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Abbreviations and acronyms

3TC	lamivudine
ABC	abacavir
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
AZT	zidovudine
BCG	Bacille Calmette-Guerin
CD4+	T-lymphocyte-bearing CD4 receptor
% CD4+	percentage of total lymphocytes that are CD4+
d4T	stavudine
ddI	didanosine
DNA	deoxyribonucleic acid
EFV	efavirenz
FTC	emtricitabine
HIV	human immunodeficiency virus
IMCI	Integrated Management of Childhood Illness
IRIS	immune reconstitution inflammatory syndrome
LPV	lopinavir
LPV/r	lopinavir with a ritonavir boost
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NRTI	nucleoside or nucleotide reverse-transcriptase inhibitor
NVP	nevirapine
PI/r	protease inhibitor boosted with ritonavir
PCR	polymerase chain reaction
RNA	ribonucleic acid
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
VL	viral load
WHO	World Health Organization

Definitions for strength and quality of recommendations

Concepts relating to strength of recommendations for use of a given intervention

Strong	strong recommendation for the statement
Moderate	moderate recommendation for the statement
Optional	optional recommendation for the statement
No recommendation	no evidence to inform use of intervention

Concepts relating to quality of evidence guiding recommendations for use of interventions

A	data from reasonable powered randomized controlled trials using relevant endpoints (high quality of evidence)
B	data only from well-designed prospective observational studies assessing clinical endpoints only (moderate quality of evidence)
C	data from case stories and/or expert opinion only (low or very low quality of evidence)

Acknowledgement

This document is an updated version of this clinical protocol released in 2007. It is one of 13 clinical protocols released by the WHO Regional Office for Europe as part of the HIV/AIDS Treatment and Care Clinical Protocols of the WHO European Region.

The updated version of the protocol is based on new evidence of HIV treatment for children and the 2010 WHO recommendations on *Antiretroviral therapy for HIV infection in infants and children: towards universal access. Recommendations for a public health approach*. The process included consultation with regional clinical experts through a 2010 meeting in Kyiv (Ukraine) and electronic communication with them to ensure that the updated version of the protocol corresponds to the countries' needs and reflects diverse capacity to implement it.

This update was carried out by Steven Welch, consultant paediatrician in Birmingham Heartlands Hospital, in collaboration with the WHO Regional Office for Europe, and a panel of experts provided valuable comments on draft versions: Esmira Almamedova (AIDS Center, Baku, Azerbaijan), Larisa Afonina (Republican Clinical Infectious Diseases Hospital, Ust-Izora, the Russian Federation), Valentina Baltag, Masoud Dara, Pierpaolo de Colombani, Irina Eramova (WHO, Copenhagen, Denmark), Shaffiq Essajee (WHO, Geneva, Switzerland), Kamila Fatykhova (NGO "Qualdirgoch", Tashkent, Uzbekistan), Svetlana Komar (National Children Hospital "Ohmadet", Kyiv, Ukraine), Olga Kim (National Institute of Paediatrics, Tashkent, Uzbekistan), Aigul Kuttumuradova (WHO, Copenhagen, Denmark), Ruslan Malyuta (UNICEF, Geneva, Switzerland), Armen Mkrtychyan (National AIDS Center, Yerevan, Armenia), Anarkul Sultanova (National AIDS Center, Bishkek, Kyrgyzstan).

I. Introduction

This regional guidance follows updated global WHO guidance in 2010 (1,2) and is intended to adapt this guidance to the Regional context. The updated global guidance followed a formal review of the available evidence. Although this review noted some important new high-quality evidence from randomized controlled trials, it recognized that many recommendations that are more appropriate for the European Region are still based on low-quality evidence, expert opinion and practical considerations. The United States National Institutes of Health (3) and the Paediatric European Network for the Treatment of AIDS (4) have also published guidance on managing HIV among children. This publication should also be read in conjunction with guidelines for treating adults and adolescents with HIV (5–7) and Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents (2012 revision)*.

The goals of HIV treatment and care for children are preventing children from acquiring HIV infection, providing early accurate diagnosis and providing optimal health care to children living with HIV to minimize the number of children dying and to optimize their quality of life.

Optimal health care is centred on providing antiretroviral therapy (ART) but should also include holistic care to maximize physical health and mental well-being for children and adolescents living with HIV as a chronic condition.

Provision of ART should aim to achieve viral suppression with a minimal risk of short- and long-term side effects, viral resistance or interference with normal daily living. Viral suppression aims to maximize immune system functioning, optimize long-term growth and development and minimize the risks of opportunistic infections, cancer and non-AIDS associated morbidity and mortality.

The policy on ART among children living with HIV should be based on the following principles.

ART should be available as part of a comprehensive package of HIV treatment and care for children:

- It should be consistent with Protocol 10, *Prevention of HIV transmission from HIV-infected mothers to their infants (2012 revision)*.
- Paediatricians should provide routine care and collaborate closely with paediatric HIV specialists to monitor HIV progression and the need for ART.
- A continuum of care should be assured during childhood, during transition to adolescence and adulthood and in accordance with future treatment and care for adolescents and adults (see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents (2012 revision)*).

II. Laboratory diagnosis of HIV

1. Background

Infants and children¹ can be infected with HIV during mother's pregnancy, during delivery and postpartum, through breastfeeding or through sexual or parenteral exposure. Infants infected in utero usually have detectable HIV infection on virological testing at birth. Infants infected at or around delivery usually have undetectable HIV on virological testing at birth, and a short time (1–2 weeks) may pass before the virus is detectable by virological assays.

Data from studies in resource-limited settings confirm that, for infants who acquire HIV infection before or around delivery, the disease progresses very rapidly in the first few months of life, often leading to death (8). In recent studies in South Africa, up to 80% of infants living with HIV who were well at 6 weeks progressed to become eligible to start ART by 6–12 months of age (9,10). European cohort data in a high-income country also show that 75% fewer infants living with HIV die with early versus late initiation of ART (11). Determining whether an infant has been exposed to HIV and definitive diagnosis at an early stage are therefore critical to enable potentially life-saving ART to be initiated early.

Because maternal HIV antibodies pass across the placenta to the baby, a positive HIV serological test in infancy does not confirm HIV infection but does indicate that the mother is living with HIV and that the infant has been exposed. HIV serological tests used for clinical diagnostic testing should have a minimum sensitivity of 99% and specificity of 98% under standardized and validated laboratory conditions (2). Diagnosing HIV infection definitively among infants younger than 18 months of age requires assays that detect the virus or its components. Virological tests that can be used for infants and children include assays to detect HIV DNA, assays to detect HIV RNA and ultrasensitive assays to detect p24 antigen (12).

Assays to detect HIV DNA or RNA or both (collectively known as nucleic acid amplification tests) are commercially available using a variety of manual and automated platforms. Nucleic acid amplification tests have become less expensive and easier to standardize and provide several advantages for the early diagnosis of HIV infection among children and for monitoring the effectiveness of ART (13). The sensitivity of virological tests depends in part on the timing of the test. HIV DNA and RNA are not detected in early blood specimens but usually become detectable at or after 1–2 weeks of age (12). Among infants infected with HIV in utero, HIV DNA and RNA can be detected in peripheral blood specimens obtained within 48 hours of birth. HIV DNA assays have good accuracy in whole blood and dried blood spot. HIV RNA assays have good accuracy in plasma and dried blood spot, as do the ultrasensitive p24 antigen assays. Only the newer immune complex–dissociated ultrasensitive version of the p24 antigen assays should be used (12).

Virological testing may produce false-positive and false-negative results, and positive test results need to be confirmed. Confirmatory testing may stretch already constrained health care systems, but ensuring accuracy with confirmatory tests reduces the risk of unnecessarily starting uninfected infants on lifelong ART.

Dried blood spot specimens are easy to collect, store and process; they do not require venepuncture since they can be obtained by using blood from a finger-stick or heel-stick. They carry a

¹ Child is everyone under the age of 18 years <http://www.unicef.org.uk/Documents/Publication-pdfs/crcsummary.pdf?epslanguage=en>

smaller biohazard risk than liquid samples, are stable at room temperature for prolonged periods and are easier to transport, allowing for centralized laboratory testing (12). The use of dried blood spot is very practical for testing HIV-exposed infants in primary-level health facilities and should be more widely implemented to improve access to diagnostic testing in a range of resource-limited settings.

Among children 18 months or older, HIV serological tests, including rapid serological tests (either rapid HIV tests or laboratory-based HIV enzyme immunoassays or a combination of both), followed by confirmatory immunoblotting test can be reliably used to diagnose HIV infection definitively in the same manner as they are used in adults. HIV serological testing can also be used among infants with unknown maternal HIV status (in case mother can not be reached for HIV testing) to screen for HIV exposure and to identify infants who have seroreverted and are likely to be uninfected (2).

Virological testing of infants and children younger than 18 months of age who are known or suspected to have been exposed to HIV should not be delayed.

A single negative maternal test for HIV, especially early in pregnancy, does not exclude HIV exposure of the infant, as the mother may have become infected with HIV later in pregnancy or during breastfeeding. All infants and children with signs or symptoms suggesting possible HIV infection should therefore be tested for HIV, even if they have no known history of exposure during pregnancy, delivery or breastfeeding, meaning that the mother has had previous negative HIV serostatus.

Children may or may not have a living parent or identified legal guardian, and issues of consent, competence to provide consent, disclosure, confidentiality and counselling must be considered. National policies need to be clear in their recommendations on how to provide HIV testing services to infants and children, and programmes should ensure that tools and resources provide clear specific guidance on counselling, informed consent (from the child, parent and/or caregiver) and disclosure of HIV test results. If a young child or infant is diagnosed with HIV infection, the mother is usually living with HIV, and partners and other siblings may also be living with HIV. Appropriate counselling and support should therefore be provided to families when testing children for HIV.

2. Diagnosing HIV infection among infants and children

- All infants² born to HIV infected mothers or mothers not tested on HIV should have their HIV exposure status established at their first contact with the health system, at or around birth, but always before six weeks of age. If the mother has not been HIV tested or the HIV status of the mother remains unclear for the duration of the pregnancy, then an HIV serological test should be performed on the mother after obtaining informed consent.
- If the mother is unavailable or does not consent to maternal HIV testing, then HIV serological testing of the infant is recommended to detect HIV exposure. Consent of a parent is required for such testing.

² Infants are children younger than 12 months of age.

HIV testing for infants should consider the following:

- First virological testing should be conducted about 48 hours after birth (if resources allow). Positive test would indicate provisional HIV infection, and cotrimoxazole prophylaxis should be initiated at age of 4 weeks.
- Next HIV virological test should be performed at 4–6 weeks of age. Virological testing at 4–6 weeks of age will identify more than 95% of infants who were infected in utero and intrapartum (14–17). Delaying testing beyond this time delays diagnosis and puts infants living with HIV at risk of disease progression and death. A second positive virological test at 4–6 weeks would indicate the need for initiation of ART. Results of repeat tests should be obtained promptly in order not to delay initiation of ART. A repeat test on a separate specimen should be performed to confirm the initial positive test. The reliability of the laboratory (determined by standard quality assessment) is fundamental to ensure reliable test results (12).
- Virological test at the age of 3 months can be considered as confirmatory one for HIV.

Please see figure 1 presenting the algorithm of HIV virological diagnosis in non-breastfed infants born to HIV-infected mothers.

For children 12–18 months of age, diagnosis using virological testing is recommended. However, if access to virological testing is limited, it is recommended that, for this age group, virological tests be performed only after positive serological testing.

HIV infection can be definitively diagnosed among children 18 months or older (with known or unknown HIV exposure) with HIV serological tests, including rapid serological tests following the standard testing algorithms used for adults. The use of rapid serological tests for diagnosis has the advantage that the results become available at the time of the clinic visit.

3. Diagnosing HIV infection among breastfeeding infants and children

The WHO Regional Office for Europe does not recommend breastfeeding for infants born to mothers living with HIV if formula feeding does not meet the AFASS criteria (acceptable, feasible, affordable, safe and sustainable) (see Protocol 10, *Prevention of HIV transmission from HIV-infected mothers to their infants, 2012 revision*).

