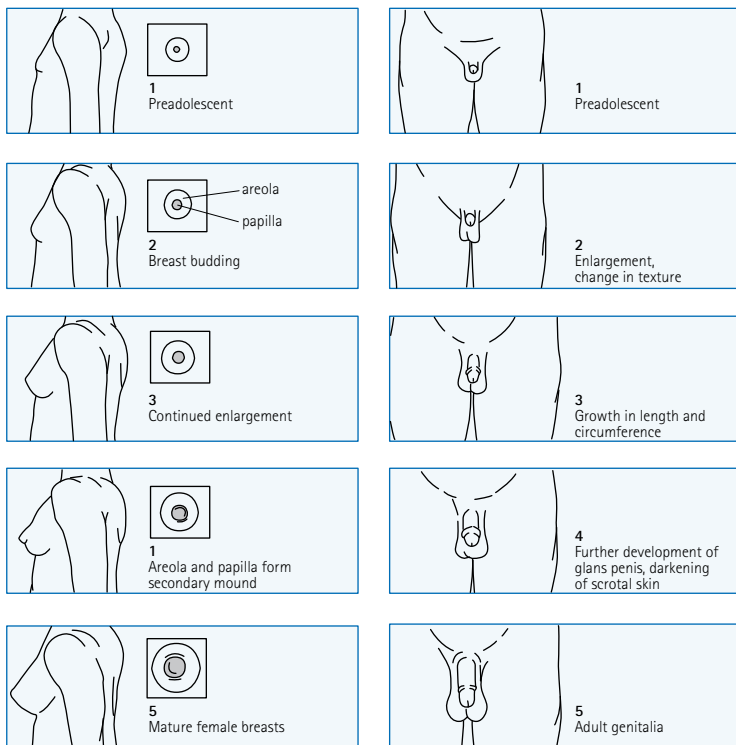
**Breast stage 4**  
The breast continues to expand. The papilla and areola project to form a secondary mound above the rest of the breast tissue.



**Breast stage 5**  
The mature adult stage. The secondary mound made by the areola and nipple, present in stage 4, disappears. Only the papilla projects. The diameter of the breast tissue (as opposed to the height) has extended to cover most of the area between the sternum and lateral chest wall.

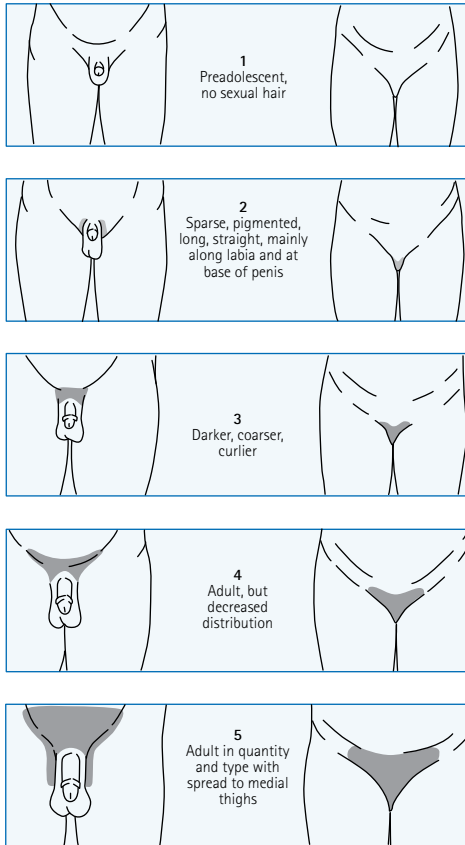
Source: Tool Kit for Teen Care, Second edition, American Academy of Obstetricians and Gynaecologists, 2009.

**Figure F2** Tanner staging as determined by breast development for females and genitalia for males.



Source: Feingold D. Pediatric Endocrinology. Atlas of Pediatric Physical Diagnosis, Second edition, Philadelphia. WB Saunders, 1992, 9: 16-19.

**Figure F3** Tanner staging as determined by pubic hair development in both males and females.



Source: Feingold D. Pediatric Endocrinology. Atlas of Pediatric Physical Diagnosis, Second edition, Philadelphia. WB Saunders, 1992, 9: 16-19.

## Appendix G: Toxicity grading and management

The tables on the following pages have been adapted from the Division of AIDS (DAIDS) tables for grading of severe adverse events (published in 2004, clarification in 2009), WHO guidelines for ART (2007) and NIH paediatric toxicity tables (2007).

ULN=Upper limit of normal; LLN = Lower limit of normal

CLINICAL				
Parameter	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Potentially life threatening
<b>ESTIMATING SEVERITY GRADE</b>				
Clinical adverse event NOT identified elsewhere in this DAIDS AE grading table	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
<b>SYSTEMIC</b>				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR mild angio-oedema with no medical intervention indicated	Generalized urticaria OR angio-oedema with medical intervention indicated OR symptomatic mild bronchospasm	Acute anaphylaxis OR life-threatening bronchospasm OR laryngeal oedema
Chills	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	N/A

<b>Fatigue/malaise</b>	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Incapacitating fatigue/malaise, symptoms causing inability to perform basic self-care functions
<b>Fever</b> (nonaxillary)	37.7–38.6 °C	38.7–39.3 °C	39.4–40.5 °C	>40.5 °C
<b>Pain</b> (indicate body site) <b>DO NOT</b> use for pain due to injection (see injection site reactions: Injection site pain)	Pain causing no or minimal interference with usual social and functional activities	Pain causing greater than minimal interference with usual social and functional activities	Pain causing inability to perform usual social and functional activities	Disabling pain causing inability to perform basic self-care functions OR hospitalization (other than emergency room visit) indicated
<b>Unintentional weight loss</b>	N/A	5–9% loss in body weight from baseline	10–19% loss in body weight from baseline	≥20% loss in body weight from baseline OR aggressive intervention indicated (e.g. tube feeding or total parenteral nutrition (TPN))

