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Pharmacotherapy of Pediatric HIV Infection

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SYNOPSIS

With the ongoing epidemic of human immune deficiency virus (HIV) infections in the pediatric age group, the delivery of safe and effective antiretroviral therapy to children and adolescents is crucial to save the lives of millions of children worldwide. Antiretroviral drugs have been demonstrated to significantly decrease HIV-associated morbidity and mortality, assure normal growth and development, and improve survival and quality of life in children and adolescents. The immunologic response to HIV infection is closely related to the child's development and creates age specific parameters for the evaluation of therapeutic response to antiretroviral therapy in pediatric HIV disease. In addition to the changes in immunological response to HIV infection, the development and maturation of organ systems involved in drug absorption, distribution, metabolism, and elimination determines significant changes in the pharmacokinetics of antiretroviral drugs throughout the childhood. Multiple factors including age-specific adherence barriers, changes in social and economical surroundings, and psychological and sexual maturation affect the choices and outcomes of the treatment of pediatric HIV disease. In this chapter we will review the evolution of antiretroviral treatment from early infancy through adolescence.

Keywords

HIV; AIDS; Antiretroviral Drugs; Children; Adolescents

INTRODUCTION

Human immune deficiency (HIV) infection represents one of the most serious pediatric diseases globally with an estimated 3.4 million children living with HIV on our planet.⁽¹⁾ The predominant majority of infection among children is acquired through mother-to-child

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transmission (MTCT) of the virus from HIV-infected women during pregnancy, delivery and breastfeeding. In 1990 the landmark Pediatric AIDS Clinical Trials Group (PACTG) 076 study has demonstrated that the antiretroviral (ARV) drug zidovudine (AZT) administered to the mother and infant around delivery significantly reduced MTCT.⁽²⁾ Since then, the use of antiretroviral therapy (ART) during pregnancy, delivery and postpartum has become the widespread method of the prevention of MTCT (PMTCT). Such unique and unprecedented pharmacological intervention has been shown to be highly efficient by decreasing the natural rates of MTCT from 30–40% to less than 2%.^(3, 4)

Currently available ART utilizes five major classes of ARV drugs: nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs/NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), entry and fusion inhibitors, and integrase inhibitors. The combination ART, also defined as highly active ART (HAART), is comprised of 3 ARV drugs from at least two major classes in order to achieve maximal suppression of HIV replication and preservation of immune function affected by HIV disease.⁽⁵⁾ Another major benefit of ART is its capacity to reduce the transmission of the virus from one person to another, including prevention of vertical transmission of HIV from the infected mother to her fetus, newborn child and infant.^(5, 6)

In the countries with guaranteed access to ARV drugs the number of perinatally acquired pediatric HIV infections is very low and is limited to cases of missed opportunities for the timely identification of HIV, lack of prenatal care and poor adherence to ARV prophylaxis.⁽⁷⁾ In resource-limited settings, which are most heavily affected by the HIV epidemic, the major barriers to effective PMTCT are the lack of adequate prenatal care, lack of HIV testing, limited access to ART and the need for continued breastfeeding to assure infant's survival. Despite ongoing efforts to guarantee universal access to PMTCT in the world, the World Health Organization (WHO) reports that approximately half (48% [44–54%]) of pregnant women living with HIV currently receive ARV prophylaxis for MTCT.⁽⁸⁾ Due to the limited access to universal diagnostics and PMTCT, WHO estimates that 1000 children continue to be infected with HIV each day, with the majority of new cases (97%) occurring in middle and low income countries.^(1, 9) In addition to perinatally infected children, approximately 2520 new HIV infections per day occur through horizontal transmission in adolescents 15–24 years of age, with almost half (48%) of cases among adolescent females, creating the potential for continued MTCT.⁽¹⁰⁾

With the ongoing epidemic of pediatric HIV infection in the world, the delivery of efficient ART to children and adolescents is crucial to saving and improving lives of millions of children worldwide. Per WHO estimates, without therapeutic intervention approximately one third of infected infants will die by one year of age, and about half will die by two years of age.⁽³⁾ ART has been demonstrated to significantly decrease HIV-associated morbidity and mortality, assure normal growth and development, and improve survival and quality of life in children and adolescents.^(11–13)

Following the adult ART development, the treatment of pediatric HIV infection has evolved from monotherapy with zidovudine (AZT), to a dual therapy with nucleoside reverse transcriptase inhibitors (NRTIs) and subsequently to multi-drug therapy involving a combination of three or more ARV drugs.⁽¹⁴⁾ The pathogenesis and the general virologic and immunologic principles of HIV generates an infectious inflammatory process that is similar in HIV-infected adults and children. However, the important etiological, physiological, psychological and social differences between children and adults create an unique consideration for ART in pediatric patients.