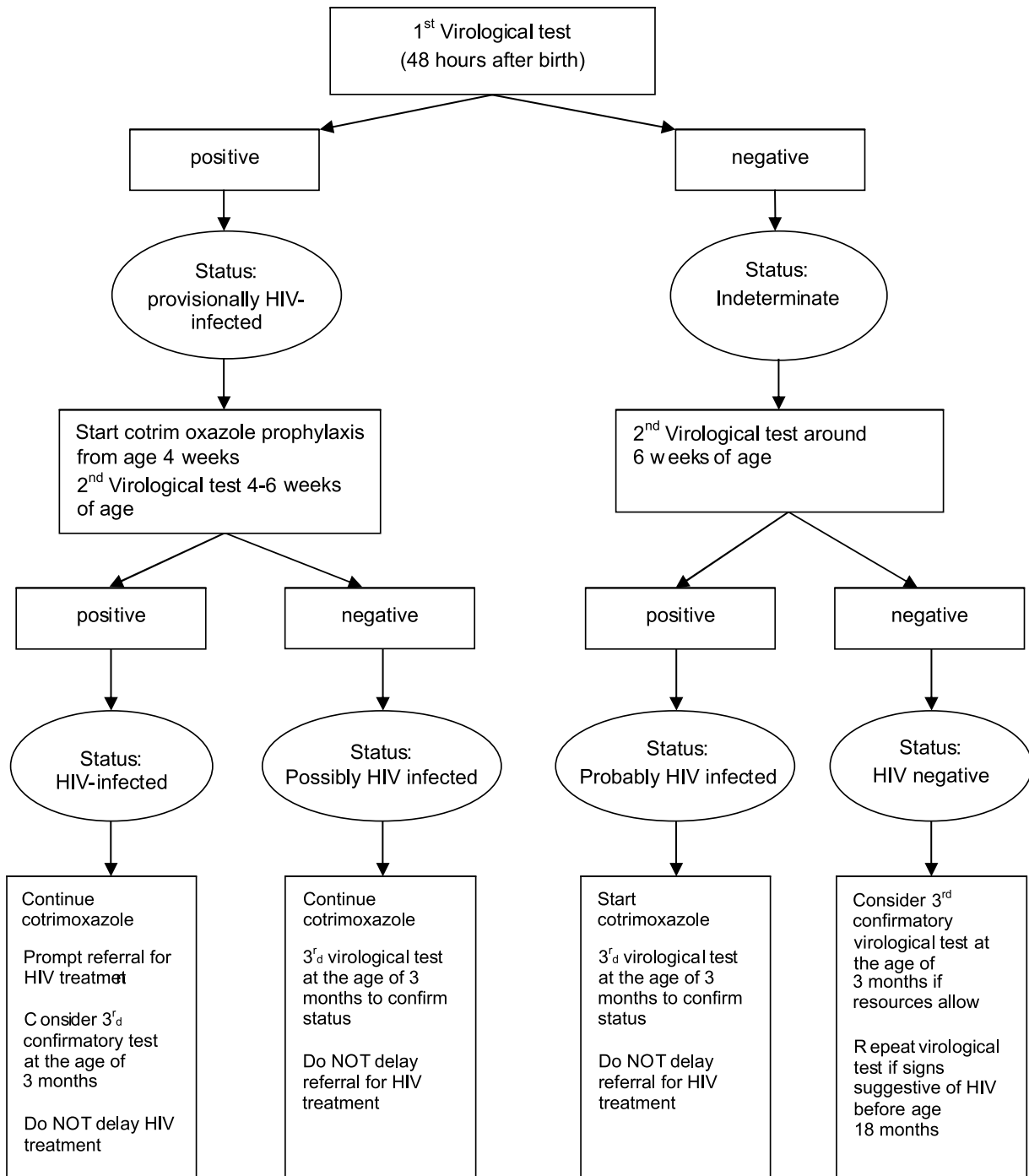
If alternative feeding is not available and the infant is breastfeeding, virological assays can be performed at any time. If the result is negative, then it should be repeated at least 6–12 weeks after breastfeeding ends, to confirm that the infant is not living with HIV.

4. Presumptively diagnosing HIV-exposed infants and children younger than 18 months of age with severe HIV disease

No single clinical diagnostic algorithm has proved highly sensitive or specific for diagnosing HIV infection. Clinical algorithms vary in their sensitivity and specificity (18–20), especially with respect to the age of the child. In particular, they are less reliable among infants (21). However, if access to virological testing is not yet available, infants and children can be presumptively diagnosed with severe HIV disease if they are younger than 18 months of age with a positive serological HIV test (either the mother or child) and have specific symptoms suggesting HIV infection:

- oral thrush
- severe pneumonia
- severe sepsis

Fig. 1. HIV virological diagnosis in non-breastfed infants born to HIV-infected mothers



or

- any AIDS-indicator condition³
- child's % of CD4 < 20%
- maternal advanced HIV disease or HIV related death.

An infant or child who meets these criteria has severe HIV disease and needs immediate ART. If virological testing is not available, HIV serological testing should be repeated at 18 months of age to confirm HIV infection.

The WHO Integrated Management of Childhood Illness (IMCI) programme has the following definitions.

- **Oral thrush:** creamy white-to-yellow soft small plaques on red or normally coloured mucosa that can often be scraped off (pseudomembranous) or red patches on the tongue, palate or lining of mouth, usually painful or tender.
- **Severe pneumonia:** cough or difficult breathing in a child with chest indrawing, stridor or any of the IMCI general danger signs: lethargic or unconscious, not able to drink or breast-feed, vomiting and presence or history of convulsions during current illness; responding to antibiotics.
- **Severe sepsis:** fever or low body temperature in a young infant with any severe sign, such as rapid breathing, chest indrawing, bulging fontanelles, lethargy, reduced movement, not feeding or sucking breast-milk and convulsions.

It is unclear how often the CD4 count is lowered in these conditions in HIV-uninfected children.

5. Recommendations

- It is strongly recommended that HIV serological assays used for clinical diagnostic testing have a minimum sensitivity of 99% and specificity of 98% under quality-assured, standardized and validated laboratory conditions. For children younger than 18 months, this should be used as a screening assay to determine HIV exposure. For children older than 18 months, this should be used as a diagnostic assay.

(Strong recommendation, B)

- It is strongly recommended that the HIV virological assays used for clinical diagnostic testing (usually at or after 6 weeks of age) have a sensitivity of at least 95% and ideally greater than 98%, and specificity of 98% or more under quality-assured, standardized and validated laboratory conditions.

(Strong recommendation, B)

- It is strongly recommended that HIV virological testing be used to diagnose HIV infection among infants and children younger than 18 months of age.

(Strong recommendation, A)

- Among infants and children undergoing virological testing, it is strongly recommended using the following assays (and respective specimen types): HIV DNA on whole blood speci-

³ AIDS-indicator conditions include some but not all HIV clinical stage 4 conditions among children as Pneumocystis jirovecii pneumonia, cryptococcal meningitis, severe wasting or severe malnutrition, Kaposi sarcoma and extrapulmonary TB

men or dried blood spot; HIV RNA on plasma or dried blood spot; or ultrasensitive p24 antigen on plasma or dried blood spot.

(Strong recommendation, A)

- It is strongly recommended that all HIV-exposed infants undergo HIV virological testing at 4–6 weeks of age or at the earliest opportunity thereafter.

(Strong recommendation, A)

- It is strongly recommended that test results from virological testing among infants be returned to the clinic and child, mother or caregiver as soon as possible, but at the very latest within four weeks after the specimen is collected. Positive test results should be fast-tracked to the mother and baby as soon as possible to enable ART to be promptly initiated.

(Strong recommendation, A)

- It is strongly recommended that all infants with unknown or uncertain HIV exposure being seen in health care facilities at or around birth or at the first postnatal visit (usually at 4–6 weeks of age), or other child health visit, have their HIV exposure status ascertained.

(Strong recommendation, A)

- In settings where access to virological diagnostic testing is limited it is strongly recommended that infants exposed to HIV who are well, but not tested earlier, undergo HIV serological testing at about nine months of age (or at the time of the last immunization visit). Those who have reactive serological assays at age nine months should have a virological test to identify infants living with HIV who need ART.

(Strong recommendation, C)

- It is strongly recommended that infants with signs or symptoms suggesting HIV infection undergo HIV serological testing and, if positive (reactive), virological testing.

(Strong recommendation, C)

- It is strongly recommended that children 18 months of age or older suspected of being infected with or exposed to HIV undergo HIV serological testing performed according to the standard diagnostic HIV serological testing algorithm used for adults.

(Strong recommendation, A)

- For sick infants for whom HIV infection is being considered as an underlying cause of symptoms and signs and for whom virological testing is not available, it is strongly recommended using HIV serological testing and the clinical algorithm for presumptive clinical diagnosis of HIV infection.

(Strong recommendation, C)

These recommendations are adapted from global WHO recommendations (1,2). Early establishment of a definite or probable diagnosis of HIV among infants is emphasized because good evidence indicates that early initiation of ART among infants reduces the probability that they will die from AIDS-related causes (9,22).

III. Clinical management of HIV infection among children

1. Baseline evaluation

All infants and children who are diagnosed with HIV infection should undergo clinical and laboratory evaluations to determine the stage of HIV clinical disease and immunodeficiency, eligibility for ART and other illnesses or issues to be addressed. This baseline assessment also provides an opportunity to initiate co-trimoxazole (trimethoprim-sulfamethoxazole) preventive therapy and should serve as an opening to offer counselling and support to children living with HIV and their parents.

Clinical evaluation of a child living with HIV should include:

- growth
- feeding history
- the child's history of exposure to ARV drugs, including exposure in utero to drugs prescribed to the mother
- the history of exposure to ARV drugs of the person who is the source of infection (usually the mother)
- clinical condition, including opportunistic infections, and staging of HIV disease
- developmental assessment
- existence of opportunistic infections and coinfections, especially tuberculosis (TB) and hepatitis B and C and
- determination of pregnancy status for adolescent girls.

Useful laboratory measurements include:

- basic haematology and biochemistry
- CD4 count
- where available, measuring HIV viral load (VL) and
- if available, the HLA B*5701 genotype testing in children for whom abacavir (ABC) treatment is planned.

Baseline antiviral resistance testing is widely practised in the western part of the European Region, although evidence that it improves clinical outcome is lacking. It may be omitted at baseline if it is not easily available, but careful history of drug exposure as above is essential.

Other evaluations to be undertaken during the visit:

- anthropometric measurements: weight, height and head circumference
- nutritional assessment, including:
 - types of foods consumed and estimated amounts;
 - appetite and length of eating time;
 - problems associated with food intake;
 - identification of the adult who feeds the child;
- social assessment:
 - general household hygiene and access to safe drinking-water;
 - availability of a secure refrigerator for storing medication;
 - the ability of family members and other caregivers to monitor adherence and
 - the mental status of both the parents and the child and a cognitive assessment of the child.

2. Initiation of ART

Considerations in deciding when to start ART encompass the child's social environment, including identifying a clearly defined caregiver who understands the prognosis of HIV and the implications of ART: lifelong therapy, effects of non-adherence and the administration, toxicity and storage of drugs. Further, identifying a secondary (back-up), informed caregiver is advised. Access to adequate nutrition and support for families is equally important. Informing older children that they are living with HIV improves adherence. Disclosure to family members may improve adherence and should be encouraged (23).

2.1. Initiation of ART in infants living with HIV

Recent studies demonstrated that more than 80% of infants living with HIV become eligible to start ART before six months of age according to the 2006 clinical and/or immune criteria for initiation (10). Starting asymptomatic infants on ART as soon as possible after diagnosis reduces the number of children dying compared with those delaying treatment initiation until immune system decline or clinical symptoms develop (9, 11, 22).

2.2. Initiation of ART in children living with HIV 12 months of age and older

For children 12–24 months old, global WHO recommendations (1) advocate initiating ART irrespective of CD4 count or WHO clinical stage. However, where close clinical and CD4 monitoring are available, using clinical and CD4 criteria to decide when to start treatment in this age group is reasonable, and the WHO Regional Office for Europe recommends this approach.

2.2.1. Clinical criteria for starting ART

The WHO clinical staging of HIV for children (Annex 1) living with HIV is consistent with the adult clinical classification system. Clinical staging should be used once HIV infection has been confirmed with serological and/or virological evidence.

A preliminary analysis of the revised WHO staging, based on clinical signs at baseline and disease history, for children enrolled in the Children with HIV Antibiotic Prophylaxis (CHAP) trial (24) showed that clinical staging for children not receiving ART predicts the risk of dying (25). The clinical stage is therefore useful to identify when to start ART (Table 1). However, clinical staging is not as useful among children younger than two years of age.

Asymptomatic or mildly symptomatic children living with HIV (clinical stages 1 and 2) should be considered for ART when the immune system values decline to near the described threshold. A drop below the threshold values should be avoided.

Treatment with a potent and efficient ART regimen improves clinical status and effectively reverses the clinical stage. Nevertheless, relying solely on clinical criteria may inappropriately delay the initiation of ART.

2.2.2. Immunological criteria for starting ART

The immune system parameters of children 12 months of age and older living with HIV should be measured to assess the severity of HIV-related immunodeficiency and to guide decision-making on initiating ART. The results of CD4 measurement should be used in conjunction with clinical assessment:

- All children 1–2 years old with CD4 cells <25% or CD4 absolute count <1000 cells/ mm³ are eligible for ART.
- All children 2–5 years old with CD4 cells <25 or CD4 absolute count of <750 cells/ mm³ are eligible for ART.

The CD4 levels of HIV-negative healthy infants are considerably higher than those of uninfected adults and slowly decline to adult values by about 5–6 years of age. The absolute CD4 cells count is naturally less constant and more age-dependent than the percentage CD4 cells among children younger than five years. A single threshold for when to start ART cannot therefore be defined.

