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# Initiating anti-retroviral therapy in HIV-infected infants and children

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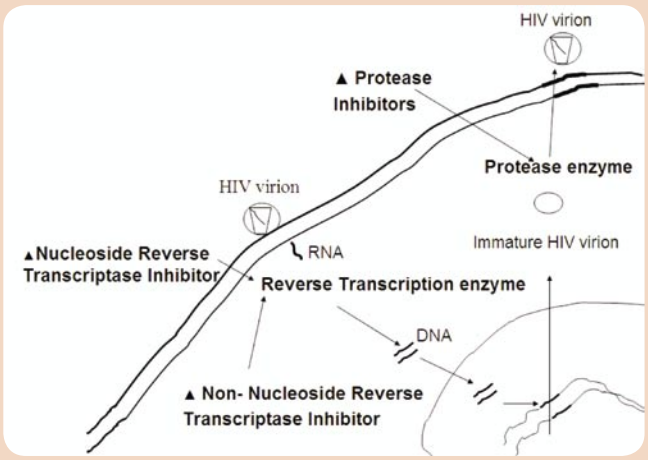
## INTRODUCTION

Highly active antiretroviral therapy (HAART) has brought about a dramatic reduction in the morbidity and mortality associated with human immunodeficiency virus (HIV) infection. With the availability of HAART, HIV has become a manageable chronic disease.[1] Doctors may be intimidated by the prospect of managing HIV-infected children, but the basic principles of care are surprisingly simple. However, as HIV establishes latent reservoirs that are not eradicated with current treatment regimens, patients require life-long treatment and optimal patient management is crucial.[2] The

**Figure 1:** Mode of action of the three main drug classes




▲ Drug class

**Table 1:** Antiretroviral drugs and child friendly drug formulations available in South Africa

| Class | Sub-class | Drug | Available formulations | Most important adverse events | Prescriber's points of 2 tablets |
|---|---|---|---|---|---|
| Nucleoside Reverse Transcriptase Inhibitors (NRTI's) | Thymidine analogue | Stavudine (D4T) | Solution 1mg/ml*<br>Capsule 15, 20, 30 or 40mg | Lactic acidosis, particularly in combination with DDI<br>peripheral neuropathy<br>lipodystrophy, lipoatrophy (uncommon in children) | Do not prescribe with AZT - Both thymidine analogue<br>Do not prescribe with DDI - risk of lactic acidosis<br>Didanosin |
| | | Zidovudine (AZT) | Solution 10mg/ml<br>Capsule 100mg<br>Tablet 150mg | Anemia, Neutropenia, myopathy | Do not prescribe with D4T - Both thymidine analogue |
| | Non-Thymidine analogue | Lamivudine (3TC) | Solution 10mg/ml<br>Tablet 150mg | Pancreatis (Rare) | |
| | | Didanosine (DDI) | Suspension 10 mg/ml*<br>Chew tablets 25, 50, 100 or 150mg<br>Enteric coated capsule | Lactic acidosis particularly in combination with D4T<br>Pancreatitis | 2 hr before meal (empty stomach)<br>1hr before or after Kaletra®<br>DDI should be made up of 2 tablets<br>eg. if on 100mg dose = 2x50mg |
| | Guanosine analogue | Abacavir (ABC) | Solution 20mg/ml<br>Tablet 300mg | Severe life threatening hypersensitivity | eg. if on<br>Never re-initiate after previous hypersensitivity, regardless of severity<br>Teratogenic |
| Non-nucleoside reverse transcriptase Inhibitors (NNRTI's) | | Neviripine (NVP) | Solution 10mg/ml<br>Tablet 200mg | Hypersensitivity - skin and hepatitis | Reduce risk by initiating at ½ dose |
| | | Efavirenz (EFV) | Capsules 50, 200 or 600mg | Poor attention, nightmares<br>Hypersensitivity - skin and hepatitis | Teratogenic<br>Not used in children <3yrs and/or 10kg |
| Protease Inhibitors (PI's) | | Kaletra ® (lopinavir/ ritonovir) | Solution 80mg/20mg/ml♦<br>Capsule 133,3mg/33,3mg♦ | Metabolic adverse events<br>Loose stools | Bad taste |
| | | Ritonovir | Solution 80mg/ml♦<br>Capsule 100mg♦ | Metabolic adverse events<br>Loose stools | Bad taste |
| | | Nelvinavir | Powder 50mg/g<br>Tablet 250mg | Metabolic adverse events | Powder not easy to use<br>High pill burden |