CLINICAL				
Parameter	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Potentially life threatening
<b>INFECTION</b>				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND symptoms causing no or minimal interference with usual social and functional activities	Systemic antimicrobial treatment indicated OR symptoms causing greater than minimal interference with usual social and functional activities	Systemic antimicrobial treatment indicated AND symptoms causing inability to perform usual social and functional activities OR operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g. septic shock)
<b>INJECTION SITE REACTIONS</b>				
Injection site pain (pain without touching) OR tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR pain/tenderness causing greater than minimal interference with usual social and functional activities	Pain/tenderness causing inability to perform usual social and functional activities	Pain/tenderness causing inability to perform basic self-care function OR hospitalization (other than emergency room visit) indicated for management of pain/tenderness



Injection site reaction (localized)				
<ul style="list-style-type: none"> <li>• <b>Adult &gt;15 years</b></li> </ul>	Erythema OR induration of 5 x 5 cm – 9 x 9 cm (or 25 cm <sup>2</sup> – 81 cm <sup>2</sup> )	Erythema OR induration OR oedema >9 cm any diameter (or >81 cm <sup>2</sup> )	Ulceration OR secondary infection OR phlebitis OR sterile abscess OR drainage	Necrosis (involving dermis and deeper tissue)
	Erythema OR induration OR oedema present but ≤2.5 cm diameter	Erythema OR induration OR oedema >2.5 cm diameter but <50% surface area of the extremity segment (e.g. upper arm/thigh)	Erythema OR induration OR oedema >2.5 cm diameter but <50% surface area of the extremity segment (e.g. upper arm/thigh)	Erythema OR induration OR oedema involving ≥50% surface area of the extremity segment (e.g. upper arm/thigh) OR ulceration OR secondary infection OR phlebitis OR sterile abscess OR drainage
<ul style="list-style-type: none"> <li>• <b>Paediatric ≤15 years</b></li> </ul>	Erythema OR induration OR oedema present but ≤2.5 cm diameter	Erythema OR induration OR oedema >2.5 cm diameter but <50% surface area of the extremity segment (e.g. upper arm/thigh)	Erythema OR induration OR oedema >2.5 cm diameter but <50% surface area of the extremity segment (e.g. upper arm/thigh)	Erythema OR induration OR oedema involving ≥50% surface area of the extremity segment (e.g. upper arm/thigh) OR ulceration OR secondary infection OR phlebitis OR sterile abscess OR drainage
<ul style="list-style-type: none"> <li>• <b>Puritis associated with injection.</b> See also: Skin: pruritis (itching – no skin lesions)</li> </ul>	Itching localized to injection site AND relieved spontaneously or with <48 hours treatment	Itching beyond the injection site but not generalized OR itching localized to injection site requiring ≥48 hours treatment	Generalized itching causing inability to perform usual social and functional activities	N/A

CLINICAL				
Parameter	Grade 1 : Mild	Grade 2 : Moderate	Grade 3 : Severe	Grade 4 : Potentially life threatening
<b>SKIN – DERMATOLOGICAL</b>				
<b>Alopecia</b>	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	N/A
<b>Cutaneous reaction – rash</b>	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles of limited number of bullae OR superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR ulceration of mucous membrane involving two or more distinct mucosal sites OR toxic epidermal necrolysis (TEN)
<b>Hyperpigmentation</b>	Slight or localized	Marked or generalized	N/A	N/A
<b>Hypopigmentation</b>	Slight or localized	Marked or generalized	N/A	N/A
<b>Pruritis</b> (itching – no skin lesions) (See also injection site reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social and functional activities	Itching causing greater than minimal interference with usual social and functional activities	Itching causing inability to perform usual social and functional activities	N/A

<b>CARDIOVASCULAR</b>				
<b>Cardiac arrhythmia (general)</b> (by ECG or physical exam)	Asymptomatic AND no intervention indicated	Asymptomatic AND non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND non-urgent medical intervention indicated	Life-threatening arrhythmia OR urgent intervention indicated
<b>Cardiac-ischaemia/infarction</b>	N/A	N/A	Symptomatic ischaemia (stable angina) OR testing consistent with ischaemia	Unstable angina OR acute myocardial infarction
<b>Haemorrhage</b> (significant acute blood loss)	N/A	Symptomatic AND no transfusion indicated	Symptomatic AND transfusion of $\leq 2$ units packed RBCs (for children $\leq 10$ cc/kg) indicated	Life-threatening hypotension OR transfusion of $> 2$ units packed RBCs (for children $> 10$ cc/kg) indicated
<b>Hypertension</b>				
<ul style="list-style-type: none"> <li><b>Adult <math>&gt; 17</math> years</b> (with repeat testing at same visit)</li> </ul>	$> 140$ – $159$ mm Hg systolic OR $> 90$ – $99$ mm Hg diastolic	$160$ – $179$ mm Hg systolic OR $100$ – $109$ mm Hg diastolic	$\geq 180$ mm Hg systolic OR $\geq 110$ mm Hg diastolic	Life-threatening consequences (e.g. malignant hypertension) OR hospitalization indicated (other than emergency room visit)

CLINICAL				
Parameter	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Potentially life threatening
Hypertension (continued)				
<ul style="list-style-type: none"> <li>• <b>Paediatric <math>\leq 17</math> year</b> (with repeat testing at same visit)</li> </ul>	N/A	91st–94th percentile adjusted for age, height and gender (systolic and/or diastolic)	$\geq 95$ th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g. malignant hypertension OR hospitalization indicated (other than emergency room visit)
<b>Hypotension</b>	N/A	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
<b>Pericardial effusion</b>	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR effusion with non-urgent intervention indicated	Life-threatening consequences (e.g. tamponade) OR urgent intervention indicated