Serial measurements are more informative than individual values and also reflect trends over time. If possible, these measurements should compare the same parameter: either absolute CD4 cells count or, among children younger than five years of age, the percentage of CD4 cells. Similar to clinical status, the immune system recovers with successful ART; thus, measuring the CD4 count is useful for monitoring the response to treatment.

The CD4 levels that identify thresholds for when to start ART are derived from longitudinal data on infants and children living with HIV and, except for children younger than 24 months of age, correspond to a 12-month mortality risk of up to 5% (26,27). The younger the child, the less well the % CD4 cells or absolute CD4 count predicts the risk of dying. Infants have a high risk of death, even at high CD4 levels such as >1500 cells/mm³ or CD4 cells >25%.

The available CD4 data for children are mostly based on studies from resource-rich countries. For children five years and older, the thresholds used for adults initiating ART are recommended to be used to simplify programme approaches (28).

2.2.3. Virological criteria for starting ART

Plasma HIV VL is an independent predictor of HIV disease progression but is less powerful than clinical status and CD4 count. Clinicians may therefore consider starting ART among children older than 12 months in WHO HIV clinical stage 1 or 2 who do not meet age-specific CD4 criteria if the plasma HIV VL exceeds 100 000 copies/ml (see Table 1).

2.3. Criteria for starting ART for children younger than 18 months with a presumptive diagnosis of severe HIV disease

If access to virological testing is not yet available, WHO has developed criteria for making a presumptive diagnosis of severe HIV disease among children younger than 18 months of age to enable potentially life-saving ART to start (See chapter II.4. above).

For infants and children who have started ART based on a presumptive diagnosis of severe HIV disease, treatment should be closely monitored and HIV infection should be confirmed as soon as possible using age-appropriate testing methods. In addition, HIV serological testing should be performed at 18 months of age to definitively confirm the child's HIV infection status. Decisions on further treatment should be adjusted at that time in accordance with the results.

ART should be stopped among infants and children only if HIV infection can be confidently ruled out and when such children are no longer exposed to HIV (such as through breastfeeding from a mother living with HIV). Initiating ART based on a presumptive diagnosis of severe HIV disease is not recommended for providers who are not appropriately trained in HIV care or administering ART. Presumptive diagnosis of severe HIV disease should not be used among children 18 months and older, since antibody testing establishes their HIV infection status.

2.4. Recommendations

2.4.1. Infants

- Initiate ART for all infants diagnosed with HIV infection in the first year of life, irrespective of CD4 count or WHO clinical stage.

(Strong recommendation, B)

- Among infants with an initial positive virological test result, it is strongly recommended that ART be started without delay and, at the same time, a second specimen be collected to confirm the initial positive virological test result. Do not delay ART. Among infants living with HIV, immediately starting ART saves lives, and this should not be delayed while waiting for the results of the confirmatory test.

(Strong recommendation, A)

2.4.2. Children

- Initiate ART for all children in WHO HIV clinical stages 3 and 4, irrespective of CD4 count.

(Strong recommendation, C)

- Initiate ART for all children 12–24 months old in WHO HIV clinical stages 1 and 2 with CD4 count ≤ 1000 cells/mm³ or CD4 cells $<25\%$.

(Strong recommendation, C)⁴

- If CD4 measurement is not readily available, initiate ART for all children 12–24 months old in WHO HIV clinical stages 1 and 2.

(Conditional recommendation, C)⁵

- Initiate ART for all children 24–59 months old in WHO HIV clinical stages 1 and 2 with CD4 count <750 cells/mm³ or % CD4+ $<25\%$.

(Strong recommendation, C)

- Initiate ART for all children living with HIV older than five years with CD4 count <350 cells/mm³ (as in adults), irrespective of WHO clinical stage.

(Strong recommendation, B)

- Consider initiating ART for children older than 12 months in WHO HIV clinical stages 1 and 2 with HIV VL $>100\,000$ copies/ml, irrespective of CD4 count.

(Conditional recommendation, C)

- Initiate ART for any child younger than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection.

(Strong recommendation, C)

⁴ This recommendation resulted from modification of global guidance, considering capacity, available resources and the relatively manageable burden of HIV disease among children in countries in the European Region.

Table 1 summarizes the recommendations for initiating ART for infants and children living with HIV according to the clinical stage and the availability of immunological and virological markers.

TABLE 1. AGE-RELATED CLINICAL, IMMUNE AND VIRAL THRESHOLDS FOR INITIATING TREATMENT		
Age	Criteria	When to treat
0–11 months		Treat everyone
12–24 months ^a	Clinical Immune Viral	Treat if WHO clinical stage 3 or 4 Treat if CD4 is <25% or <1000 cells/mm ³ Consider treating if HIV VL >100 000 copies/ml
2–<5 years	Clinical Immune Viral	Treat if WHO clinical stage 3 or 4 Treat if CD4 <25% or <750 cells/mm ³ Consider treating if HIV VL >100 000 copies/ml
≥5 years	Clinical Immune Viral	Treat if WHO clinical stage 3 or 4 Treat if CD4 count ≤350 cells/mm ³ Consider treating if the HIV VL >100 000 copies/ml

^aTreat everyone if regular clinical and CD4 count monitoring cannot be ensured.

3. First-line ART regimens for infants and children

3.1. Drug regimens

Standard first- and second-line regimens should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) and either a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or a ritonavir-boosted protease inhibitor (PI/r). Recently published data from the PENPACT study (29) show that, in combination with two NRTIs, regimens containing either an NNRTI or a PI/r are equally effective.

Among infants and children younger than two years with significant exposure to maternal nevirapine either in utero or during breastfeeding, recent data (30) show better outcomes with LPV/r-based regimens, which are therefore preferred to NVP in these circumstances.

Preliminary data suggesting that LPV/r produces better results than NVP even among infants without a documented history of previous NVP exposure (31) have led to recent guidelines in the United States of America (2) recommending LPV/r as the first choice ahead of NVP among all infants and young children. However, the PENPACT study (29) does not support this conclusion, and NVP remains a valuable first-line ARV medicine for infants and young children.

Some experts use a regimen of three NRTIs + NVP or LPV/r for infants with a very high VL or concern about developmental delay or HIV encephalopathy. This is based on theoretical considerations without supportive clinical evidence.

For coinfection with drug-sensitive TB, the use of rifampicin may cause interactions with nevirapine or PIs. For children older than three years, an ART regimen of EFV and two NRTIs is therefore recommended.

For children with TB coinfection younger than three years or with previous exposure to an NNRTI, a combination of three NRTIs may be used. There is some concern that this may be less effective than other first-choice regimens, and the regimen should be reviewed once TB treatment has been completed.

ABC + 3TC is the preferred combination of NRTIs and has been shown to be more effective than AZT + 3TC or AZT + ABC (32). Its main problem is the potential for hypersensitivity reactions to ABC, although this may be minimized by testing for the HLA B*5701 genotype before starting ART and avoiding the use of ABC for children who are HLA B*5701 positive (33). AZT + 3TC therefore remains a useful first-line NRTI combination where HLA B*5701 testing is not widely available. Using AZT may be problematic for children with severe anaemia.

Alternative NRTIs include didanosine (ddI), FTC and TDF. Didanosine may be associated with hepatic steatosis in long-term use and is best saved for second-line regimens. It should never be used together with TDF or d4T. FTC is very similar to 3TC and should not be used in combination with 3TC. TDF is an effective drug, but safety data and appropriate formulations are not yet available for younger children. The main concerns are potential renal toxicity (34–36) and bone demineralization (37,38). It is a useful alternative first-line NRTI for older children. Using d4T is no longer recommended because of its toxicity (39–42), and it should never be used together with ddI or AZT.

NVP is the only NNRTI available for use among children younger than three years. For older children, EFV is the first-choice NNRTI, and NVP is an alternative. Concerns about potential teratogenicity limit the use of EFV among older girls of childbearing age, but no prospective data support this concern. Mental side effects are the most common significant reported side effect of EFV. Hepatotoxicity and Stevens-Johnson syndrome are the most important types of NVP-related toxicity.

All use of PIs should be boosted with low-dose ritonavir; LPV/r is the first-line choice. Ritonavir-boosted alternatives for older children include atazanavir (ATZ/r), darunavir (DRV/r), fosamprenavir (FPV/r), saquinavir (SQV/r) and tipranavir (TPV/r). These are more suitable for second-line regimens and use among older children.

3.2. Recommendations

3.2.1. Infants

- For infants not previously exposed to ARV medicines, start ART with two NRTIs plus either nevirapine (NVP) or ritonavir-boosted lopinavir (LPV/r).
(*Strong recommendation, B*)
- For infants exposed to maternal or infant NVP or other NNRTIs used for maternal treatment or preventing mother-to-child transmission, start ART with two NRTIs + LPV/r.
(*Strong recommendation, B*)
- For infants whose exposure to ARV medicines is unknown, start ART with two NRTIs plus either NVP or LPV/r.
(*Conditional recommendation, C*)
- For infants with high VL or for whom there is concern about developmental delay or possible HIV encephalopathy, a regimen of three NRTIs plus NVP or LPV/r as appropriate from above may be considered.
(*Conditional recommendation, C*)

3.2.2. Children

- For children 12–24 months old previously exposed to maternal or infant NVP or other NNRTIs used for maternal treatment or preventing mother-to-child transmission, start ART with two NRTIs + LPV/r.

(Conditional recommendation, C)

- For children 12–24 months old not previously exposed to NNRTIs, start ART with two NRTIs plus either NVP or LPV/r.

(Strong recommendation, B)

- For children older than 24 months and less than 36 months old, start ART with two NRTIs plus either NVP or LPV/r.

(Strong recommendation, B)

- For children three years of age and above, start ART with two NRTIs plus either NVP or efavirenz (EFV) or LPV/r.

(Strong recommendation, B)

- For infants and children, the preferred NRTI backbone for an ART regimen should be one of the following:

- 3TC + ABC
- 3TC + AZT

(Strong recommendation, C)

- For infants for whom a three-drug NRTI backbone is used together with NVP or LPV/r, the backbone should be 3TC + ABC + AZT.

(Conditional recommendation, C)

- For children 12 years and older, an alternative NRTI backbone is TDF + either 3TC or FTC.

(Conditional recommendation, C)

The recommendations are also summarised in Table 2 below.

TABLE 2. PREFERRED FIRST-LINE ART REGIMENS	
Age group	Standard first-line regimen
Children younger than 24 months	
Infant or child <24 months previously exposed to NNRTI	Two (or three) NRTIs + LPV/r
Infant or child <24 months not previously exposed to ARV medicines	Two (or three) NRTIs + NVP or LPV/r
Infant or child <24 months with unknown exposure to ARV medicines	Two (or three) NRTIs + NVP or LPV/r
Children older than 24 months	
Children 24–36 months old	Two NRTI + NVP or LPV/r
Children >3 years	Two NRTI + EFV or LPV/r

3.2.3. Infants and children with specific conditions

- For children older than three years of age with TB, the preferred regimen is EFV plus two NRTIs.

(Conditional recommendation, C)

- For infants and children younger than three years of age with TB, the preferred regimens are NVP plus two NRTIs or a triple nucleoside regimen.

(Conditional recommendation, C)

- For a child or adolescent with severe anaemia (haemoglobin <7.5 g/dl) or severe neutropenia (<500 neutrophils per mm³), the preferred NRTI backbone is 3TC + ABC (avoid AZT).

(Conditional recommendation, C)

- For adolescents younger than 12 years of age with hepatitis B, the preferred regimen is an NNRTI + TDF + FTC or 3TC.

(Conditional recommendation, C)

The recommendations are also summarised in Table 3.

TABLE 3. PREFERRED FIRST-LINE ART REGIMENS IN SPECIFIC SITUATIONS	
Concomitant conditions	Standard first-line regimen
Child or adolescent with severe anaemia	Two NRTIs (avoid AZT) + EFV or NVP or LPV/r
Child <3 years with TB treatment	NVP + 2 NRTIs or three NRTIs: AZT + 3TC + ABC
Child >3 years or adolescent being treated for TB	EFV + 2 NRTIs or Three NRTIs: AZT + 3TC + ABC
Adolescent with hepatitis B	TDF + FTC or 3TC + NNRTI

4. Adherence to ART

Adherence is the key to achieving an effective clinical, immune and viral response to ART and should be no less than 95% of the prescribed dosage. Unfortunately, there is little good evidence on effective strategies to promote adherence, so specific recommendations cannot be made, but every ART programme should address adherence.

4.1. Background knowledge and evidence

Adherence is directly related to the clinical and viral outcomes of ART among infants and children (43–45). Studies of drug adherence among adults in high-income countries have suggested that higher levels of drug adherence are associated with improved viral and clinical responses and that rates exceeding 95% are desirable to maximize the benefits of ART. In low- and middle-income countries, research suggests that adherence to ART can be associated with family structure, socioeconomic status, disclosure and medication regimen (45). Ensuring optimal adherence is critical to maximize the durability of first-line ART and minimize the emergence of drug resistance. A range of approaches to support and improve adherence have been investigated and have begun to be explored.