*Refrigeration required
♦ Refrigeration preferred

development of resistance (often related to poor adherence) limits future treatment options; therefore, careful preparation and continuous support are essential components of an optimal management plan.[3,4]

The principle underlying HAART is that antiretroviral drugs (ARV's) from different classes are combined to achieve maximal and long term suppression of viral repli-cation, as it reduces the risk of random drug resistance. Achieving and maintaining a significant reduction in the viral load, preferably down to undetectable levels, is the main therapeutic aim. A significantly reduced viral load is required for immune recovery and clinical improvement[1,5] while an undetectable viral load is the best safeguard against the acquisition of drug resistance.[6]

**Anti-retroviral drugs**

ARV's are classified according to their mode of action. (Figure 1) Adverse effects may be related to a specific class of drugs [e.g. the lactic acidosis associated with nucleoside reverse transcriptase inhibitor (NRTI) use], or to an individual drug in particular [e.g. the anemia associated with zidovudine (AZT)]. Clinicians should familiarize themselves with the most important adverse effects associated with each drug. (Table 1) Routine monitoring assists with the early detection of adverse events and these are managed according to their severity. Severe and/or unexpected adverse events (i.e. lactic acidosis or birth defects associated with in utero exposure to ARVs) should be reported to the Medicines Control Council and/or other appropriate bodies.

ARV's do interact with various commonly used medications, which may influence the plasma concen-trations of the ARV and/or the other medication, leading to reduced efficacy and/or increased adverse events.

**Important considerations**

Vertically infected infants have exceptionally high viral loads and complete suppression of viral repli-cation may be difficult to achieve, considerably increasing the risk of acquired drug resistance.[7] In addition, infants who failed single dose nevirapine (NVP) preventive chemotherapy may harbour viruses that are resistant to all non-nucleoside reverse transcriptase inhibitors (NNRTI's).[8] Infants and children depend on adult caretakers to bring them to the clinic and give their medication; therefore, stable social circumstances and the identification of a reliable caregiver are essential. Small children are unable to swallow capsules and pills, although with adequate training, they may master this at an unexpectedly early age. In practice, the treatment of young children depends on the availability of child friendly formulations, as adult pills often contain inappropriately high drug dosages. Unfortunately, many suspensions and syrups are unpalatable and/or require refrigeration,

**Table 2:** New (2005) WHO clinical staging of HIV/AIDS in infants and children

| |
|---|
| Stage 1<br>• Asymptomatic<br>• Persistent Generalized Lymphadenopathy (PGL) |
| Stage 2<br>• Hepatosplenomegaly<br>• Papular pruritic eruptions, Seborrhoeic dermatitis<br>• Extensive human papilloma virus infection , Molluscum contagiosum<br>• Herpes zoster<br>• Fungal nail infections<br>• Parotid enlargement<br>• Recurrent oral ulcerations, Lineal gingival erythema (LGE), Angular cheilitis<br>• Recurrent or chronic RTI's (otitis media, otorrhoea, sinusitis) |
| Stage 3<br>Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations<br>• Moderate unexplained malnutrition(between the 3rd percentile and 60% of expected weight)<br>• Unexplained persistent diarrhoea (14 days or more )<br>• Unexplained persistent fever (intermittent or constant, for longer than one month)<br>• Oral candidiasis (outside neonatal period )<br>• Oral hairy leukoplakia, Acute necrotizing ulcerative gingivitis/periodontitis<br>• Severe recurrent presumed bacterial pneumonia<br>• Pulmonary TB<br>Conditions where confirmatory diagnostic testing is necessary<br>• Chronic HIV-associated lung disease, including brochiectasis<br>• Lymphoid interstitial pneumonitis (LIP)<br>• Unexplained anaemia (<8g/dl), and or neutropenia (<1000/mm3) and or thrombocytopenia (<50 000/ mm3) for more than one month |
| Stage 4<br>Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations<br>• Unexplained severe wasting or severe malnutrition<br>• Pneumocystis pneumonia<br>• Extrapulmonary TB<br>• Oesophageal candidiasis<br>• Recurrent severe presumed bacterial infections (excluding pneumonia)<br>• Chronic herpes simplex infection; (orolabial or cutaneous of more than 1 month duration)<br>• Kaposi's sarcoma<br>• CNS toxoplasmosis (outside the neonatal period)<br>• HIV-associated encephalopathy |
| Conditions where confirmatory diagnostic testing is necessary<br>• CMV infection (CMV retinitis or infection of organs other than liver, spleen or lymph nodes; onset at age one month or more)<br>• Extrapulmonary cryptococcosis including meningitis<br>• Any disseminated endemic mycosis<br>• Cryptosporidiosis, Isosporiasis<br>• Disseminated non-tuberculous mycobacteria infection<br>• Candida of trachea, bronchi or lungs<br>• Visceral herpes simplex infection<br>• Acquired HIV-associated rectal fistula<br>• Cerebral or B cell non-Hodgkin lymphoma<br>• Progressive multifocal leukoencephalopathy (PML)<br>• HIV-associated cardiomyopathy or nephropathy |