Early initiation of ART in children allows achieving maximal suppression of HIV replication, to preserve immunologic function and to prevent disease progression while allowing for normal growth and development. The immunologic outcome (activation and suppression of the CD4+ cell count) of HIV infection is closely related to the child's development and creates age specific parameters for the evaluation of therapeutic response to ART in pediatric HIV disease. In addition to the changes in immunological response to the HIV infection, the development and maturation of organ systems involved in drug absorption, distribution, metabolism, and elimination determine significant changes in the pharmacokinetics (PK) of ARV drugs throughout the childhood. As a child grows and matures, ART transforms from the administration of small amounts of liquid preparations to tablet formulations of co-formulated ARV drugs. In this manuscript we will review the evolution of ART throughout childhood from early infancy into adolescence.

PERINATAL EXPOSURE TO ANTIRETROVIRAL THERAPY

Antiretroviral therapy during pregnancy and delivery

ART during pregnancy can be used for the purpose of maternal therapy and/or PMTCT. When the HIV-infected woman meets the standard treatment initiation criteria for her disease, ART is used for both maternal therapeutic and neonatal prophylactic purposes. When there are no indications for treatment initiation, ART in pregnancy will be used solely for the purpose of PMTCT. The use of ART during delivery is based solely on the purpose of PMTCT.

In order to achieve a high level of PMTCT *in utero*, ARV drugs need to cross the placenta and produce adequate systemic drug levels in the unborn infants. Pregnancy affects the disposition of ART through physiological changes affecting absorption, biotransformation and elimination of ARV drugs.^(15–19) In addition, placental transport, compartmentalization, biotransformation and elimination of ARV drugs in the embryo, fetus and placenta, can all affect the PK of ARV drugs in mother and child.

Current data indicate that despite some changes in the PK parameters of the NRTIs and NNRTIs during pregnancy, overall exposure to these classes of medications is similar between pregnant and non-pregnant women, and a dose change is not warranted for these ARV drugs. The effect of pregnancy on the already highly variable PK parameters of the PIs appears to be more significant. Reports of decreased PIs exposure during the third trimester of pregnancy when compared to non-pregnancy stage warrants dose adjustment (increase) considerations during the last trimester of pregnancy for lopinavir (LPV) and atazanavir (ATV) in combination with a standard dose of boosting ritonavir (RTV).^(6, 20)

In developed countries three drug ART throughout pregnancy followed by intrapartum intravenous AZT is considered standard of care for PMTCT. In case a woman is not requiring ART for her HIV disease, delayed initiation of ART at the end of the first trimester of the pregnancy can be recommended, though earlier initiation can be considered as well. Maintaining adequate levels of ARV exposure in infants becomes further important during delivery when infants come in close contact with maternal genital tract virus during the birth process. With chronic ART use during pregnancy the exposure to ARV drugs are at steady state at time of delivery. If initial ARV doses are administered during labor, however, several PK parameters (clearance, plasma elimination half life) are increased while the area under the time vs. concentration curve (AUC) and peak concentration (C_{max}) are decreased.⁽²¹⁾ The choice of intravenous AZT is based on the ability to achieve high plasma, cord blood and genital fluid concentrations of the ARV drug during delivery.⁽²²⁾

Due to the cost and storage requirement considerations, a full schedule of prenatal PMTCT (prenatal ART starting at the end of the 1st trimester plus intravenous AZT during delivery) is limited to the developed world settings. More practical (e.g. oral drugs only), less intensive and less expensive shorter duration ART regimens have been designed for the PMTCT in the resource-limited settings and include the following schemes:

- mono or dual ART with AZT and lamivudine (3TC) starting at 28–36 weeks gestation, triple ART with AZT/3TC plus abacavir (ABC), nevirapine (NVP), nelfinavir (NFV) or LPV/RTV starting at 26–34 weeks gestation
- single dose NVP (sdNVP) intrapartum in combination with an antepartum course of AZT plus 3TC
- sdNVP plus oral AZT plus oral 3TC intrapartum
- sdNVP intrapartum without additional ART (no longer considered the most optimal approach for PMTCT)

The choice of sdNVP administered to the mother during labor, is based on the rapid absorption and distribution of NVP in adults, high penetration of the drug to the umbilical cord blood (80%), prolonged NVP elimination half-life, affordable costs and high heat resistance.^(23–25)

Multiple studies with these ARV regimens conducted through the international networks in diverse settings around the globe have clearly shown that the combination ART is more efficient in assuring higher levels of PMTCT than mono and dual ARV drug combinations.^(6, 26) Equally, the three component ARV exposure (antepartum, intrapartum and postpartum in neonates) has been shown to be superior to alternative regimens which choice is primarily dictated by cost and availability considerations.