4.2. Challenges

Adherence among children is a special challenge because of factors relating to children, caregivers, medicines and the interrelationships of these factors. The limited number of formulations for children, poor palatability, high pill burden or liquid volume, frequent dosing requirements, dietary restrictions and side effects may hamper the regular intake of required medicine. Further, successfully treating a child requires commitment from and the involvement of a responsible caregiver. This may be particularly complicated if the family unit is disrupted because of adverse health or economic conditions. Many mothers of children living with HIV are living with HIV themselves. As a result, the care of the child may be less than optimal because the mother's health is compromised. Adherence may vary with time: families may have periods when adherence is excellent and other periods when it fails, often because of changing life circumstances. Adherence may also suffer as the child responds to therapy, health improves and the impetus to take daily medicine decreases.

In addition, caregivers are often concerned about disclosing HIV status to family members, friends or schoolteachers, thus restricting the child's options for seeking support.

4.3. Maximizing adherence

Efforts to support and maximize adherence should begin before treatment starts (46). Developing an adherence plan and educating children and their parents and other caregivers are important first steps. Initial education should cover basic information about HIV and its natural history, the benefits and side effects of ARV medicines, how the medicines should be taken and the importance of not missing any doses. If medicine is mixed with food or dispersed in water, all the food or water must be taken to ensure the full dose. Especially for young children, additional elements may be necessary, including practising measuring and administering liquids with caregivers and training children in how to swallow pills. When choosing regimens, policy-makers, programmers and providers should consider ways to minimize the number of pills, the volumes of liquids and the number of doses. Regimens that avoid food restrictions and that can be dosed using fixed-dose combinations, blister packs or other child-friendly formulations should be used whenever possible. Fitting the ARV medicines into the child's (and parents' and other caregiver's) lifestyle or, where possible and appropriate, matching the drug regimens for children to the regimens of parents or other family members, as well as being prepared for common, non-severe adverse effects, may facilitate successful adherence.

Adherence during the first days and weeks of treatment can be critical to the long-term success of a regimen, especially for some ART combinations with a higher risk of developing resistance to ARV medicine.

If children stop ARV drugs within first-line regimens (either intentionally or unintentionally), the half-lives of NNRTI components are several days to weeks longer than the half-lives of NRTI components. Suddenly interrupting first-line therapy may therefore result in the persistence of subtherapeutic NNRTI drug levels, which can lead to the premature development of NNRTI-resistant virus. Emphasizing the need to consistently take all the ARV drugs is therefore especially important with an NNRTI- and NRTI-based first-line regimen. An uninterrupted supply of ARV medicines at both the facility and household level is clearly essential.

4.4. Measurement and evaluation

Measuring adherence may be especially difficult among children. Quantitative methods are generally used (asking children or caregivers how many doses of medication have been missed during the past 3, 7 or 30 days), but the responses may not reflect true adherence, since children and caregivers learn that reporting complete adherence is socially desirable. Reviewing

pharmacy records and pill counts can provide valuable information about adherence. VL can be measured to assess adherence.

Qualitatively evaluating adherence can more effectively identify barriers to optimal medicine consumption but can be more difficult and time-consuming for health care providers and for children and/or their parents and other caregivers. These evaluations focus on describing any impediments to adherence or the problems encountered. Further, assessing adherence can be complicated by diverging reports between children and parents and other caregivers and by the limited availability of information when the caregivers bringing children to clinics are not the ones responsible for supervising the administration of ART (47).

4.5. Ongoing support

In addition to assessing adherence, ongoing support for adherence is a vital component of successful treatment (44). Practical aids can be helpful, including the use of calendars, pillboxes, blister packs and labelled syringes. Directly observed therapy and the use of treatment buddies or partners have been successful in some settings but have not been widely studied among children. Community and psychological support can be critical for the parents and other caregivers and the children, and peer support groups may especially benefit mothers with young children receiving ART. In cases where care of the child may be less than optimal due to mother's health condition or another reason, a secondary (back-up) informed caregiver such as the father should preferably be involved in the care of a child living with HIV. Finally, an understanding of how the developmental stage of the child influences the extent to which he or she will cooperate with the regular administration of medicine helps to guide planning and support for the process.

4.6. Programmatic issues

Programmatic issues can affect the adherence of children and must be considered. Problems with adherence among children, their caregivers and adolescents (in particular, those who are in transition from paediatric health care to adult health care) should be anticipated; they are encountered at every level of the health care system involved in providing ART. Continuous access to a supply of ARV drugs free of charge and developing well-functioning systems for forecasting, procurement and supply management are essential components of treatment programmes for children. The limited formulations currently available for children present significant barriers to optimal adherence. The development of formulations appropriate for use among infants and young children is strongly encouraged.

4.7. Disclosure of diagnosis

How a child's or adolescent's knowledge of their HIV diagnosis affects their adherence to ART is not clear, but every HIV treatment programme for children should have clear policies for talking to children and adolescents about their HIV diagnosis. In some settings, it is normal practice to mention a child's HIV diagnosis to them from their very first clinic visit. If this is not the case, clear policies should be in place aiming to inform them of the diagnosis by the time they reach age 10 or 11 years. This needs to be within the context of broader psychosocial support for the child and family.

4.8. Recommendation

- Assessment and promotion of adherence should form part of every ART programme. *(Strong recommendation, C)*

5. Adolescents living with HIV

5.1. Important considerations

- The physical and mental changes associated with adolescence have implications for the provision of appropriate HIV treatment and care.
- The choice of ART regimen and dosages for adolescents should be based on a rating of sexual maturity.
- Prescribing EFV and NVP for adolescent girls requires special clinical considerations.
- Adherence to long-term therapy is especially difficult among adolescents, and education and providing support systems may be most effective if specifically tailored to the considerations relevant to this age group.

5.2. Background

WHO considers adolescence as the period between 10 and 19 years of age⁵, during which healthy adolescents pass through well-described stages of physical, mental and sexual maturation. These have implications for providing appropriate treatment and care for adolescents living with HIV.

Two distinct groups of adolescents living with HIV may require ART: adolescents with long-standing HIV infection who were infected around birth and survived, and those who become infected during later childhood or adolescence. Most adolescents with long-standing HIV infection who began ART during early childhood have had many years of contact with the health system and have experienced various ART regimens. In addition, their parents are often aware of their HIV status. In this group of adolescents, the challenges relate mainly to the following:

- disclosure of HIV status to them if their parents have not done this;
- developmental delay;
- the transition from paediatric to adult health care, including the choice of appropriate ART regimens; and
- adherence (4).

Adolescents with long-standing HIV infection often face considerable physical challenges. They may experience delayed growth and development, often resulting in late puberty and, in girls, delayed or irregular menstrual cycles (48). Stunting and/or wasting caused by progressing HIV illness, sometimes exacerbated by malnutrition, may further complicate decision-making on whether to follow the ART guidelines for adults or for children.

5.3. Considerations for regimens and ARV drugs dosing

WHO recommends basing the choice of ART regimen and doses for adolescents on rating of sexual maturity (Tanner staging): adolescents in Tanner stages I, II and III should be started on the regimen and doses for children and monitored with particular care because they are undergoing hormonal changes associated with the growth spurt. Adolescents in Tanner stages IV and V are considered adults, and the same recommendations and special considerations apply as for adults. However, choosing an appropriate ART regimen and doses requires transcending the consideration of maturity. Simplifying treatment regimens and anticipated long-term adherence are also important criteria. Other considerations relate to EFV and NVP for adolescent girls. Adolescent girls who risk becoming pregnant (are sexually active and not using adequate contraception) or those in the first trimester of pregnancy should not use EFV.

⁵ http://whqlibdoc.who.int/trs/WHO_TRS_731.pdf

Symptomatic NVP-associated hepatotoxicity or serious rash, while uncommon, is more frequent among females than among males and is more common in ARV-naive females with higher absolute CD4 cell counts (>250 cells/mm³). NVP should therefore be prescribed with caution for adolescent girls with absolute CD4 counts between 250 and 350 cells/mm³. If NVP is prescribed for such adolescent girls, careful monitoring, preferably including liver enzymes, is needed during the first 12 weeks of therapy.

5.4. Adherence for adolescents

Adherence to long-term therapy is especially difficult among adolescents. In addition to providing routine adherence assessment and support (see section III.4), health care providers should consider issues especially relevant to adolescents that may impair optimal adherence. These include adolescents' possible perception of being immortal, their desire for independence, lack of disclosure of HIV status and stigma. The parents of adolescents who became infected as infants or young children may find it hard to tell their children that they are living with HIV because of fear of stigma or blame from their own children. However, this knowledge is required for adolescents to progress completely through the transition process into adult care. Sharing this diagnosis with peers is difficult for adolescents who are aware of their HIV status (49).

For these reasons, it is especially important that young people (50):

- be informed of their HIV status;
- be well educated about their condition, its treatment and the importance of adhering to care and ART;
- be confident of their ability to talk about HIV with the people with whom they want to share knowledge of their condition; and
- have a support system so that they know where to obtain help and advice when necessary.

6. First-line ART regimen failure

No clear definition of treatment failure is supported by high-quality evidence of its effect on clinical outcome.

Routine virological monitoring detects viral failure before clinical or immune system failure is apparent, limiting the clinical complications of failure and the selection of viral resistance to ART. Thus, adult guidelines (see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents, 2012 revision*) for settings with routinely available virological monitoring suggest a much lower threshold of 200 copies/ml as the definition of viral failure, based on the likelihood of viral resistance among adults (51–55). Conversely, the only randomized controlled trial of VL thresholds for switching therapy among children (29) showed no difference in clinical outcome between switching thresholds of 1000 and 30 000 copies/ml but an increase in the number of NRTI resistance mutations among children receiving NNRTI-based regimens switched at higher VLs. Achieving viral suppression is more difficult among children than among adults, and further treatment options may be limited. Persistent viraemia over 1000 copies/ml is therefore a reasonable evidence-informed definition of viral failure among children.

If routine virological monitoring is not available, the global definitions of clinical and immune failure should be used (1):

- new WHO stage 3 or 4 clinical events (clinical failure);
- CD4 count <200 or 10% among children 2–5 years old or CD4 count <100 among children older than 5 years (immune failure); and
- persistent VL over 5000 copies/ml (viral failure).

7. Second-line ART regimens

Adherence should always be reassessed before changing regimen. If failure has resulted from poor adherence, simply switching to another regimen risks further failure and the development of more resistance.

7.1. Second-line regimen following a first-line regimen of two NRTIs plus one NNRTI

Failure of an NNRTI-based regimen is often associated with resistance to NNRTIs and sometimes with resistance to the NRTI component. Performing and appropriately interpreting a resistance assay enables this to be confirmed, and a new regimen can be selected from drugs to which the assay shows the virus remains susceptible.

Where resistance testing has not been performed, the new regimen is recommended to consist of a ritonavir-boosted PI (PI/r) and two NRTIs. The PI should usually be LPV/r, although section III.3.1 lists alternatives.

The NRTIs in the new regimen may also be guided by viral susceptibility in a resistance assay. Where this has not been performed, a regimen of 3TC + ABC may be switched to AZT + ddI with predicted full viral susceptibility. AZT + 3TC may be used as an alternative; it may not have full viral susceptibility but is predicted to have adequate potency to achieve suppression in a combination regimen based on a PI/r. TDF with AZT, 3TC or FTC may be a potent alternative, especially suitable for children older than 12 years.

If the first-line NRTI combination has been AZT + 3TC, appropriate second-line NRTI regimens include ABC + ddI or ABC + 3TC. Especially among older children, TDF + ABC or 3TC or FTC may be considered. TDF + ddI should not be used.

7.2. Second-line regimen following a first-line regimen of two NRTIs plus one PI/r

The failure of a PI/r based ART regimen is much less likely to result in viral resistance than the failure of an NNRTI-based regimen. It is more likely to result from poor adherence, and assessment of adherence is essential before starting a new regimen. Performing a resistance assay may confirm that resistance did not cause failure. In this case, it is important to establish whether enhanced adherence support is needed on the same regimen or a switch to a new regimen. Switching from a PI/r to an NNRTI based ART regimen may be appropriate if poor adherence resulted from drug-related factors such as side effects or number of daily doses, but if poor adherence persists in an NNRTI-based regimen, further drug resistance is highly probable. Switching from a PI/r to an NNRTI is therefore recommended with caution. The NNRTI should not replace the PI/r with the same NRTI backbone without resistance testing, as there may be resistance to the NRTIs. If resistance testing is performed, the new NRTI backbone may be selected according to the susceptibility results. If resistance testing is not performed, the considerations for the new NRTI backbone are the same as in section III.7.1.

7.3. Second-line regimen following an alternative first-line regimen with 3 NRTIs

Treatment failure on an alternative triple NRTI regimen can be managed with a wider choice of drug options because two important drug classes (NNRTIs and PIs) have been spared. The PI component remains essential in constructing a second-line regimen.