<b>Prolonged PR interval</b>					
<ul style="list-style-type: none"> <li>• <b>Adult &gt;16 years</b></li> </ul>	PR interval 0.21–0.25 sec	PR interval >0.25 sec	Type II 2nd degree AV block OR ventricular pause >3.0 sec	Complete AV block	
<ul style="list-style-type: none"> <li>• <b>Paediatric ≤16 years</b></li> </ul>	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block	
<b>Prolonged QTc</b>					
<ul style="list-style-type: none"> <li>• <b>Adult &gt;16 years</b></li> </ul>	Asymptomatic, QTc interval 0.45–0.47 sec OR increase in interval <0.03 see above baseline	Asymptomatic, QTc interval 0.48–0.49 sec OR increase in interval 0.03–0.05 see above baseline	Asymptomatic QTc interval ≥0.50 sec OR increase in interval ≥0.06 sec above baseline	Life-threatening consequences, e.g. torsade de pointes or other associated serious ventricular dysrhythmia	
<ul style="list-style-type: none"> <li>• <b>Paediatric ≤16 years</b></li> </ul>	Asymptomatic, QTc interval 0.45–0.464 sec	Asymptomatic, QTc interval 0.465–0.479 sec	Asymptomatic, QTc interval ≥0.480 sec	Life threatening consequences, e.g. torsade de pointes or other associated serious ventricular dysrhythmia	
<b>Thrombosis/embolism</b>					
	N/A	Deep vein thrombosis AND no intervention indicated (e.g. anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND intervention indicated (e.g. anticoagulation, lysis filter, invasive procedure)	Emboic event (e.g. pulmonary embolism, life-threatening thrombus)	

CLINICAL				
Parameter	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Potentially life threatening
<b>Vasovagal episode</b> (associated with procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	N/A	N/A
<b>Verticular dysfunction</b> (congestive heart failure)	N/A	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
<b>Anorexia</b>	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR aggressive intervention indicated (e.g. tube feeding or total parenteral nutrition (TPN))
<b>Comment:</b> Please note that, while the grading scale provided for unintentional weight loss may be used as a guideline when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgement.				
<b>Ascites</b>	Asymptomatic	Symptomatic AND intervention indicated (e.g. diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences

<b>Cholecystitis</b>	N/A	Symptomatic AND medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g. sepsis or perforation)
<b>Constipation</b>	N/A	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Constipation with manual evacuation indicated	Life-threatening consequences (e.g. obstruction)
<b>Diarrhoea</b>				
<ul style="list-style-type: none"> <li><b>Adult and paediatric <math>\geq 1</math> year</b></li> </ul>	Transient or intermittent episodes of unformed stools OR increase of $\leq 3$ stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR increase of 4–6 stools over baseline per 24-hour period	Bloody diarrhoea OR increase of $\geq 7$ stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g. hypotensive shock)
<ul style="list-style-type: none"> <li><b>Paediatric <math>&lt; 1</math> year</b></li> </ul>	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR hypotensive shock
<b>Dysphagia-odynophagia</b>	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake

**CLINICAL**

Parameter	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Potentially life-threatening
<b>Mucositis/stomatitis</b> (clinical exam) Indicate site (e.g. larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-odynophagia and proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR mucosal bleeding with minor trauma	Tissue necrosis OR diffuse spontaneous mucosal bleeding OR life-threatening consequences (e.g. aspiration, choking)
<b>Nausea</b>	Transient (<24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for >48 hours OR aggressive rehydration indicated (e.g. IV fluids)	Life-threatening consequences (e.g. hypotensive shock)
<b>Pancreatitis</b>	N/A	Symptomatic AND hospitalization not indicated (other than emergency room visit)	Symptomatic AND hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g. circulatory failure, hemorrhage, sepsis)
<b>Proctitis</b> (functional-symptomatic) Also see mucositis/stomatitis for clinical exam	Rectal discomfort AND no intervention indicated	Symptoms causing greater than minimal interference with usual social and functional activities OR medical intervention indicated	Symptoms causing inability to perform usual social and functional activities OR operative intervention indicated	Life-threatening consequences (e.g. perforation)



<b>Vomiting</b>	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR aggressive rehydration indicated (e.g. IV fluids)	Life-threatening consequences (e.g. hypotensive shock)
<b>NEUROLOGIC</b>				
<b>Alteration in personality-behaviour or in mood</b> (e.g. agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social and functional activities	Alteration causing greater than minimal interference with usual social and functional activities	Alteration causing inability to perform usual social and functional activities	Behaviour potentially harmful to self or other (e.g. suicidal and homicidal ideation or attempt, acute psychosis) OR causing inability to perform basic self-care functions
<b>Altered mental status</b> For dementia, see cognitive and behavioural/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social and functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social and functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social and functional activities	Delirium OR obtundation OR coma

CLINICAL				
Parameter	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Potentially life threatening
<b>Ataxia</b>	Asymptomatic ataxia detectable on exam OR minimal ataxia causing no or minimal interference with usual social and functional activities	Symptomatic ataxia causing greater than minimal interference with usual social and functional activities	Symptomatic ataxia causing inability to perform usual social and functional activities	Disabling ataxia causing inability to perform basic self-care functions
<b>Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)</b>	Disability causing no or minimal interference with usual social and functional activities OR specialized resources not indicated	Disability causing greater than minimal interference with usual social and functional activities OR specialized resources on part-time basis indicated	Disability causing inability to perform usual social and functional activities OR specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR institutionalization indicated
<b>CNS ischaemia (acute)</b>	N/A	N/A	Transient ischaemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit

<p><b>Developmental delay</b> – Paediatric <math>\leq 16</math> years</p>	<p>Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting</p>	<p>Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting</p>	<p>Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting</p>	<p>Development regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting</p>
<p><b>Headache</b></p>	<p>Symptoms causing no or minimal interference with usual social and functional activities</p>	<p>Symptoms causing greater than minimal interference with usual social and functional activities</p>	<p>Symptoms causing inability to perform usual social and functional activities</p>	<p>Symptoms causing inability to perform basic self-care functions OR hospitalization indicated (other than emergency room visit) OR headache with significant impairment of alertness or other neurologic function</p>
<p><b>Insomnia</b></p>	<p>N/A</p>	<p>Difficulty sleeping causing greater than minimal interference with usual social and functional activities</p>	<p>Difficulty sleeping causing inability to perform usual social and functional activities</p>	<p>Disabling insomnia causing inability to perform basic self-care functions</p>