and are expensive. In addition, there are few combination medi-cations and some drugs, eg. efavirenz cannot be used in young children due to a lack of pharmacokinetic information. Table 1 contains a list of child friendly ARV's commonly used in South Africa.

**Staging of disease**

Clinical and immunological staging are essential compo-nents of the management of HIV-infected children, as accurate staging provides valuable prognostic information. It also identifies children who require HAART and those who experience treatment failure. Because HIV is a chronic illness, meticulous attention should be paid to basic principles of pediatric care. Clinicians should always take a good history, document intercurrent events, and monitor growth and neurological development carefully. Making appropriate use of side room investigations (urine dipstix and haemoglobin) and basic special investigations, such as chest radiography (CXR), are also important. Occult proteinuria may suggests HIV related nephro-pathy, a condition that requires HAART[9], and urinary tract infections may be asymptomatic; a suggestive CXR may be the only way of establishing a diagnosis of probable tuberculosis.

In the absence of HAART, the prognosis of African children is worse than that of children in industrialized countries; a shorter median survival time and increased risk of developing AIDS has been reported.[10] Young infants often present with severe clinical disease and there may be discordance between the severity of clinical events and their immunological status (as measured by CD4%). Some authors suggest that infants in whom HAART is started early (<5 months of age) show better CD4 recovery.[11]

*Clinical staging*

Although the clinical classification system developed by the United States Centers for Disease Control and Prevention (CDC) is useful and predictive[12], problems were experienced when this approach was applied to African settings. In response, the World Health Organization (WHO) published a new 4 stage pediatric clinical staging system in 2005.[13] The new WHO clinical staging system takes into consideration frequently observed problems facing clini-cians in the developing world, such as rectal fistulas and poorly defined chronic lung disease. (Table 2) The correct placing of pulmonary tuberculosis (TB), particularly in TB-endemic areas, remains a challenge. The staging system differentiates conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations, from those where confirmatory tes-ting is required. All serious and potentially fatal conditions such as nephropathy and cardiomyopathy are now categorized as stage 4, the most severe disease category. The creation of four stages provides the additional advantage of synchronizing paediatric and adult staging systems, resulting in less confusion for healthcare workers and allowing an easier transition from paediatric to adult care. Although it has not been formally validated, the use of the new WHO clinical staging system is encouraged in resource-limited settings.

*Immunological staging*

The normal CD4 cell count varies with age, starting high and then declining slowly to reach adult values around 5 years of age, however, the number of CD4 cells expressed as a percentage of the total lymphocyte count remains fairly stable.[14] Therefore immunological staging of childhood HIV utilizes the CD4 percent. It is important to remember that lymphocyte sub-sets may be influenced by intercurrent illness, and conditions causing transient lymphopenia, such as bacterial sepsis, may lead to a "falsely elevated" CD4%.[15] Dunn et al confirmed that CD4% was the most important predictor of disease progression in young children; in addition, they showed that immune suppression in young infants occur at higher CD4 percentages than previously appreciated,[16] providing the rationale for the new WHO immunological classification system. (Table 3) The total lymp-hocyte count also has value as an immunological marker of disease severity, but its use is only advocated in settings where CD4 measurement is unavailable.[17] In South Africa all children should have access to CD4 measurement. Determination of the viral load has predictive value,[16] but it is inferior to CD4% percent and is not used for this purpose.