NRTI, NNRTI and PI combination regimens have been studied in treatment-experienced children and have been well tolerated. A multi-class regimen can be considered if these drugs are available. Because EFV and NVP are potent inducers of the enzymes required to metabolize some PIs, the doses may need to be adjusted, and the use of a ritonavir-boosted PI is recommended to ensure adequate levels of the PI drug.

7.4. Recommendations

- Treatment should be considered failing if children have a persistent VL > 1000 copies/ml while receiving ART.
(*Strong recommendation, B*)
- Always assess adherence to ART when treatment fails before deciding on a second-line regimen.
(*Strong recommendation, C*)
- If resistance testing is available, consider testing for viral resistance to ART when treatment fails.
(*Conditional recommendation, C*)
- After treatment with a first-line boosted PI regimen fails, an NNRTI plus two NRTIs are recommended for second-line ART, but strong adherence counselling is required.
(*Strong recommendation, B*)
- After treatment with a first-line NNRTI-based regimen fails, a PI/r plus two NRTIs are recommended for second-line ART.
(*Strong recommendation, B*)
- LPV/r is the preferred boosted PI for a second-line ART regimen after treatment with a first-line NNRTI-based regimen fails.
(*Strong recommendation, A*)
- After treatment on a first-line regimen of AZT + 3TC fails, the preferred NRTI backbone options for second-line ART are ABC + 3TC or ABC + ddI. ABC + TDF or TDF + 3TC or FTC are alternatives.
(*Strong recommendation, C*)
- After treatment with a first-line regimen of ABC + 3TC fails, AZT + 3TC or AZT + ddI are the preferred NRTI backbone options for second-line ART. AZT + TDF or TDF + 3TC or FTC are alternatives.
(*Strong recommendation, C*)

8. Second-line ART regimen failure

Multidrug resistance among children who have received multiple ART regimens is an increasing problem.

Limited data are available on which to base recommendations about treatment options. The objective of treatment should be to maintain a high CD4 count, reduce adverse reactions and enhance the prevention of opportunistic infections. If children have end-stage HIV disease and no further suitable ARV medicines are available, stopping ART and keeping them comfortable with symptom-based care may have to be considered.

8.1. Considerations for the use of ARV salvage regimens

Several treatment approaches have been considered in clinical trial settings, mainly for adults. These approaches include adding or substituting new drugs (such as enfuvirtide/T20), mega-highly active ART (combination of five or more drugs, including two or more PIs), strategic recycling of drugs, structured treatment interruptions and continuing current therapy until

additional drugs become available. An analysis of 13 HIV cohorts involving adults who had three-class viral failure indicates that achieving and maintaining an absolute CD4 count above 200 cells/mm³ becomes the primary aim. Treatment regimens that suppress VL below 10 000 copies/ml may be associated with better maintenance of CD4 levels (56). Immune and clinical benefits have been reported even among people who have partial viral response or viral rebound, presumably as a result of decreased viral fitness attributable to the presence of multiple resistance mutations. Studies among adults suggest therapeutic benefit from NRTI treatment in the presence of drug-resistant HIV (57–63). Decisions about therapy in such situations are complex and require, at a minimum, consultation with an HIV specialist.

However, in the current era of new treatment options, every chance should be given to finding an effective treatment regimen before discontinuing ART altogether.

8.2. Suggestions

- Strategies that balance benefits and risks for children need to be explored if second-line treatment fails.
- For older children who have more therapeutic options available to them, third-line ART regimens may be able to be constructed using novel drugs used in treating adults such as darunavir and raltegravir.
- Children receiving a failing second-line regimen with no new ARV medicine options should continue with a tolerated regimen.
- If ART has to be stopped, opportunistic infections still need to be prevented, symptoms relieved and pain managed.

9. Monitoring HIV treatment

Once an infant or child is receiving ART, the frequency of clinical monitoring depends on their response to ART. At a minimum, after ART starts, follow-up visits should occur:

- for infants, at weeks 2, 4 and 8 and then every 4 weeks for the first year; and
- for children, at weeks 2, 4, 8 and 12 and then every 2–3 months once the child has stabilized on therapy.

Routine clinical assessment should include addressing the child's and/or caregiver's understanding of and adherence to therapy, along with their need for additional support. Key signs of a child's response to ART include:

- improvement in growth among infants and children who have been failing to grow;
- improvement in nervous system symptoms and development among children with encephalopathy or those who have demonstrated delay in achieving developmental milestones; and
- decreased frequency of infections: bacterial infections, oral thrush and/or other opportunistic infections.

Observation of the child's responses to therapy should include vigilance for symptoms of potential drug toxicity or treatment failure, including reassessing WHO clinical stage. Laboratory assessment of CD4 values is desirable at a minimum of six months after ART starts and every six months thereafter. More frequent CD4 monitoring is indicated in cases of new or recurrent clinical staging events, growth faltering or neurodevelopmental delay. VL should be routine monitored whenever possible to confirm treatment success.

Laboratory assessment of the child's response to treatment and monitoring of adverse reactions should be directed by clinical symptoms, although some routine monitoring tests are advisable for specific drugs:

- Among infants and children receiving AZT-containing regimens, haemoglobin should be measured eight weeks after starting ART, or more frequently if symptoms indicate.
- Liver function tests (liver enzymes) are recommended during the first few months of treatment for infants and children receiving NVP who have any signs of hepatitis or hepatotoxicity, who are coinfecting with hepatitis viruses or who are receiving hepatotoxic medicine.

The first six months of ART is critical. Clinical and immune system improvement is expected, but drug toxicity and/or immune reconstitution inflammatory syndrome may emerge. Among most children, CD4 cell counts rise with ART and immune recovery. Some children fail to respond as expected or may even deteriorate clinically during this time.

9.1. CD4 recovery

For most children, CD4 cell counts rise with therapy and immune recovery. Generally, CD4 levels increase during the first year of treatment, reach a plateau and then continue to rise further during the second year (64). However, severe immunosuppression may persist among some children. The lower the CD4 levels at the start of ART, the slower the recovery. At the same time, persistent failure to see a CD4 response should alert the clinician to potential adherence problems or non-response to ART. In this case, determining VL can be useful.

9.2. Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) is a spectrum of clinical signs and symptoms thought to be associated with immune recovery brought about by a response to ART (65,66). Although most children living with HIV experience rapid benefit from ART, some undergo clinical deterioration. This is the result of either the unmasking of latent or subclinical infection or the reactivation of previously diagnosed and often treated conditions (infectious or non-infectious), sometimes termed paradoxical IRIS (65,67–69).

There are limited data on IRIS among infants and children, and the causes are not clearly understood. IRIS most often begins among children within the first weeks to months after ART starts and is most common among children who initiate ART with very low % CD4+ (<15%) (67,70).

The most common opportunistic infection associated with IRIS among children is TB, but those receiving treatment for *Pneumocystis jirovecii* pneumonia or cryptosporidiosis, or who have herpes simplex virus, fungal, parasitic or other infections may also develop IRIS (71,72). BCG-associated IRIS (localized and systemic) is frequent where BCG immunization of infants and children is routine (70,73).

Most cases of paradoxical IRIS resolve spontaneously or can be managed with nonsteroidal anti-inflammatory drugs, although some episodes can be severe and even lead to death (74). Unmasking IRIS generally requires treating the opportunistic infection and concomitant anti-inflammatory therapy. In clinical settings in which IRIS is suspected, excluding other acute infectious illnesses is often difficult, and starting empiric anti-infective therapy may be necessary in addition to specific treatment for IRIS syndrome. IRIS occasionally becomes progressively worse and may require a short course of treatment with corticosteroids and, rarely, temporary discontinuation of ART (67). The same ART regimen should be restarted once IRIS has improved.

9.3. Antiretroviral drug toxicity

ARV medicine can be responsible for a wide range of toxicity, from low-grade intolerance that may be self-limiting to life-threatening side effects. Differentiating between the complications of HIV disease and the toxicity of ART may be difficult. Alternative explanations for observed toxicity could include a concurrent infectious process or a reaction to medicines other than ARV medicine (such as isoniazid-induced hepatitis among children receiving treatment for TB or a rash induced by co-trimoxazole). Non-drug-related clinical events or adverse reactions that are not caused by an ARV drug do not require changing ARV drugs. Although there are fewer data on ARV drug toxicity for children than for adults, the full spectrum of ARV toxicity observed in adults has also been reported among children (75). However, some types of toxicity are less common among children than among adults (for example, NVP-related symptomatic hepatotoxicity is rare among children), and others are more commonly reported among children than among adults, such as EFV-related rash or TDF-related loss of bone density).

Drug-related adverse reactions among people receiving ART can occur immediately (soon after taking a drug), early (within the first days or weeks of treatment) or late (after months or more of treatment).

Adverse reactions can vary in severity from mild to severe to life-threatening and may be specific to the drug or generic to the class of drugs in use.

9.3.1. Types of toxicity

The most common types of toxicity include the following:

- Toxicity affecting the blood and the blood-forming organs includes drug-induced bone-marrow suppression, most common with AZT (anaemia, neutropaenia and, more rarely, thrombocytopenia).
- Mitochondrial dysfunction is primarily seen with the NRTI drugs and includes lactic acidosis, hepatic toxicity, pancreatitis and peripheral neuropathy. The NRTIs differ in their ability to affect mitochondrial function: d4T and ddI are worse than AZT; 3TC and ABC have the least toxicity of all.
- Lipodystrophy and other metabolic abnormalities are primarily seen with d4T and PIs and to a lesser degree with other NRTI drugs. Abnormalities include fat maldistribution and body habitus changes, hyperlipidaemia, hyperglycaemia, insulin resistance, diabetes mellitus, osteopaenia, osteoporosis and osteonecrosis.
- Allergic reactions include skin rashes and hypersensitivity reactions. These are more common with the NNRTI drugs but also seen with certain NRTI drugs, such as ABC.
- Because NVP is associated with the risk of potentially life-threatening hepatotoxicity, liver dysfunction with any cause in a child receiving NVP requires carefully considering whether NVP should be discontinued.

9.3.2. Monitoring and management of toxicity

Toxicity can be monitored clinically, based on child or parent reporting and physical examination and can also be assessed by laboratory tests, depending on the ART regimen being used.

Regardless of their severity, adverse reactions may affect adherence to therapy. A proactive approach to managing toxicity is recommended. Discussing the potential side effects of the ART regimen before starting therapy and during the early stages of treatment with the child and his or her parents and other caregivers, as well as offering support during minor and moderate adverse reactions, can increase the likelihood of adherence to therapy (see section III.4). Many types of ARV drug toxicity are time-limited and resolve spontaneously even when the

same ART regimen is continued. The child and parents and other caregivers should be familiar with the signs of toxicity that are serious and require immediately returning to the health facility. This is particularly important for toxicity that can be life-threatening, including the NVP-associated Stevens-Johnson syndrome, drug-induced hepatitis, lactic acidosis, pancreatitis or ABC-associated hypersensitivity.

Moderate or severe toxicity may require substitution with a drug in the same ARV class but with a different toxicity profile or with a drug in a different class but does not require discontinuing all ART.

Severe life-threatening toxicity requires discontinuing all ARV drugs and initiating appropriate supportive therapy until the person is stabilized and the toxicity is resolved.

NNRTIs have a longer half-life than NRTIs, and stopping all first-line drugs simultaneously may result in exposure to subtherapeutic levels of the NNRTI and subsequently to the development of NNRTI resistance. However, if a child has life-threatening toxicity, all ARV drugs should be stopped simultaneously until he or she is stabilized.

Clinical examination may identify types of toxicity that are not life-threatening and that appear months to years after therapy starts, such as lipodystrophy. In such cases, referral for management to higher-level health facilities or for consultation with an HIV expert is recommended.

Steps in management of ARV drug toxicity include the following:

- Determine the seriousness of the toxicity.
- Evaluate concurrent medications and establish whether the toxicity may be attributable to an ARV drug or drugs or to a non-ARV medication taken at the same time.
- Consider other disease processes, such as viral hepatitis in a child receiving ARV medicine who develops jaundice. ARV drugs do not cause all the problems that arise during treatment.
- Manage the adverse reaction according to its severity (Table 4).

TABLE 4. MANAGEMENT OF ADVERSE REACTIONS	
Severity of adverse reactions	Management
Severe life-threatening reactions	<ul style="list-style-type: none"> • Immediately discontinue all ARV drugs, • Manage the event (provide symptomatic and supportive therapy) and • Reintroduce ARV drugs using a modified regimen (with an ARV substitution for the offending drug) when the person is stabilized
Severe reactions	<ul style="list-style-type: none"> • Replace the offending drug without stopping ART
Moderate reactions	<ul style="list-style-type: none"> • Consider continuing ART as long as feasible • If the person does not improve on symptomatic therapy, consider substituting a single drug • Stress the maintenance of adherence despite toxicity
Mild reactions	<ul style="list-style-type: none"> • Reassure the child and caregiver that, although the reaction may be bothersome, it does not require a change in therapy • Provide counselling and support to mitigate adverse reactions • Stress the maintenance of adherence despite toxicity

10. Considerations for palliative care and stopping ART

Opportunistic infections still need to be prevented, symptoms relieved and pain managed, even when the option of stopping ART may have to be considered. Symptoms and pain are a major cause of discomfort and poor quality of life among infants and children living with HIV. Many of these symptoms can be prevented, treated or controlled by using basic medicines and therapies. Non-pharmaceutical methods are an important adjuvant to managing symptoms. Efforts to identify the cause of symptoms and pain should be pursued as much as possible, without adversely affecting the quality of the child's life. Symptoms and related pain should be anticipated and prevented to the extent possible.