CLINICAL				
Parameter	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Potentially life threatening
<b>Neuromuscular weakness</b> (including myopathy and neuropathy)	Asymptomatic with decreased strength on exam OR minimal muscle weakness causing no or minimal interference with usual social and functional activities	Muscle weakness causing greater than minimal interference with usual social and functional activities	Muscle weakness causing inability to perform usual social and functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR respiratory muscle weakness impairing ventilation
<b>Neurosensory alteration</b> (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social and functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social and functional activities	Sensory alteration or paresthesia causing inability to perform usual social and functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
<b>Seizure (new onset)</b> – Adult $\geq 18$ years. See also Seizure (known pre-existing seizure disorder)	N/A	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (e.g. status epilepticus), or difficult to control (e.g. refractory epilepsy)

<p><b>Seizure (known pre-existing seizure disorder) Adult ≥18 years.</b> For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels</p>	<p>N/A</p>	<p>Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR infrequent breakthrough seizures while on stable medication in a previously controlled seizure disorder</p>	<p>Change in seizure character from baseline either in duration or quality (e.g. severity or focality)</p>	<p>Seizures of any kind that are prolonged, repetitive (e.g. status epilepticus), or difficult to control (e.g. refractory epilepsy)</p>
<p><b>Seizure – Paediatric &lt;18 years</b></p>	<p>Seizure, generalized onset with or without secondary generalization, lasting &lt;5 minutes with &lt;24 hours post ictal state</p>	<p>Seizure generalized onset with or without secondary generalization lasting 5–20 minutes with &lt;24 hours post ictal state</p>	<p>Seizure generalized onset with or without secondary generalization lasting &gt;20 minutes</p>	<p>Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation</p>
<p><b>Syncope (not associated with a procedure)</b></p>	<p>N/A</p>	<p>Present</p>	<p>N/A</p>	<p>N/A</p>
<p><b>Vertigo</b></p>	<p>Vertigo causing no or minimal interference with usual social and functional activities</p>	<p>Vertigo causing greater than minimal interference with usual social and functional activities</p>	<p>Vertigo causing inability to perform usual social and functional activities</p>	<p>Disabling vertigo causing inability perform basic self-care functions</p>

CLINICAL				
Parameter	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Potentially life threatening
<b>RESPIRATORY</b>				
Bronchospasm (acute)	FEV 1 or peak flow reduced to 70–80%	FEV or peak flow 50–69%	FEV 1 or peak flow 25–49%	Cyanosis OR FEV 1 or peak flow <25% OR intubation
<b>Dyspnoea or respiratory distress</b>				
<ul style="list-style-type: none"> <li>• <b>Adult ≥14 years</b></li> </ul>	Dyspnoea on exertion with no or minimal interference with usual social and functional activities	Dyspnoea on exertion causing greater than minimal interference with usual social and functional activities	Dyspnoea at rest causing inability to perform usual social and functional activities	Respiratory failure with ventilatory support indicated
<ul style="list-style-type: none"> <li>• <b>Paediatric &lt;14 years</b></li> </ul>	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR intercostal retractions OR pulse oximetry 90–95%	Dyspnoea at rest causing inability to perform usual social and functional activities OR pulse oximetry <90%	Respiratory failure with ventilatory support indicated
<b>Arthralgia</b> See also Arthritis	Joint pain causing no or minimal interference with usual social and functional activities	Joint pain causing greater than minimal interference with usual social and functional activities	Joint pain causing inability to perform usual social and functional activities	Disabling joint pain causing inability to perform basic self-care functions

<b>MUSCULOSKELETAL</b>					
<b>Arthritis</b> See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social and functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social and functional activities	Stiffness or joint swelling causing inability to perform usual social and functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions	
	<b>Bone mineral loss</b>	<ul style="list-style-type: none"> <li>• <b>Adult <math>\geq 21</math> years</b></li> <li>• <b>Paediatric <math>\leq 21</math> years</b></li> </ul>	<ul style="list-style-type: none"> <li>• <b>Myalgia (non-injection site)</b></li> </ul>		
	Stiffness or joint swelling causing minimal interference with usual social and functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social and functional activities	Stiffness or joint swelling causing inability to perform usual social and functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions	
	BMD t-score $-2.5$ to $-1.0$	BMD t-score $< -2.5$	Pathological fracture (including loss of vertebral height)	Pathological fracture causing life-threatening consequences	
	BMD z-score $-2.5$ to $-1.0$	BMD z-score $< -2.5$	Pathological fracture (including loss of vertebral height)	Pathological fracture causing life-threatening consequences	
	Muscle pain causing no or minimal interference with usual social and functional activities	Muscle pain causing greater than minimal interference with usual social and functional activities	Muscle pain causing inability to perform usual social and functional activities	Disabling muscle pain causing inability to perform basic self-care functions	

CLINICAL				
Parameter	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Potentially life threatening
<b>Osteonecrosis</b>	N/A	Asymptomatic with radiographic findings AND no operative intervention indicated	Symtomatic bone pain with radiographic findings OR operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
<b>GENITOURINARY</b>				
<b>Cervicitis (symptoms)</b> (for use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care functions
<b>Cervicitis (clinical exam)</b> (for use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR epithelial disruption <25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge or friability) OR epithelial disruption 25–49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR epithelial disruption 50–75% total surface	Epithelial disruption >75% total surface



<b>Inter-menstrual bleeding</b>	Spotting observed by participant OR minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Haemorrhage with life-threatening hypotension OR operative intervention indicated
<b>Urinary tract obstruction</b> (e.g. stone)	N/A	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences
<b>Vulvovaginitis (symptoms)</b> (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care functions
<b>Vulvovaginitis (clinical exam)</b> (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR epithelial disruption <25% of total surface	Moderate vaginal abnormalities on examination OR epithelial disruption 25–49% total surface	Severe vaginal on normalities on examination OR epithelial disruption 50–75% total surface	Vaginal perforation OR epithelial disruption >75% total surface