**Indications to initiate HAART**

Currently there are two sets of guidelines in South Africa, one for the public and another for the private sector [18,19], but they are high-ly comparable. The WHO recently published new guidelines that differ slightly from current South African guidelines. For the purpose of this article we will focus on the current treatment guidelines provided by the South African Department of Health, which can be accessed at http://www.doh.gov.za/docs/fact-sheets/guidelines/hiv.

Indications for treatment initiation in children with confirmed HIV infection include both clinical and/or immunological criteria. Any child with severe immune suppression should be considered for treat-ment (current SA guidelines; CD4 percentage <20% if <18 months, or <15% if >18 months).

**Table 3:** New (2005) WHO Immunological staging of HIV/AIDS in infants and children

| IMMUNE STATUS | AGE | | |
|---|---|---|---|
| | <1 year | 1-6 years | >6 years |
| No Suppression | > 35% | >25% | >500 Cells |
| Mild Suppression | 25-35% | 20-24% | 350-499 Cells |
| Advanced Suppression | 20-24% | 15-19% | 200-349 Cells |
| Severe Suppression | <20% | <15% | < 200 Cells |

Conversely, any child with WHO Stage III or IV clinical disease qualifies for treatment, irrespective of the CD4%. Young children may experience severe disease manifestations with a fairly well-preserved CD4% or absolute count and early treatment initiation may be associated with better long term outcome,[11] but the optimal timing of treatment initiation is the focus of numerous ongoing studies. If pulmonary TB is the only AIDS defining illness in a TB-endemic area, the child is not severely immune suppressed and responds well to standard treatment, then HAART initiation may be deferred. Some children may not meet either the clinical or immunological criteria mentioned, but experience repeated or prolonged episodes of hospitalization or disfiguring con-ditions e.g. multiple papilomas, in which case the initiation of HAART may also be considered.

**Preparation for treatment initiation**

*Social preparation*

Because the development of viral resistance to HAART is a major concern and limited treatment options are available, treatment initiation should not be considered lightly and brings with it the re-sponsibility of ensuring optimal treatment support. A reliable caregiver, someone who will attend future clinic appointments and give the drugs diligently, should be identified and should receive appropriate training. Although social circumstances and lack of an appropriate caregiver should never exclude a child from HIV care, they are crucial for long term treatment success. If the barriers seem in-surmountable and the child is in desperate need of treatment, short-term alternative care arrangements should be considered. If treatment was initiated in hospital, these issues should be resolved before discharge or alternative care arrangements should be made in the interim.

Adequate preparation of the child and caregiver is the most important aspect of treatment initiation. They should understand the following basic concepts:

1. Antiretroviral treatment is not a cure for HIV
2. HAART is a life-long commitment that may not be broken, and have the necessary basic knowledge:

- How to use the drugs,
- Adverse effects that may arise and
- Realistic expectations for their child (this should be individualized according to the child's clinical condition).

Most clinics expect care givers to attend at least 3 counseling sessions before initiating HAART. Clinicians must re-emphasize the hope that HAART offers to the infected child, but also the risk of developing resistance if this life giving opportunity is not utilized correctly. An attitude of empathy and support must be maintained throughout; the child's best long term interests must remain the focus and treatment initiation may have to be delayed if the necessary parental / care-giver commitment and insight are not in place.

It is prudent to address issues such as disclosure, within the home/family and where appropriate to the child, before initiating treatment. Accessing grants, identifying local facilities for follow-up and addres-sing pressing material needs will be helpful. The physical and mental health of the caretaker plays an important role in their ability to care for the child and issues in this regard may also need to be resolved. As HIV is affects the whole family it is appropriate that parents and/or caregivers and children should be treated at the same family orientated clinic if at all possible.

*Medical preparation*

The necessary base-line tests should be performed in advance of treatment initiation, including a full blood count, CD4 count, liver function and viral load if possible. In addition, the presence of opportunistic infections (OI) should be identified and treated prior to treatment initiation, especially those conditions that may deteriorate following immune reconstitution; in some instances HAART can be initiated whilst the patient is still on treatment for the OI.