At the end of life, more symptoms must typically be addressed, and the child may need to take multiple drugs to control and treat a variety of symptoms and conditions. Preparing for terminal care for children and their families is a long-term process and requires continuity among care providers and services.

Critical factors in effective long-term planning include early and active communication with and involvement of parents and their ongoing support, community-level support structures, a functional health infrastructure, knowledgeable human resources and access to essential drugs and supplies. Terminally ill children are often placed in acute care facilities that may not be appropriate for their needs. The families of children with end-stage HIV disease must be involved in decisions about the best place for care and the preferred place of death.

11. Management of TB/HIV coinfecting infants and children

TB represents a significant threat to children's health, and HIV infection increases susceptibility to infection with *Mycobacterium tuberculosis* and the risk of rapid progression to TB disease. Section III.3 discusses the effect of the diagnosis and treatment of active TB on the choice of ART.

11.1. TB screening and diagnosis

All infants and children living with HIV should be evaluated at every visit to a health care facility for contact with any person with TB that could be a potential source of infection. Those presenting with poor weight gain, current cough or fever should be evaluated for TB.

Primary TB disease among children presents with a broad range of non-pulmonary and pulmonary manifestations. For children with TB, bacteriological confirmation should be sought whenever possible, even if this is difficult and the results frequently negative. Appropriate clinical samples may include sputum (by expectoration, gastric aspiration or sputum induction), fine-needle aspiration of enlarged lymph nodes, pleural fluid or ear swab from chronically discharging ears.

In many cases, especially among young children, diagnosis is presumptive and based on several factors. These include a constellation of clinical signs and symptoms, known contact with a household member with TB disease, a positive tuberculin skin test and radiographic findings on chest X-ray. A "trial of TB treatment" should not be used as a diagnostic test for TB among children.

11.2. Isoniazid preventive therapy

Overall, there is little high-quality evidence on the use of isoniazid preventive therapy for infants. No evidence indicates that isoniazid preventive therapy confers benefits among infants with no history of exposure to TB, but any such exposure should be actively sought and care-

fully ascertained. HIV-exposed infants should be carefully evaluated for possible active TB, and isoniazid preventive therapy should be started if active TB is not found.

A randomized study showed that providing isoniazid preventive therapy to children living with HIV reduces the incidence of TB by 72% and all-cause mortality by 64% (76), confirming the beneficial effect of isoniazid preventive therapy observed among adults (77). However, a randomized controlled trial in South Africa (78) showed that isoniazid preventive therapy provides no benefit when infants living with HIV with no known exposure to any person with active TB are identified in the first 3–4 months of life, started immediately on ART and carefully monitored monthly for new TB exposure or disease.

11.3. Treatment of active TB

The underlying principles for the treating children living with HIV for TB are the same as for children who are not HIV infected. However, the co-management of TB and HIV and the treatment of HIV infection are complicated by drug–drug interactions, especially between rifampicin and the NNRTI and PI classes of ARV medicines. These drugs have similar routes of metabolism, and co-administration may result in subtherapeutic drug levels. ART should not be interrupted, but the doses of ART may need to be adjusted when taken with rifamycins, especially rifampicin. The potential use of rifabutin, considered to overcome drug–drug interactions among adults, is not recommended because data are insufficient and no formulation for children is available. In addition, the choice of ART regimen for children with both TB and HIV is complicated by the relatively limited number of available ARV medicine formulations for children and the lack of dosing information for some (especially for children younger than three years of age).

11.3.1. Choice of first-line ART regimens for children receiving rifampicin

Pharmacokinetic data are limited regarding the concomitant use of rifampicin and ARV medicines among children.

Among adults, both standard (600 mg) and increased (800 mg) EFV doses have been used with rifampicin. However, adequate viral and immune response with standard 600-mg dosing has been documented (79), and higher doses are associated with a higher incidence of toxicity and are not recommended. NVP levels are reduced with concurrent administration of rifampicin (80,81). The use of higher doses of NVP with rifampicin has not been evaluated. In addition, NVP, like rifampicin and isoniazid, has potential hepatotoxicity. As with EFV, some clinical reports indicate adequate viral and immune responses and acceptable toxicity with standard doses of NVP administered concomitantly with rifampicin. Prescribing the maximum dose of 200 mg per m² of body surface area is therefore currently recommended as a safer approach for avoiding subtherapeutic drug levels, but more data are urgently needed to address the exact dose requirements.

A regimen of two NRTIs plus NVP should be considered only when careful clinical and laboratory monitoring for potential liver toxicity can be assured.

Alternatively, a triple NRTI regimen can be used, especially for infants previously exposed to NVP. A previous study of adults living with HIV demonstrated that a regimen of AZT + 3TC + ABC has lower antiretroviral potency than an EFV-based regimen (82). However people receiving triple NRTIs do not appear to have any clinical disadvantage (83).

Table 5 lists the recommendations for children with both TB and HIV infection.

TABLE 5. PREFERRED ART REGIMENS FOR INFANTS AND CHILDREN YOUNGER AND OLDER THAN THREE YEARS OLD WITH BOTH TB AND HIV	
Age group	ART regimen
Younger than three years old	Two NRTIs + NVP ^a (except for infants and children younger than two years if previously exposed to NVP) or Three NRTIs: (d4T or AZT) + 3TC + ABC
Older than three years old	Two NRTIs + EFV or Three NRTIs: (d4T or AZT) + 3TC + ABC

^aSince rifampicin is known to reduce levels of NVP, do not use lead-in dosing of NVP when initiating NVP-containing ART with TB treatment

11.3.2. Initiation of ART after starting rifampicin-containing TB treatment

ART is a priority for children with WHO clinical stages 3 and 4. Because the degree of immunodeficiency among children with both TB and HIV is highly correlated with the probability of dying, initiating ART earlier is critical among children with both TB and HIV who have low CD4 values.

Among children living with HIV who have TB disease, initiating TB treatment is the priority. However, the optimal timing for starting ART during TB treatment is not known. The decision on when to start ART after initiating TB treatment involves a balance between the child's age, pill burden, potential drug–drug interactions, overlapping toxicity and the possible development of IRIS versus the risk of further progression of immunosuppression, with the associated increase in the illness and the risk of dying.

Early initiation of ART is advocated for anyone with TB disease regardless of clinical stage and degree of immunosuppression. A randomized controlled trial (SAPIT) provides moderate evidence for early initiation of ART in terms of reduced all-cause mortality and improved TB outcomes in adults (84). Similar data are not available for children, and additional research is urgently needed to address this. However, the expected benefits in terms of reducing the number of children dying and TB transmission outweigh the potential concerns related to the onset of IRIS caused by TB treatment and drug–drug interactions. Moreover, harmonizing the recommendations for children with those for adults will probably facilitate programme uptake.

The potential for IRIS should be considered among all children starting ART, especially those with low CD4 values.

11.3.3. Considerations for children diagnosed with drug-resistant TB

There are few data on the care of children living with HIV who are exposed to multidrug-resistant TB or extensively drug-resistant TB. These children will require referral to local TB experts familiar with the regional drug resistance profile. Treatment of the person with drug-resistant TB must be a priority. ART should also be initiated at the earliest possible opportunity. Because treatment regimens usually do not contain rifampicin, there is less need to alter ART regimens. The risk of combined drug toxicity from ART and multidrug-resistant TB treatment is high but is outweighed by the high probability of dying with no treatment.

11.3.4. Considerations for children diagnosed with TB while receiving ART

Children already on a first-line ART regimen who are then diagnosed with TB should continue ART. However, the ART should be reviewed and may need to be adjusted to ensure optimal treatment of both TB and HIV and to reduce the potential for toxicity and drug–drug interactions. For children on a standard NNRTI-based first-line regimen who develop TB because of either primary infection or unmasking of existing TB, consider substituting NNRTI-based therapy with a triple NRTI regimen. Alternatively, the children could remain on their standard regimen of two NRTIs + one NNRTI, which is preferred for children receiving EFV-based regimens. Children and adolescents for whom EFV is not recommended and who are taking NVP should be administered an increased dose (up to 200 mg per m² of body surface area). Because of possible overlapping toxicity and drug–drug interactions, children given rifampicin and NVP concomitantly should be followed up more frequently, and their laboratory parameters should be checked.

For children receiving a regimen with ritonavir-boosted PIs who are diagnosed with TB, choosing a ART regimen is more difficult because of varying interactions between rifampicin and the PIs. Unboosted PIs are not recommended to be administered with rifampicin because the concentrations of PIs decline.

Although there are few published data relating to children, for children with both TB and HIV whose anti-TB treatment includes rifampicin, the dosage of ritonavir in the LPV/r regimen can be increased to a ratio of 1:1 to achieve adequate LPV exposure. Where available, therapeutic drug levels should be monitored when these medicines are co-administered.

11.4. Recommendations

11.4.1. Isoniazid preventive therapy for children living with HIV

- Children living with HIV who have any one of the following symptoms – poor weight gain, fever, 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, such children should be offered isoniazid preventive therapy regardless of their age.

(Strong recommendation, B)

- Children living with HIV who are older than 12 months of age are unlikely to have active TB on symptom-based screening and have no contact with any person with TB should receive six months of isoniazid preventive therapy (10 mg/kg per day) as part of a comprehensive package of HIV prevention and care services.

(Strong recommendation, B)

- Among children living with HIV who are younger than 12 months of age, only those who have contact with a person with TB and who are evaluated for TB (using investigations) should receive six months of isoniazid preventive therapy if the evaluation shows no TB disease.

(Conditional recommendation, C)

- All children living with HIV who have successfully completed treatment for TB disease should receive isoniazid for an additional six months.

(Strong recommendation, C)

11.4.2. Infants and children diagnosed with TB and HIV

- Any child living with HIV who has active TB disease should begin TB treatment immediately and start ART as soon as tolerated in the first eight weeks of TB therapy, regardless of the CD4 count and clinical stage.

(Strong recommendation, C)

- The preferred first-line ART regimen for infants and children younger than three years of age who are taking a rifampicin-containing regimen for TB is two NRTIs + NVP or a triple NRTI regimen.

(Conditional recommendation, C)

- The preferred first-line ART regimen for children older than three years of age who are taking a rifampicin-containing regimen for TB is two NRTIs + EFV.

(Conditional recommendation, C)

- The preferred first-line ART regimen for infants and children younger than three years of age who have been exposed to NVP and are taking a rifampicin-containing regimen for TB is a triple NRTI regimen.

(Conditional recommendation, C)

11.4.3. Infants and children living with HIV who develop TB while receiving ART

- For all children living with HIV, anti-TB therapy should be started immediately when they are diagnosed with TB; ART should continue.

(Conditional recommendation, C)

- Adjust ART regimens as needed to reduce the potential for toxicity and drug–drug interactions:

- If the regimen is two NRTIs + NVP, substitute EFV for NVP if the child is 3 years or older.
- If the regimen is two NRTIs + NVP and substitution with EFV is not possible, ensure that NVP is dosed at the maximum dose of 200 mg per m² of body surface area per dose twice daily.
- If the regimen is LPV/r, consider adding ritonavir in a 1:1 ratio of LPV to ritonavir to achieve a full therapeutic dose of LPV.

IV. Preventing and managing opportunistic and other infections

Successful ART dramatically reduces the incidence of serious opportunistic infections in HIV, although often not to the background rates among uninfected children. However, many children continue to present with HIV for the first time with an opportunistic infection, and children remain susceptible to opportunistic infections after starting ART before immune reconstitution and if they do not adhere to treatment or treatment fails. Clinicians must therefore remain vigilant and informed about preventing, recognizing and managing opportunistic infections and the interactions between ART and drugs used for prophylaxis or treatment of opportunistic infections. Chronic coinfection with TB or hepatitis B or C may be especially important in this regard. The recommendations in this section have not been classified according to the GRADE system in Europe, however they follow available evidence. Where evidence is lacking, the recommendations represent expert opinion and best practice. The United States Centers for Disease Control and Prevention published a comprehensive review (85).

1. Acute bacterial infections

Untreated HIV significantly increases the incidence of invasive bacterial infections among children (86). Successful treatment with ART significantly reduces the incidence. In particular, the rates of pneumonia fall from about four times the rate among uninfected children to the same as uninfected children (86–90). However, although the rates of bacteraemia, sinusitis and otitis are substantially lower than in untreated HIV, they remain greatly above the background rates among uninfected children (87,88,91–93). The commonest organisms are encapsulated *Streptococcus pneumoniae* and *Haemophilus influenzae*. *Staphylococcus aureus* and gram-negative infections, especially *Pseudomonas aeruginosa*, are also more common among children with severe HIV infection.