CLINICAL				
Parameter	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Potentially life threatening
<b>OCULAR/VISUAL</b>				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR medical intervention indicated	Posterior or pan-uveitis OR operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social and functional activities	Visual changes causing greater than minimal interference with usual social and functional activities	Visual changes causing inability to perform usual social and functional activities	Disabling visual loss in affected eye(s)
<b>ENDOCRINE/METABOLIC</b>				
Abnormal fat accumulation (e.g. back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR obvious changes on casual visual inspection	N/A
Diabetes mellitus	N/A	New onset without need to initiate medication OR modification of current medications to regain glucose control	New onset with initiation of medication indicated OR diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g. ketoacidosis, hyperosmolar non-ketotic coma)

<b>Gynaecomastia</b>	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by healthcare provider	Disfiguring OR obvious on casual visual inspection	N/A
<b>Hyperthyroidism</b>	Asymptomatic	Symptomatic causing greater than minimal interference with usual social and functional activities OR thyroid suppression therapy indicated	Symptomatic causing inability to perform usual social and functional activities OR uncontrolled despite treatment modification	Life-threatening consequences (e.g. thyroid storm)
<b>Hypothyroidism</b>	Asymptomatic	Symptomatic causing greater than minimal interference with usual social and functional activities OR thyroid replacement therapy indicated	Symptoms causing inability to perform usual social and functional activities OR uncontrolled despite treatment modification	Life-threatening consequences (e.g. myxedoema coma)
<b>Lipoatrophy</b> (e.g. fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by healthcare provider	Disfiguring OR obvious on casual visual inspection	N/A

LABORATORY				
Parameter	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Potentially life threatening
<b>HAEMATOLOGY</b>				
<i>Standard International Units are listed in italics</i>				
<b>Absolute CD4+ count – Adult and paediatric &gt;13 years</b> (HIV NEGATIVE ONLY)	300–400/mm <sup>3</sup> 300–400/μℓ	200–299/mm <sup>3</sup> 200–299/μℓ	100–199/mm <sup>3</sup> 100–199/μℓ	<100/mm <sup>3</sup> <100/μℓ
<b>Absolute lymphocyte count – Adult and paediatric &gt;13 years</b> (HIV NEGATIVE ONLY)	600–650/mm <sup>3</sup> 0.600 × 10 <sup>9</sup> – 0.650 × 10 <sup>9</sup> /ℓ	500–599/mm <sup>3</sup> 0.500 × 10 <sup>9</sup> – 0.599 × 10 <sup>9</sup> /ℓ	350–499/mm <sup>3</sup> 0.350 × 10 <sup>9</sup> – 0.499 × 10 <sup>9</sup> /ℓ	<350/mm <sup>3</sup> <0.350 × 10 <sup>9</sup> /ℓ
<b>Comment:</b> Values in children ≤13 years are not given for the two parameters above because the absolute counts are variable				
<b>Absolute neutrophil count (ANC)</b>				
• <b>Adult and paediatric, &gt;7 days</b>	750– <1 000/mm <sup>3</sup> 0.75 × 10 <sup>9</sup> – <1.0 × 10 <sup>9</sup> /ℓ	500–749/mm <sup>3</sup> 0.25 × 10 <sup>9</sup> – 0.499 × 10 <sup>9</sup> /ℓ	250–499/mm <sup>3</sup> 0.25 × 10 <sup>9</sup> – 0.499 × 10 <sup>9</sup> /ℓ	<250/mm <sup>3</sup> <0.250 × 10 <sup>9</sup> /ℓ
• <b>Infant<sup>6,5</sup>, 2– ≤7 days</b>	1 250–1 500/mm <sup>3</sup> 1.250 × 10 <sup>9</sup> – 1.500 × 10 <sup>9</sup> /ℓ	1 000–1 249/mm <sup>3</sup> 1.000 × 10 <sup>9</sup> – 1.249 × 10 <sup>9</sup> /ℓ	750–999/mm <sup>3</sup> 0.750 × 10 <sup>9</sup> – 0.999 × 10 <sup>9</sup> /ℓ	<750/mm <sup>3</sup> <0.750 × 10 <sup>9</sup> /ℓ
• <b>Infant<sup>6,5</sup>, ≤1 day</b>	4 000 – 5 000/mm <sup>3</sup> 4.000 × 10 <sup>9</sup> – 5.000 × 10 <sup>9</sup> /ℓ	3 000 – 3 999/mm <sup>3</sup> 3.000 × 10 <sup>9</sup> – 3.999 × 10 <sup>9</sup> /ℓ	1 500 – 2 999/mm <sup>3</sup> 1.500 × 10 <sup>9</sup> – 2.999 × 10 <sup>9</sup> /ℓ	<1 500/mm <sup>3</sup> <1.500 × 10 <sup>9</sup> /ℓ