**Suggested regimens (table 4)**

Regimens are chosen according to age, prior drug exposure and concurrent anti-TB treatment. (Table 4)

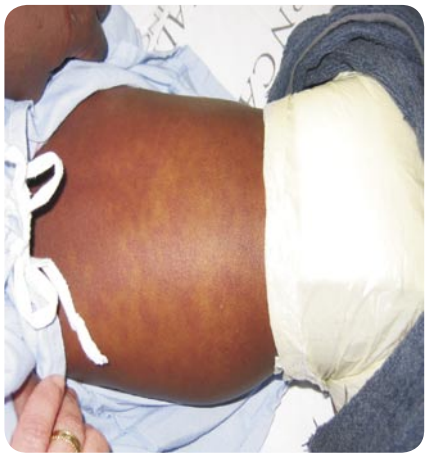
Efavirenz is teratogenic and therefore sexually active adolescent girls should have a pregnancy test before it is initiated and should commit to safe sexual practice and birth control. If caregivers have no access to refrigeration, stavudine can be given

**Table 4**
**Regimens currently recommended by the South African National Department of Health#**

| REGIMEN | CATEGORY | |
|---|---|---|
| | **<3 years and/or <10 kg or exposed to SD-NVP** | **>3 years and > 10 kg and not exposed to SD-NVP** |
| **First regimen** | Stavudine *<br>Lamivudine<br>Kaletra®♦ | Stavudine *<br>Lamivudine<br>Efavirence / Nevirapine |
| **Second regimen** | Zidovudine<br>Didanosien *<br>Efavirence / Nevirapine | Zidovudine<br>Didanosien *<br>Kaletra®♦ |

SD-NVP – single dose Nevirapine
*Refrigerate suspention/solution
♦Refrigeration of capsules and solution preferable but not essential
#See text for recommendations in the presence of anti-tuberculosis therapy

**Figure 2:** Nevirapine associated rash



by suspending the capsule in water, but they require specific training to do this reliably at home.

Optimal dosing is extremely important. Traditionally ARV's were dosed by using mg/kg or mg/m$^2$, but in order to facilitate treatment access, a simple dosing chart that uses weight bands has been developed. Clinicians comfortable with calculating exact dosages can continue as before [the formula to calculate body surface is square root (weight in kg x height in cm / 3600)]. On the weight band chart there are no dosages for children <5kg, in which case clinicians who feel uncomfortable with calculating the correct dosages should seek advice.

Table 5 includes both the conventional and weight band approach. It is important to note that the dosing schedule in very young infants may differ from older children. The dose of ritonovir (not stated in table 5) is; 450mg/ m$^2$ per dose twice daily in infants <3 months and 400/ m$^2$ per dose twice daily in older children. Ritonovir should be initiated at 250mg/ m$^2$ per dose twice daily and the dose escalated by 50mg/ m$^2$ per dose twice daily every 2 days until the target dose is reached.

**TB and HIV co-treatment:**

Due mainly to the interactions of ARV's, in particular NNRTI's and protease inhibitors (PI's), with rifam-picin, TB and HIV co-treatment presents many challenges. Other considerations include the high medication load and the risk of developing immune reconstitution inflammatory syndrome (IRIS). Despite these considerations, TB and HIV co-treatment is sometimes required, particularly in TB-endemic areas where children frequently present with a combination of advanced TB and HIV disease.

Current recommendations are the following:

***Child with TB needing HAART***

- Complete TB treatment if possible or alternatively try to delay HAART initiation by 2 months.
- If the child is >3yrs and >10 kg and did not receive previous NVP, use standard doses of efafvirenz with stavudine and lamivudine.
- If the child is <3yrs and/or <10 kg and/or did receive previous NVP use ritonavir 450mg/ m$^2$ per dose twice daily with stavudine and lamivudine.

***Child on HAART developing TB***

- If the child is already on efavirenz continue with standard dose
- If the child is on NVP and >3yrs > 10kg switch to efavirenz
- If the child is on NVP and <3yrs < 10kg, discuss with an experienced paediatric HIV clinician
- If the child is on Kaletra® switch to ritonavir 450mg/ m$^2$ per dose twice daily.