1.1. Prevention

Uptake of conjugate vaccines against *S. pneumoniae* and *H. influenzae* should be promoted among children living with HIV.

1.2. Treatment

Antibiotic treatment should be tailored according to clinical presentation and local bacterial susceptibility patterns. Broad-spectrum antibacterial coverage should be instituted early among children with low CD4 counts. For children with good immune reconstitution, culture results may be awaited, but coverage of *S. pneumoniae* should always be included.

2. Mycobacterial infections

Management of HIV infected children with TB is described in chapter 11.

2.1. *Mycobacterium avium* complex

Disseminated *Mycobacterium avium* complex infection in HIV is associated with severe immune suppression and carries a poor prognosis (94,95).

2.1.1. Prophylaxis

Prophylaxis with azithromycin or clarithromycin can reduce the incidence of severe *Mycobacterium avium* complex disease, based on evidence from adults. However, the main priority is starting ART to reduce the risk of *Mycobacterium avium* complex. For newly diagnosed children with very low CD4 counts, a pragmatic decision needs to be made as to whether

an additional drug will compromise adherence to ART or is worth giving. If prophylaxis for *Mycobacterium avium* complex is believed to be likely to compromise adherence to ART or a rapid response to ART is anticipated, prophylaxis may reasonably be withheld. Prophylaxis for *Mycobacterium avium* complex may be worthwhile for people with end-stage HIV who have severe immunosuppression and for whom multiple ART regimens have failed.

2.1.2. Treatment

Regarding prophylaxis for *Mycobacterium avium* complex, the best hope for successful treatment is ART resulting in restoration of CD count and immune reconstitution, although this does carry a significant risk of IRIS. There is a significant risk of morbidity and mortality, and expert input is required in treatment regimens. Ethambutol and azithromycin or clarithromycin should be included in the treatment regimen; the addition of rifabutin has improved survival among adults but carries the risk of drug–drug interactions with ART.

3. Fungal infections

3.1. Aspergillosis

Aspergillosis is an uncommon opportunistic infection in HIV that may present with fever, cough, dyspnoea and pleuritic pain. Isolation of *Aspergillus* spp. from respiratory samples in the absence of such symptoms and supportive radiology may represent a false-positive result. Prophylaxis is not recommended. Treatment is with voriconazole or amphotericin B.

3.2. Candidiasis

Candidiasis is the most common fungal infection in HIV. Oropharyngeal candidiasis is the most common manifestation and may occur among children with high CD4 counts (87). Oesophageal candidiasis is a manifestation of severe immunosuppression (96). Disseminated candidiasis or candidaemia is uncommon but may occur among children with indwelling venous catheters (97). Routine prophylaxis is not recommended. Oropharyngeal candidiasis can be effectively treated with fluconazole, itraconazole, ketoconazole or nystatin.

Oesophageal candidiasis should be treated systemically with fluconazole; voriconazole or caspofungin are alternatives. Systemic candidaemia requires removal of the source of entry and treatment with amphotericin B. Fluconazole may be used in refractory cases, and caspofungin or micafungin may be alternatives.

3.3. Cryptococcal infection

Cryptococcal infection occurs when immune compromise is severe and is less common among children than adults. It may be diagnosed by detecting cryptococcal antigen in blood or cerebrospinal fluid or by culture. There are few data for children, but based on studies of adults, combination treatment with amphotericin B and flucytosine is recommended (98–100). Primary prophylaxis is not indicated.

3.4. *Pneumocystis jirovecii* pneumonia

Pneumocystis jirovecii pneumonia is one of the most common HIV-associated opportunistic infections, occurring in about 40–50% of children living with HIV. It has also been identified as the leading cause of death among infants living with HIV and accounts for 50–60% of AIDS diagnoses among infants (101,102). *Pneumocystis jirovecii* pneumonia is most common among infants younger than one year old, for whom chemoprophylaxis is recommended.

3.4.1. Prophylaxis

Prophylaxis with co-trimoxazole is recommended for:

- all infants younger than one year old with documented HIV infection, regardless of symptoms or CD4 percentage;
- children aged 1–5 years with CD4 <500 cells/mm³ or % CD4+ <15%; and
- children older than five years with CD4 <200 cells/mm³ or % CD4+ <15%.

Alveolar infiltrates progress peripherally, with late apical sparing and small pleural effusions reported. Bullae, cysts or pneumothorax may occasionally be seen.

3.4.2. Treatment

The first-line treatment for *Pneumocystis jirovecii* pneumonia is co-trimoxazole at a dose for children older than two months of 15–20 mg/kg per day of trimethoprim and 75–100 mg/kg per day of sulfamethoxazole given intravenously in 3–4 divided doses for 21 days. After the acute pneumonitis has resolved, children with mild to moderate disease who do not have malabsorption or diarrhoea can receive the same dose of co-trimoxazole orally to complete the 21-day course. If the child fails to respond to co-trimoxazole, repeated bronchial lavage or lung biopsy should be considered.

A second-line treatment should be undertaken with pentamidine, dapsone, atovaquone or clindamycin in case of allergic reaction to co-trimoxazole or a failure to respond to it.

Cytomegalovirus is frequently found in bronchial lavage with *Pneumocystis jirovecii* pneumonia infection, but ganciclovir should only be used for children with *Pneumocystis jirovecii* pneumonia and cytomegalovirus if they are not responding to standard *Pneumocystis jirovecii* pneumonia therapy.

For children with moderate or severe *Pneumocystis jirovecii* pneumonia, oral prednisolone is an option.

4. Toxoplasmosis

Toxoplasma gondii encephalitis is relatively uncommon among children with HIV. Among susceptible children with severe immunosuppression, the regimen of prophylaxis against *Pneumocystis jirovecii* usually also protects against *Toxoplasma gondii*. Treatment is with pyrimethamine and sulfadiazine.

5. Viral infections

5.1. Cytomegaloviral infection

Children with HIV are at increased risk of severe cytomegalovirus infection; the risk varies with CD4 count and is significantly reduced by successful ART (86,87). Clinical manifestations may include retinitis, hepatitis, pneumonitis, colitis and central nervous system manifestations (103–106).

5.1.1. Prophylaxis

There is no indication for prophylaxis for cytomegalovirus, but early detection is important, and dilated retinal examination should be performed at diagnosis among all children and at regular intervals among infants with low CD4 counts.

5.1.2. Treatment

First-line treatment is with intravenous ganciclovir; oral valganciclovir is an attractive alternative, especially for completing treatment. Foscarnet and cidofovir are alternatives.

5.2. Hepatitis B viral infection

Children with HIV may acquire hepatitis B virus at birth but may also remain at risk of household transmission through childhood if a parent has hepatitis B virus, and there is a risk of sexual transmission in adolescence. The risks of chronic hepatitis B are increased by early acquisition of the virus and by HIV infection.

5.2.1. Prophylaxis

All children with HIV, and their parents, should be tested for hepatitis B virus, so that both their infection status and risk of acquiring infection can be assessed. All children with HIV who do not have hepatitis B virus should be vaccinated against hepatitis B virus, but the vaccine is less effective among children with HIV (107,108), and checking antibody responses and providing booster vaccination may be necessary, especially before the onset of sexual activity increases the risk of transmission.

5.2.2. Treatment

The evidence base for treating HIV and hepatitis B virus coinfection among children is sparse. Treatment is complicated by the fact that some but not all antiviral drugs used to treat HIV and hepatitis B virus act against both viruses and therefore may select for resistant virus if a combination treatment regimen for one virus contains only one drug active against the other virus. Typically, 3TC is active against HIV and hepatitis B virus, but ABC and NVP are not. Thus, a standard HIV regimen for infants of 3TC, ABC and NVP contains only one active drug against hepatitis B virus (3TC) and, if it is given to a coinfecting child, may select for hepatitis B virus with resistance to 3TC.

The indications and treatment regimens for hepatitis B virus among coinfecting children are extrapolated from adults and hepatitis B virus monoinfected children (109,110).

Treatment should be initiated if there is either:

- evidence of ongoing hepatitis B virus replication (persistent hepatitis B virus DNA load >2000 IU/ml, hepatitis B virus e antigen positive) with no evidence to suggest spontaneous control of hepatitis B virus (emergence of anti-e antibody, which may precede the clearance of hepatitis B virus e antigen) and persistent elevation of transaminases (exceeding twice the upper limit of normal for more than six months); or
- evidence of inflammation on liver biopsy.

Using the above criteria to determine the need for treating the person for hepatitis B virus and standard age-related criteria (section III.2) to determine the need for treating the child for HIV infection, there are four possible scenarios.

1. The child meets the criteria for treatment for neither HIV nor hepatitis B virus: continue to monitor.
2. The child needs treatment for hepatitis B virus but not for HIV: use standard treatment for HIV-uninfected children with chronic hepatitis B virus: interferon-alpha with or without adefovir. Avoid using drugs for hepatitis B virus that may have activity against HIV (3TC, FTC, TDF and entecavir), since these may select for HIV mutations and compromise the future treatment of HIV.
3. The child needs treatment for HIV but not for hepatitis B virus: avoid selecting an ART regimen that contains only a single drug active against hepatitis B virus (3TC, FTC or TDF), as

this may select resistant hepatitis B virus and compromise future treatment. An ART combination containing two dually active drugs (TDF + (3TC or FTC) + (NNRTI or PI)) may be used, as this will provide effective treatment against both viruses and not select for resistant hepatitis B virus.

4. The child needs treatment for both HIV and hepatitis B virus. If the child has not previously received 3TC or FTC, an ART regimen containing one of these drugs should be selected as well as TDF if the child is old enough, and standard treatment for hepatitis B virus should be given. If the child previously received 3TC or FTC without TDF and had ongoing hepatitis B virus replication, it should be assumed that the hepatitis B virus is resistant to 3TC or FTC, and although these may be retained in the ART regimen, they should be assumed to be ineffective and not counted as an active component of the hepatitis B virus regimen, which should be composed of other active agents.

5.3. Hepatitis C viral infection

Mothers with HIV and hepatitis C virus are more likely to transmit hepatitis C virus to their infants than women who only have hepatitis C virus (*111–118*), and the infants living with HIV of women with HIV and hepatitis C virus may be more likely to be hepatitis C virus positive (*117–120*). Similar to HIV, positive hepatitis C virus serostatus in infancy may only reflect maternal antibody, and the diagnosis must be confirmed among children by positive hepatitis C virus polymerase chain reaction (PCR) or the persistence of antibody beyond age 18 months.

Evidence to inform the treatment of children with hepatitis C virus but without HIV is sparse, and the evidence on children with both HIV and hepatitis C virus is even more sparse. The treatment issues are different to hepatitis B, as current treatments do not have overlapping antiviral activity and resistance. The important issues are interactions between drugs and appropriate timing of the initiation of treatment. The recommended treatment in adults is pegylated interferon-alpha plus oral ribavirin. Factors improving treatment outcome among adults are hepatitis C virus genotype (types 2 and 3 are favourable and types 1 and 4 are unfavourable), low hepatitis C virus VL, elevated transaminases and lack of liver fibrosis (*121*). A higher CD4 count is also favourable, and thus prior initiation of ART may be considered. For hepatitis C virus–monoinfected children, treatment is not recommended below age three years as hepatitis C virus may still clear spontaneously. In older children, the risk factors for disease progression remain poorly identified, but treatment responses have been observed (*110, 122–126*). An expert should direct the treatment of coinfecting children, which should consist of pegylated interferon-alpha and ribavirin. Ribavirin may increase the risk of ddI toxicity, so ddI should be avoided in the ART regimen. Ribavirin and AZT may cumulatively worsen anaemia. New drug development for hepatitis C is progressing rapidly, and treatment regimens may change dramatically during the next few years.

5.4. Herpes simplex viral infection

The most severe manifestation of herpes simplex virus in childhood is neonatal herpes simplex virus, which may cause life-threatening disseminated disease or encephalitis with a high risk of disability. Older children are almost invariably exposed to herpes simplex virus during childhood but may be at increased risk of more severe disease if they have low CD4 counts. Sexually active adolescents may acquire genital herpes simplex virus.

5.4.1. Prophylaxis

Standard obstetric precautions to prevent neonatal herpes simplex virus should be applied to pregnant women presenting with genital herpes simplex virus close to the time of delivery (*127*). Primary prophylaxis is not recommended for older children, but secondary prophylaxis

with aciclovir may be effective for children who get frequent troublesome recurrences of herpes simplex virus (128). Using condoms may reduce the risk of genital herpes simplex virus among sexually active adolescents.

5.4.2. Treatment

Neonatal herpes simplex virus should be treated with three weeks of high-dose intravenous aciclovir (129). Disseminated disease among older children also requires intravenous aciclovir. Mucocutaneous herpes simplex virus among older children and genital herpes among adolescents can be treated with oral aciclovir.

Alternative drugs include valaciclovir and famciclovir (130–133), but these have the same resistance profile as aciclovir, and resistant disease requires treatment with foscarnet or cidofovir (134–137).