<b>Fibrinogen, decreased</b>	100–200 mg/dL 1.0–2.00 g/L OR 0.75–0.99 × LLN	75–99 mg/dL 0.75–0.99 g/L OR 0.50–0.74 × LLN	50–74 mg/dL 0.50–0.74 g/L OR 0.25–0.49 × LLN	<50 mg/dL <0.50 g/L OR <0.25 × LLN OR Associated with gross bleeding
<b>Haemoglobin (Hb)</b>				
<b>Comment:</b> The Hb values in mmol/L have changed because the conversion factor used to convert g/dL to mmol/L has been changed from 0.155 to 0.6206 (the most commonly used conversion factor). For grading Hb results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for that laboratory.				
<ul style="list-style-type: none"> <li>• <b>Adult and paediatric</b> ≥57 days (HIV POSITIVE ONLY)</li> </ul>	8.5–10.0 g/dL 5.24–6.23 mmol/L	7.5–8.4 g/dL 4.62–5.23 mmol/L	6.50–7.4 g/dL 4.03–4.64 mmol/L	<6.5 g/dL <4.03 mmol/L
<ul style="list-style-type: none"> <li>• <b>Adult and paediatric</b> ≥57 days (HIV NEGATIVE ONLY)</li> </ul>	10.0–10.9 g/dL 6.18–6.79 mmol/L OR Any decrease 2.5–3.4 g/dL 1.58–2.13 mmol/L	9.0–9.9 g/dL 5.55–6.17 mmol/L OR Any decrease 3.5–4.4 g/dL 2.14–2.78 mmol/L	7.0–8.9 g/dL 4.34–5.54 mmol/L OR Any decrease ≥4.5 g/dL ≥2.79 mmol/L	<7.0 g/dL <4.34 mmol/L
<b>Comment:</b> The decrease is a decrease from baseline.				
<ul style="list-style-type: none"> <li>• <b>Infant<sup>†§</sup>, 36–56 days</b> (HIV POSITIVE OR NEGATIVE)</li> </ul>	8.5–9.4 g/dL 5.24–5.86 mmol/L	7.0–8.4 g/dL 4.31–5.86 mmol/L	6.0–6.9 g/dL 3.72–4.50 mmol/L	<6.00 g/dL <3.72 mmol/L
<ul style="list-style-type: none"> <li>• <b>Infant<sup>†§</sup>, 22–35 days</b> (HIV POSITIVE OR NEGATIVE)</li> </ul>	9.5–10.5 g/dL 5.86–6.54 mmol/L	8.0–9.4 g/dL 4.93–5.86 mmol/L	7.0–7.9 g/dL 4.34–4.92 mmol/L	<7.00 g/dL <4.34 mmol/L

LABORATORY				
Parameter	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Potentially life threatening
<b>Haemoglobin (Hb) (continued)</b>				
<ul style="list-style-type: none"> <li>• <b>Infant*<sup>5</sup> ≤21 days</b> (HIV POSITIVE OR NEGATIVE)</li> </ul>	12.0–13.0 g/dL 7.42–8.09 mmol/L	10.0–11.9 g/dL 6.18–7.41 mmol/L	9.0–9.9 g/dL 5.59–6.17 mmol/L	<9.0 g/dL <5.59 mmol/L
<b>Comment:</b> Parameter changed from 'Infant <21 days' to 'Infant ≤21 days'				
International normalized ratio of prothrombin time (INR)	1.1–1.5 × ULN	1.6–2.0 × ULN	2.1–3.0 × ULN	>3.0 × ULN
Methaemoglobin	5.0–10.0%	10.1–15.0%	15.1–20.0%	>20.0%
Prothrombin time (PT)	1.1–1.25 × ULN	1.26–1.50 × ULN	1.51–3.00 × ULN	>3.00 × ULN
Partial thromboplastin time (PTT)	1.1–1.66 × ULN	1.67–2.33 × ULN	2.34–3.00 × ULN	>3.00 × ULN
Platelets, decreased	100 000–124 999/mm <sup>3</sup> 100.000 × 10 <sup>9</sup> – 124.000 × 10 <sup>9</sup> /L	50 000–99 999/mm <sup>3</sup> 50.000 × 10 <sup>9</sup> – 99.999 × 10 <sup>9</sup> /L	25 000–49 999/mm <sup>3</sup> 25.000 × 10 <sup>9</sup> – 49.999 × 10 <sup>9</sup> /L	<25 000/mm <sup>3</sup> <25.000 × 10 <sup>9</sup> /L
WBC, decreased	2 000–2 500/mm <sup>3</sup> 2.000 × 10 <sup>9</sup> – 2.500 × 10 <sup>9</sup> /L	1 500–1 999/mm <sup>3</sup> 1.500 × 10 <sup>9</sup> – 1.999 × 10 <sup>9</sup> /L	1 000–1 499/mm <sup>3</sup> 1.000 × 10 <sup>9</sup> – 1.499 × 10 <sup>9</sup> /L	<1 000/mm <sup>3</sup> <1.000 × 10 <sup>9</sup> /L

<b>CHEMISTRIES</b>				<i>Standard International Units are listed in italics</i>			
Acidosis	NA	pH < normal, but $\geq 7.3$	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences			
Albumin, serum, low	3.0 g/dL – < LLN 30 g/l – < LLN	< 2.0 g/dL < 20 g/l					
Alkaline phosphatase	1.25–2.5 × ULN <sup>s</sup>	2.6–5.0 × ULN <sup>s</sup>	5.1–10.0 × ULN <sup>s</sup>	> 10.0 × ULN <sup>s</sup>			
Alkalosis	NA	pH > normal, but $\leq 7.5$	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences			
ALT (SGPT)	1.25–2.5 × ULN	2.6–5.0 × ULN	5.1–10.0 × ULN	> 10.0 × ULN			
AST (SGOT)	1.25–2.5 × ULN	2.6–5.0 × ULN	5.1–10.0 × ULN	> 10.0 × ULN			
Bicarbonate, serum, low	16.0 mEq/l – < LLN 16.0 mmol/l – < LLN	11.0–15.9 mEq/l 11.0 – 15.9 mmol/l	8.0–10.9 mEq/l 8.0–10.9 mmol/l	< 8.0 mEq/l < 8.0 mmol/l			
<b>Comment:</b> Some laboratories will report this value as bicarbonate (HCO <sub>3</sub> ) and others as total carbon dioxide (CO <sub>2</sub> ). These are the same test, values should be graded according to the ranges for bicarbonate as listed above.							
<b>Bilirubin (total)</b>							
• Adult and paediatric > 14 days	1.1–1.5 × ULN	1.6–2.5 × ULN	2.6–5.0 × ULN	> 5.0 × ULN			
• Infant <sup>**s</sup> , $\leq 14$ days (non-haemolytic)	NA	20.0–25.0 mg/dL 342–428 $\mu$ mol/l	25.1–30.0 mg/dL 429–513 $\mu$ mol/l	> 30.0 mg/dL > 513 $\mu$ mol/l			
• Infant <sup>**s</sup> , $\leq 14$ days (haemolytic)	NA	NA	20.0–25.0 mg/dL 342–428 $\mu$ mol/l	> 25.0 mg/dL > 428 $\mu$ mol/l			