Combining ARV's and anti-TB therapy is a topic of huge research interest and numerous pharmacokinetic studies are curren-tly in progress. Instead of switching children already on Kaletra® to ritonavir, an alternative that has been suggested is simply to double the dose of Kaletra®, or to "boost" the Kaletra® with an additional dose of ritonavir; the outcome of this research is eagerly awaited. In all cases, the child should be monitored carefully for adverse events and for clinical response to treatment.

**Initial monitoring**

The monitoring and frequency of routine blood tests are described in the South African national guidelines. The frequency and extent of initial monitoring depends partially on the child's clinical condition and the potential problems anticipated. Initial monitoring should include the following: 1) first follow-up visit within the 2 weeks to monitor adherence and the ability to cope with the medication, assessment for adverse drug reactions (Figure 2), and looking for signs of IRIS. If the child is on NVP, alaninine transferase (ALT) level should be performed at week 2, before the dose is routinely increased. If all is well, subsequent visits can be at month 1 and monthly thereafter; 3 monthly once the child is well-established on therapy and compliance is not a concern. In children on TB co-treatment monthly ALT is recommended.

**In conclusion**

This is the second part of a special series on HIV prevention, diagnosis and treatment in children. Additional topics to be covered in this series include:

- Preventing and diagnosing HIV infection in infants and children
- Maintaining infants and children ARV treatment
- Common opportunistic infections in HIV-infected infants and chil-dren

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**Table 5:** Antiretroviral drugs & TMP/SMZ pediatric dosing chart for use in resource-constrained settings (adapted from a table developed by the CDC)