5.5. Varicella-zoster viral infection

Varicella infection may be severe or life-threatening among children living with HIV who have low CD4 counts.

5.5.1. Prophylaxis

Varicella infection is almost ubiquitous in childhood, and it is impossible to prevent all exposure. Primary prevention with varicella zoster virus vaccine is contraindicated among children living with HIV with low CD4 counts who are at highest risk from varicella zoster virus, since the vaccine is live and may itself cause a varicella-like disease among susceptible children. Secondary prevention with varicella zoster immunoglobulin should be considered for children with HIV and low CD4 counts within 96 hours of exposure to varicella or zoster. Aciclovir prophylaxis may be given from 10 days after exposure if varicella zoster immunoglobulin is not available.

5.5.2. Treatment

Children with clinical varicella who are living with HIV and have low CD4 counts should be treated with intravenous aciclovir. Ganciclovir and foscarnet are alternatives but are seldom used.

V. Suggested minimum data to be collected at the clinical level

The suggested minimum data to be collected are important in the development of key indicators on access to treatment and its success, which assists managers in decision-making on ways to strengthen and expand these services to all children who need them.

The data should be collected at each clinical facility on a regular basis (e.g. quarterly or semi-annually) comprising:

- the number of infants born to HIV infected mother who were virologically tested on HIV;
- the number of newly HIV-infected infants <18 months of age who have been diagnosed with HIV by virological test;
- the number of newly HIV-infected infants <18 months of age who have been diagnosed by virological test and receive ART;
- the total number of children enrolled in HIV care in the facility;
- the number of eligible children newly enrolled in care during the reporting period;
- the number of newly HIV-infected infants who are receiving cotrimoxazole prophylaxis;
- the number of children alive at 6 months, 12 months, 24 months, etc. after initiation of ART, out of the total number of children who began ART at around the same time;
- the number of children swithing from first-line ART to secon-line ART within last reporting period;
- interrupting ART in the last reporting period, with the reason (e.g. death, toxicity/side effects, loss to follow-up, ARVs not available, etc);
- the number of newly diagnosed HIV-infected children diagnosed with TB;
- the number of children died in total, including the cause;
- the number of children who died while on ART.

Annex 1. WHO clinical staging of HIV for infants and children with established HIV infection

Clinical stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2
Unexplained persistent hepatosplenomegaly Papular pruritic eruptions Extensive wart virus infection Extensive molluscum contagiosum Recurrent oral ulcerations Unexplained persistent parotid enlargement Lineal gingival erythema Herpes zoster Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis and tonsillitis) Fungal nail infections
Clinical stage 3
Unexplained moderate malnutrition not adequately responding to standard therapy Unexplained persistent diarrhoea (14 days or more) Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one month) Persistent oral candidiasis (after the first six weeks of life) Oral hairy leukoplakia Acute necrotizing ulcerative gingivitis or periodontitis Lymph node TB Pulmonary TB Severe recurrent bacterial pneumonia Symptomatic lymphoid interstitial pneumonitis Chronic HIV-associated lung disease, including bronchiectasis Unexplained anaemia (<8.0 g/dl), neutropaenia (<0.5 x 10 ⁹ per litre) or chronic thrombocytopenia (<50 x 10 ⁹ per litre)
Clinical stage 4
Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy Pneumocystis pneumonia Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection and meningitis but excluding pneumonia) Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration, or visceral at any site) Extrapulmonary TB Kaposi sarcoma Oesophageal candidiasis (or candidiasis of the trachea, bronchi or lungs) Central nervous system toxoplasmosis (after the neonatal period) HIV encephalopathy Cytomegalovirus infection; retinitis or cytomegalovirus infection affecting another organ, with onset at age more than one month Extrapulmonary cryptococcosis, including meningitis Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis or penicilliosis) Chronic cryptosporidiosis (with diarrhoea) Chronic isosporiasis Disseminated non-tuberculous mycobacterial infection Cerebral or B-cell non-Hodgkin lymphoma Progressive multifocal leukoencephalopathy HIV-associated cardiomyopathy or nephropathy

Annex 2. ARV drug doses

A2.1. NRTIs

A2.1.1. ABC

Target dose

Age less than 16 years or weight less than 37.5 kg: 8 mg/kg dose twice daily

Note: Once-daily dosing has not yet been approved for children, but encouraging pharmacokinetic data are now available.

Maximum dose

300 mg/dose twice daily

A2.1.2. ddl

Target dose

- Age younger than three months: 50 mg per m² body surface area twice daily
- Age 3 months to 13 years: 90–120 mg/m² twice daily

Maximum dose

200 mg twice daily or 400 mg once daily

A2.1.3. FTC

Target dose

- Liquid 6 mg/kg
- Capsules 200-mg capsule once daily (weight more than 33 kg)

Maximum dose

200-mg capsule once daily

A2.1.4. 3TC

Target doses

- Age younger than 30 days: 2 mg/kg twice daily
- Age older than 30 days: 4 mg/kg twice daily
- Weight more than 50 kg: 150 mg twice daily

Note: Once-daily dosing has not yet been approved for children, but encouraging pharmacokinetic data are available for children switching to once-daily dosing once viral suppression occurs on ART.

Maximum dose

150 mg twice daily

A2.1.5. TDF

Target dose

300 mg/day for children 12 years of age and older

A2.1.6. AZT

Target dose

- Liquid (oral dosing) 180–240 mg/m² per dose twice daily (total daily dose 360–480 mg/m²)
- For children with suspected nervous system involvement, using a dose at the higher end of the range may be beneficial.

Maximum dose

300 mg twice daily

A2.2. NNRTIs

A2.2.1. EFV

Target dose

- Liquid 19.5 mg/kg per day or
- Capsule or tablet 15 mg/kg per day once daily
- Weight more than 40 kg: 600 mg once daily

Maximum dose

600 mg once daily

A2.2.2 NVP

Target dose

160–200 mg/m² twice daily

Maximum dose

200 mg twice daily

A2.3. Protease inhibitors

All PIs should be prescribed with low-dose ritonavir boosting.

A2.3.1. LPV/r

LPV target dose

230–350 mg/m² twice daily

Maximum dose

LPV 400 mg + ritonavir 100 mg twice daily

A2.3.2. Ritonavir-boosted atazanavir

Target dose

Treatment-naïve

- Weight 15 kg to <25 kg: 150 mg atazanavir + 80 mg ritonavir
- Weight 25 kg to <32 kg: 200 mg atazanavir + 100 mg ritonavir
- Weight 32 kg to <39 kg: 250 mg atazanavir + 100 mg ritonavir

Treatment-experienced

- Weight 25 kg to <32 kg: 200 mg atazanavir + 100 mg ritonavir
- Weight 32 kg to <39 kg: 250 mg atazanavir + 100 mg ritonavir

Maximum dose

ATV 300 mg + ritonavir 100 mg once daily

A2.3.3. Ritonavir-boosted darunavir

Target DRV dose

10–20 mg/kg twice daily

Maximum dose

600 mg darunavir + 100 mg ritonavir twice daily

Annex 3. Serious acute and chronic toxicity caused by ARV drugs: clinical presentation, laboratory abnormalities and implications for managing ART

Toxicity caused by ARV drugs may require modifying therapy. Alternative explanations for toxicity should be excluded before concluding that the ARV drug is the cause.

Table 6 describes the management of the ART regimen but does not indicate how to manage clinical toxicity in detail.

TABLE 6. MANAGEMENT OF TOXICITY IN ART		
Possible clinical manifestations (most common ARV drugs associated with the toxicity)	Possible laboratory abnormalities	Implications for ART
Acute, symptomatic hepatitis (NNRTI class, particularly NVP, more rarely EFV; NRTIs or PIs)		
Jaundice Liver enlargement Gastrointestinal symptoms Fatigue, anorexia May have hypersensitivity component (rash, fever, systemic symptoms), usually occurs within 6–8 weeks May have accompanying lactic acidosis (see below) if secondary to an NRTI drug	Elevated transaminases Elevated bilirubin	Discontinue all ARV medicines until symptoms resolve If possible, monitor transaminases, and bilirubin If the child is receiving NVP, it should not be readministered in the future Once symptoms resolve, either: <ul style="list-style-type: none"> • restart ART with substitution to alternative ARV (if the child is on an NVP regimen, this is required); or • restart same ART regimen with close observation; if symptoms recur, substitute an alternative ARV drug
Acute pancreatitis (NRTI class, particularly d4T and ddI; more rarely 3TC)		
Severe nausea and vomiting Severe abdominal pain May have accompanying lactic acidosis (see below)	Elevated pancreatic amylase Elevated lipase	Discontinue all ARV medicines until the symptoms resolve If possible, monitor serum pancreatic amylase, lipase Once the symptoms resolve, restart ART with the substitution of an alternative NRTI, preferably one without pancreatic toxicity

Hypersensitivity reaction (ABC or NVP)		
<p>ABC: combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC, including fever, fatigue, myalgia, nausea, vomiting, diarrhoea, abdominal pain, pharyngitis, cough and dyspnoea; rash (usually mild) may or may not occur; progressive worsening of symptoms soon after receiving ABC dose, usually occurs within 6–8 weeks</p> <p>NVP: Systemic symptoms of fever, myalgia, arthralgia and hepatitis with or without rash usually occur within 6–8 weeks</p>	<p>Elevated transaminases</p> <p>Elevated eosinophil count</p>	<p>Immediately discontinue all ARV medicines until the symptoms resolve</p> <p>NVP or ABC should not be readministered in the future</p> <p>Once the symptoms resolve, restart ART with the substitution of an alternative ARV drug for ABC or NVP</p>
Lactic acidosis (NRTI class, especially d4T)		
<p>Generalized fatigue and weakness</p> <p>Gastrointestinal features (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia, poor weight gain and/or sudden unexplained weight loss)</p> <p>May have hepatitis or pancreatitis (see above)</p> <p>Respiratory features (tachypnoea and dyspnoea)</p> <p>Nervous system symptoms (including motor weakness)</p> <p>Can occur at any time on ART</p>	<p>Increased anion gap</p> <p>Lactic acidosis</p> <p>Elevated aminotransferase</p> <p>Elevated creatine phosphokinase</p> <p>Elevated lactate dehydrogenase</p>	<p>Discontinue all ARV medicines until the symptoms resolve</p> <p>Symptoms associated with lactic acidosis may continue or worsen although ART is discontinued</p> <p>Once the symptoms resolve, restart ART with the substitution of an alternative NRTI with lower mitochondrial toxicity risk (such as ABC or AZT)</p>
Severe rash or Stevens-Johnson syndrome (NNRTI class, especially NVP, less common with EFV)		
<p>Rash usually occurs during first 6–8 weeks of treatment</p> <p>Mild-to-moderate rash: erythematous, maculopapular, confluent, most often on the body and arms, with no systemic symptoms</p> <p>Severe rash: extensive rash with moist desquamation, angioedema or serum sickness-like reaction; or rash with constitutional findings such as fever, oral lesions, blistering, facial oedema or conjunctivitis</p> <p>Life-threatening Stevens-Johnson syndrome or toxic epidermal necrolysis</p>	<p>Elevated transaminases</p>	<p>If the rash is mild or moderate, ART can continue without interruption staying at the induction dose until the rash settles but with close observation, and only increase to the maintenance dose once tolerated</p> <p>For severe or life-threatening rash, discontinue all ARV medicines until the symptoms resolve</p> <p>NVP should not be readministered in the future</p> <p>Once the symptoms resolve, restart ART with the substitution of an alternative ARV medicine for NVP (note: most experts would not change to another NNRTI drug if the child had severe or life-threatening Stevens-Johnson syndrome with NVP)</p>

Severe life-threatening anaemia (AZT)		
Severe pallor, tachycardia Significant fatigue Congestive heart failure	Low haemoglobin	Refractory to symptomatic treatment (such as transfusion), discontinue AZT only and substitute an alternative NRTI
Severe neutropaenia (AZT)		
Sepsis or infection	Low neutrophil count	If refractory to symptomatic treatment, discontinue AZT only and substitute an alternative NRTI
Chronic late serious adverse reactions		
Lipodystrophy and metabolic syndrome (d4T; PIs)		
Fat accumulation and/or fat loss in distinct regions of the body: <ul style="list-style-type: none"> increased fat around the abdomen, buffalo hump, breast hypertrophy fat loss from limbs, buttocks and face occurs to a variable extent Insulin resistance, including diabetes mellitus Potential risk for later coronary artery disease	Hypertriglyceridaemia Hypercholesterolaemia Low high-density lipoprotein levels Hyperglycaemia	Substituting ABC or AZT for d4T may prevent the progression of lipodystrophy Substituting an NNRTI for a PI may decrease serum lipid abnormalities
Severe peripheral neuropathy (d4T and ddi; more rarely 3TC)		
Pain, tingling, numbness of hands or feet; inability to walk Distal sensory loss Mild muscle weakness and areflexia may occur	None	Stop the suspected NRTI only and substitute a different NRTI that is not associated with neurotoxicity The symptoms may take several weeks to resolve

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