LABORATORY				
Parameter	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Potentially life threatening
Calcium, serum, high (corrected for albumin)				
• Adult and paediatric ≥7 days	10.6–11.5 mg/dL 2.65–2.88 mmol/L	11.6–12.5 mg/dL 2.89–3.13 mmol/L	12.6–13.5 mg/dL 3.14–3.38 mmol/L	>13.5 mg/dL >3.38 mmol/L
• Infant <sup>†§</sup> , <7 days	11.5–12.4 mg/dL 2.88–3.10 mmol/L	12.5–12.9 mg/dL 3.11–3.23 mmol/L	13.0–13.5 mg/dL 3.245–3.38 mmol/L	>13.5 mg/dL >3.38 mmol/L
Calcium, serum, low (corrected for albumin)				
• Adult and paediatric ≥7 days	7.8–8.4 mg/dL 1.95–21.10 mmol/L	7.0–7.7 mg/dL 1.75–1.94 mmol/L	6.1–6.9 mg/dL 1.53–1.74 mmol/L	<6.1 mg/dL <1.53 mmol/L
• Infant <sup>†§</sup> , <7 days	6.5–7.5 mg/dL 1.63–1.88 mmol/L	6.0–6.4 mg/dL 1.50–1.62 mmol/L	5.50–5.90 mg/dL 1.38–1.51 mmol/L	<5.50 mg/dL <1.38 mmol/L
<b>Comment:</b> Do not adjust calcium, serum, low or calcium, serum, high for albumin				
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer



<b>Cholesterol (fasting)</b>						
• Adult ≥18 years	200–239 mg/dL 5.18–6.19 mmol/L	240–300 mg/dL 6.20–7.77 mmol/L	>300 mg/dL >7.77 mmol/L	NA		
• Paediatric <18 years	170–199 mg/dL 4.40–5.15 mmol/L	200–300 mg/dL 5.16–7.77 mmol/L	>300 mg/dL >7.77 mmol/L	NA		
Creatine kinase	3.0–5.9 × ULN <sup>§</sup>	6.0–9.9 × ULN <sup>§</sup>	10.0–19.9 × ULN <sup>§</sup>	≥20.0 × ULN <sup>§</sup>		
Creatinine	1.1–1.3 × ULN <sup>§</sup>	1.4–1.8 × ULN <sup>§</sup>	1.9–3.4 × ULN <sup>§</sup>	≥3.5 × ULN <sup>§</sup>		
<b>Glucose, serum, high</b>						
• Nonfasting	116–160 mg/dL 6.44–8.88 mmol/L	161–250 g/dL 8.89–13.88 mmol/L	251–500 mg/dL 13.89–27.75 mmol/L	>500 mg/dL >27.75 mmol/L		
• Fasting	110–125 mg/dL 6.11–6.94 mmol/L	126–250 mg/dL 6.95–13.88 mmol/L	251–500 mg/dL 13.89–27.75 mmol/L	>500 mg/dL >27.75 mmol/L		
<b>Glucose, serum, low</b>						
• Adult and paediatric ≥1 month	55–64 mg/dL 2.78–3.55 mmol/L	40–54 mg/dL 2.22–3.06 mmol/L	30–39 mg/dL 1.67–2.23 mmol/L	<30 mg/dL <1.67 mmol/L		
• Infant* <sup>§</sup> , <1 month	50–54 mg/dL 2.78–3.00 mmol/L	40–49 mg/dL 2.22–2.77 mmol/L	30–39 mg/dL 1.67–2.21 mmol/L	<30 mg/dL <1.67 mmol/L		
Lactate	ULN– <2.0 × ULN with acidosis	≥2.0 × ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences		
<b>Comment:</b> Added ULN to grade 1 parameter						

LABORATORY				
Parameter	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Potentially life threatening
<b>LDL cholesterol (fasting)</b>				
• Adult ≥18 years	130–159 mg/dL 3.37–4.12 mmol/L	160–190 mg/dL 4.13–4.90 mmol/L	≥190 mg/dL ≥4.91 mmol/L	NA
• Paediatric 2– <18 years	110–129 mg/dL 2.85–3.34 mmol/L	130–189 mg/dL 3.35–4.90 mmol/L	≥190 mg/dL ≥4.91 mmol/L	NA
Lipase	1.1–1.5 × ULN	1.6–3.0 × ULN	3.1–5.0 × ULN	>5.0 × ULN
Magnesium, serum, low	1.2–1.4 mEq/L 0.60–0.70 mmol/L	0.9–1.1 mEq/L 0.45–0.59 mmol/L	0.6–0.8 mEq/L 0.30–0.41 mmol/L	<0.60 mEq/L <0.30 mmol/L
Pancreatic amylase	1.1–1.5 × ULN	1.6–2.0 × ULN	2.1–5.0 × ULN	>5.0 × ULN
<b>Phosphate, serum, low</b>				
• Adult and paediatric >14 years	2.5 mg/dL– < LLN 0.81 mmol/L– < LLN	2.0–2.4 mg/dL 0.65–0.80 mmol/L	1.0–1.9 mg/dL 0.32–0.64 mmol/L	<1.00 mg/dL <0.32 mmol/L
• Paediatric 1–14 years	3.0–3.5 mg/dL 0.97–1.13 mmol/L	2.5–2.9 mg/dL 0.81–0.96 mmol/L	1.5–2.4 mg/dL 0.48–0.80 mmol/L	<1.50 mg/dL <0.48 mmol/L
• Paediatric <1 year	3.5–4.5 mg/dL 1.13–1.45 mmol/L	2.5–3.4 mg/dL 0.81–1.12 mmol/L	1.5–2.4 mg/dL 0.48–0.80 mmol/L	<1.50 mg/dL <0.48 mmol/L
Potassium, serum, high	5.6–6.0 mEq/L 5.6–6.0 mmol/L	6.1–6.5 mEq/L 6.1–6.5 mmol/L	6.6–7.0 mEq/L 6.6–7.0 mmol/L	>7.0 mEq/L >7.0 mmol/L
Potassium, serum, low	3.0–3.4 mEq/L 3.0–3.4 mmol/L	2.5–2.9 mEq/L 2.5–2.9 mmol/L	2.0–2.4 mEq/L 2.0–2.4 mmol/L	<2.0 mEq/L <2.0 mmol/L