| Weight | Abacavir (Ziagen®) | | Stavudine (Zerit®, d4T) | Lamivudine (Epivir®, 3TC) | | Zidovudine (Retrovir®, ZDV, AZT) | | Didanosine (Videx®, DDI) | Nevirapine (Viramune®, NVP) | | | | | | Efavirenz (Stocrin®, Sustiva®, EFV) | | Lopinavir/ritonavir (Kaletra®) | | Nelfinavir (Viracept®) | Indinavir (Crixivan®) | Trimethoprim/ sulfamethoxazole TMP/SMZ (Septrin®, Bactrim®) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 8 mg/kg twice daily | | 1 mg/kg twice daily<br>Neonates ≤ 29 days 0.5mg/kg/ dose twice daily | 4 mg/kg twice daily<br>Neonates ≤ 29 days 2mg/kg/dose twice daily | | 180-240 mg/m² twice daily<br>Neonates ≤ 29 days 4mg/kg/dose twice daily | | 120 mg/m² twice daily<br>Neonates ≤ 29 days 50mg/m²/ dose twice daily | Induction dose: 4 mg/kg once daily Neonates ≤ 29 5mg/kg once daily<br>for first 14 days, then give maintenance dose→ | | Maintenance dose<br>< 8 yrs 7 mg/kg twice daily OR 120-200 mg/m² twice daily<br>Neonates 120 mg/m² twice daily 14days then 200 mg/m² twice daily | | ≥ 8 yrs 4 mg/kg twice daily OR 120-200 mg/m² twice daily | | Dose as shown once daily<br>(Liquid not yet registered) | | 230-300 mg/m² Lopinavir twice daily<br>Infants<6months 300 mg/m²<br>Lopinavir twice daily | | <1 year 75 mg/kg twice daily >1 year 55-60 mg/kg twice daily<br>Neonates ≤ 29 days 55-75mg/kg/ dose twice daily | 500 mg/m² every 8 hours | ~4 mg/kg once daily<br>(For prophylaxis against opportunistic illnesses. Doses for treatment of bacterial and protozoal infections are higher than listed here) | |
| KG | Liquid 20 mg/ml | Tablet 300 mg | Capsules 15, 20, 30 mg | Liquid 10 mg/ ml | Tablet 150 mg | Liquid 10 mg/ ml | Capsule 100 mg | Chewable tablets 25, 50, 100 mg | Liquid 10 mg/ml | Tablet 200 mg | Liquid 10 mg/ml | Tablet 200 mg | Liquid 10 mg/ ml | Tablet 200 mg | Liquid 30 mg/ml | Capsules 50, 100, 200 mg | Liquid 80 mg lopinavir/ ml[5] | Capsule 133.3/ 33.3 mg lopinavir/r | Tablet 250 mg | Capsule 200 mg | Liquid 8 mg/ml | Single-strength (SS) Tablet 80mg TMP/ 400mg SMZ |
| 5 – 6.9 | 2 ml | | | 2 ml | | 7 ml | | | 2 ml | | 4 ml | | | | | | | | 2 tabs[7] | 1 cap | 3 ml | |
| 7 – 9.9 | 3 ml | | 15 mg | 3 ml | | 9 ml | 1 cap | 25mg + 25mg | 3 ml | | 6 ml | | | | | | 1.5 ml | | 2 tabs[7] | 1 cap | 4 ml | ½ SS tab |
| 10 – 11.9 | 4 ml | | 15 mg or (20 mg[1]) | 4 ml | | 12 ml | 1 cap | 25mg + 25mg | 4 ml | | 8 ml | ½ tab | | | 9 ml | 200 mg | 2 ml | | 2 tabs | 1 cap | 5 ml | ½ SS tab |
| 12 – 14.9 | 5 ml | | 15 mg or (20 mg[1]) | 5 ml | | 14 ml | 1 cap | 50mg + 25mg | 5 ml | | 9 ml | ½ tab | | | 9 ml | 200 mg | 2 ml | | 3 tabs | 1 cap | 7 ml | 1 SS tab |
| 15 - 16.9 | 6 ml | | 15 mg or (20 mg[1]) | 6 ml | ½ tab | 15 ml | 2 caps | 50mg + 25mg | 6 ml | | 10 ml | ½ tab | | | 10 ml | 200 mg + 50 mg | 2.5 ml | 1 cap | 3 tabs | 2 caps | 8 ml | 1 SS tab |
| 17 – 19.9 | 7 ml | ½ tab | 20 mg | 7 ml | ½ tab | 17 ml | 2 caps | 50mg + 50mg | 7 ml | | 13 ml | 1 tab AM + ½ tab PM[4] | | | 10 ml | 200 mg + 50 mg | 2.5 ml | 2 caps[6] | 4 tabs | 2 caps | 9 ml | 1 SS tab |
| 20 – 24.9 | 9 ml | ½ tab | 20 mg | 9 ml | ½ tab | 20 ml | 2 caps | 50mg + 50mg | 9 ml | ½ tab | 16 ml | 1 tab AM + ½ tab PM[4] | 9 ml | ½ tab | 12 ml | 200 mg + 100 mg | 3 ml | 2 caps | 5 tabs | 2 caps | 11 ml | 1 SS tab |
| 25 – 29.9 | 25 – 27.9 | ½ tab | 30 mg | 11 ml | 1 tab[2] | 24 ml | 3 caps or 300 mg tab | 100mg + 25mg | 11 ml | ½ tab | 20 ml | 1 tab | 11 ml | ½ tab | 15 ml | 200 mg + 100 mg + 50 mg | 3.5 ml | 2 caps | 5 tabs | 2 caps | 14 ml | 2 SS tabs |
| | 28 – 29.9 | 1 tab | | | | | | | | | | | | | | | | | | | | |
| 30 – 34.9 | 13 ml | 1 tab | 30 mg | 13 ml | 1 tab | 27 ml | 3 caps or 300 mg tab | 100mg + 25mg | 13 ml | 1 tab[3] | | | 13 ml | 1 tab AM + ½ tab PM[4] | 30 – 32.9 | 200 mg + 100 mg + 50 mg | 4 ml | 3 caps | 5 tabs | 3 caps | 17 ml | 2 SS tabs |
| | | | | | | | | | | | | | | | 33 – 34.9 | 200 mg + 200 mg | | | | | | |
| 35 – 40 | 15 ml | 1 tab | 30 mg | 15 ml | 1 tab | 30 ml | 3 caps or 300 mg tab | 100mg + 25mg | 15 ml | 1 tab[3] | | | 15 ml | 1 tab AM + ½ tab PM[4] | 17 ml | 200 mg + 200 mg | 5 ml | 3 caps | 5 tabs | 3 caps | 20 ml | 2 SS tabs |