Sodium, serum, high	146–150 mEq/l 146–150 mmol/l	151–154 mEq/l 151–154 mmol/l	155–159 mEq/l 155–159 mmol/l	≥ 160 mEq/l ≥ 160 mmol/l
Sodium, serum, low	130–165 mEq/l 130–135 mmol/l	125–129 mEq/l 125–129 mmol/l	121–124 mEq/l 121–124 mmol/l	≤ 120 mEq/l ≤ 120 mmol/l
Triglycerides (fasting)	NA	500–700 mg/dL 5.65–8.48 mmol/l	751–1,200 mg/dL 8.49–13.56 mmol/l	> 1 200 mg/dL > 13.56 mmol/l
Uric acid	7.5–10.0 mg/dL 0.45–0.59 mmol/l	10.1–12.0 mg/dL 0.60–0.71 mmol/l	12.1–15.0 mg/dL 0.72–0.89 mmol/l	> 15.0 mg/dL > 0.89 mmol/l
<b>URINALYSIS</b>				
<i>Standard International Units are listed in italics</i>				
Haematuria (microscopic)	6–10 RBC/HPF	>10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1+	2–3+	4+	NA
<b>Proteinuria, 24 hour collection</b>				
• Adult and paediatric ≥10 years	200–999 mg/24 h 0.200–0.999 g/d	1 000–1 999 mg/24 h 1.000–1.999 g/d	2 000–3 500 mg/24 h 2.000–3.500 g/d	>3 500 mg/24 h >3.500 g/d
• Paediatric >3 mo–<10 years	201–499 mg/m <sup>2</sup> /24 h 0.201–0.499 g/d	500–799 mg/m <sup>2</sup> /24 h 0.500–0.799 g/d	800–1 000 mg/m <sup>2</sup> /24 h 0.80–1.00 g/d	> 1 000 mg/m <sup>2</sup> /24 h > 1.000 g/d

## Appendix H: WHO recommended minimum package of services for young clients

Minimum package of services	Minimum plus (in addition to the minimum package)
<i>HIV testing and counselling</i>	
<i>Treatment for:</i> <ul style="list-style-type: none"> <li>• OIs, including PCP, TB, and candidiasis</li> <li>• Diarrhoea (ORS)</li> <li>• Malaria</li> <li>• Deworming</li> </ul>	
<i>Prophylaxis (primary/secondary) for:</i> <ul style="list-style-type: none"> <li>• OIs, including PCP and cryptococcus</li> <li>• Malaria (IPT, mosquito nets)</li> </ul>	<i>Prophylaxis (primary/secondary) for:</i> <ul style="list-style-type: none"> <li>• TB</li> </ul>
<i>ARVs (first and second line)</i>	<i>ARVs (third line/experimental)</i>
<i>PMTCT and antenatal care</i>	
<i>Complete history and clinical examination</i> <ul style="list-style-type: none"> <li>• Including weight and height and</li> <li>• including a focus on STI signs and symptoms</li> </ul>	
<i>Sexual and reproductive health</i> <ul style="list-style-type: none"> <li>• Condoms/contraception/emergency contraception</li> <li>• Family planning</li> <li>• Pregnancy options and support</li> <li>• Sex education</li> </ul>	
<i>Prevention with/for positives</i> <ul style="list-style-type: none"> <li>• Counselling for prevention</li> <li>• Positive (healthy) living</li> <li>• Family testing</li> <li>• PEP</li> <li>• Condoms</li> <li>• Substance abuse counselling</li> </ul>	<i>Prevention with/for positives</i> <ul style="list-style-type: none"> <li>• Family- /home-based VCT</li> <li>• Clean needles and syringes for injection drug users (access to harm-reduction services)</li> </ul>

<p><i>Psychosocial counselling</i></p> <ul style="list-style-type: none"> <li>• Mental health screening and referral</li> <li>• Adherence counselling</li> <li>• Disclosure counselling</li> <li>• Clinic-based peer support group</li> </ul>	
<p><i>Nutrition counselling</i></p>	<p><i>Nutrition support</i></p>
<p><i>Laboratory</i></p> <ul style="list-style-type: none"> <li>• Pregnancy</li> <li>• Haemoglobin</li> <li>• Syphilis</li> <li>• Sputum</li> <li>• CD4 lymphocyte count</li> </ul>	<p><i>Laboratory</i></p> <ul style="list-style-type: none"> <li>• Pap smear</li> <li>• Viral load</li> <li>• Resistance testing</li> </ul>
<p><i>IEC materials</i></p> <ul style="list-style-type: none"> <li>• Prevention</li> <li>• Treatment literacy</li> <li>• Disease literacy</li> <li>• Living positively</li> <li>• Existing legal rights (as they apply locally)</li> </ul>	
<p><i>Effective referral system with follow-ups</i></p> <ul style="list-style-type: none"> <li>• Linkages with family, community, NGO services</li> <li>• Linkages with other youth services</li> <li>• Connections with legal institutions</li> </ul>	
<p><i>Immunizations</i></p> <ul style="list-style-type: none"> <li>• Tetanus toxoid</li> </ul>	<p><i>Immunizations</i></p> <ul style="list-style-type: none"> <li>• Hepatitis B</li> <li>• Pneumococcal</li> <li>• Human papilloma virus</li> </ul>

OI = opportunistic infection; PCP = *Pneumocystis jirovecii* pneumonia;  
 TB = tuberculosis; ORS = oral rehydration salts; IPT = intermittent preventive treatment;  
 ARV = antiretroviral; STI = sexually transmitted infection; PEP = postexposure prophylaxis;  
 NGO = non governmental organization; MAC = *Mycobacterium avium* complex;  
 VCT = voluntary counselling and testing; PMTCT = prevention of mother-to-child transmission;  
 IEC = information, education, and communication

Source: WHO and UNICEF



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## However limited the resources, there is always something that can be done for an individual child.

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