Monitoring of perinatal antiretroviral exposure

As with any pharmacological exposure *in utero*, there is a concern for the short and long term consequences of transplacental and vaginal ARV drug exposure. Despite >20 years of using ART for PMTCT, data of the effect of ART on the fetus remain limited.

Long term controversy surrounds the potential harmful effect of *in utero* NRTIs exposure on the mitochondrial function in neonates and children. Through the process of binding to the mitochondrial gamma DNA polymerase, NRTIs (particularly didanosine (ddI) and stavudine (d4T)) are capable of interfering with mitochondrial replication resulting in mitochondrial DNA depletion and dysfunction.⁽²⁷⁾ Clinical symptoms of mitochondrial toxicity in newborns associated with *in utero* NRTIs exposure including severe (rarely fatal) neurologic, muscular and cardiac disease, and hyperlactatemia were reported in large cohort of French children.^(28, 29) Observation of several other large prospective cohorts of perinatally NRTIs exposed children from the US and Europe did not find a similar association.^(30–32) A potential effect of genetic predisposition has been suggested to play a role in the etiology of mitochondrial toxicity following exposure to NRTIs *in utero*. Thorough evaluation for mitochondrial toxicity is recommended for any newborn and infant with unclear etiology of neurological, cardiac and systemic disorders.⁽⁶⁾

Animal teratogenic data and case reports of central nervous system abnormalities have raised concerns for using the first generation NNRTI efavirenz (EFV) during pregnancy (particularly during the first trimester).⁽³³⁾ While some recent data in humans have reported no increased risk of birth defects in children born with *in utero* EFV exposure, the drug remains to be classified as Food and Drug Administration (FDA) Pregnancy category D and the use of alternative regimens where possible is recommended.⁽⁶⁾ However, when potential

benefits are considered to outweigh potential risks, as in the case of the resource-limited settings without widespread access to the PIs, the use of the category D drugs (such as EFV) in pregnant women is considered permissible. In addition, the most recent version of the United States (US) perinatal treatment and prophylaxis guidelines recommend repeat (second trimester) ultrasound evaluation of fetal abnormality to women with a history of ART exposure (particularly to EFV) during the first trimester.⁽⁶⁾

In the US and Europe the most commonly used ART during pregnancy is comprised of 2 NRTIs in combination with a ritonavir (RTV)-boosted PI such as atazanavir (ATV) and LPV. A small increase in risk of prematurity has been reported in HIV-infected women on PI-based ART during pregnancy. However, the benefits of PMTCT and clinical usefulness of a PI-based ART (lack of hepatotoxicity and CD4+ cell count considerations associated with NVP) currently appear to outweigh the risks of prematurity. Among other considerations of PIs exposure, there is also a recent report from France linking *in utero* and postnatal LPV/RTV exposure to transient neonatal adrenal dysfunction.⁽³⁴⁾

The accumulation of data on the use in pregnancy of newer classes of ARV drugs such as entry and fusion inhibitors may make the pendulum swing toward the preferred choice of such agents as raltegravir (RAL) and maraviroc (MVC) for future considerations of ART in the prenatal period.

In order to collect human data on the potential risks of ART exposure in infants and their mothers, a collaborative epidemiological project (Antiretroviral Pregnancy Registry available at <http://www.APRegistry.com>) was created in collaboration with pharmaceutical manufactures with advisory committees of pediatricians and obstetricians. This anonymous, observational database is open for the reporting of any non-experimental adverse events of perinatal ARV exposure by health providers providing care to HIV-infected women and their children. Close long term follow up throughout all stages of growth and development is recommended for children with a history of *in utero* ART exposure.

NEONATAL ANTIRETROVIRAL PROPHYLAXIS AND THERAPY

Neonatal antiretroviral prophylaxis

In addition to complete elimination of breastfeeding, six weeks of neonatal AZT prophylaxis started immediately (within 6–12 hrs) postpartum is recommended for PMTCT by the perinatal ART guidelines in the US.⁽⁶⁾ The ability of AZT to induce transient macrocytic anemia, which can become clinically significant, particularly in premature infant, has raised concerns for the length of the AZT exposure. As a result of these considerations following comparative pediatric studies, a 4-week postpartum neonatal AZT prophylaxis with complete elimination of breastfeeding is now recommended for infants with a history of adequate prenatal and intrapartum ART in Europe and the United Kingdom.^(35, 36)

As with maternal prophylaxis of MTCT, the use of combination postpartum ART is considered to be more efficient in PMTCT than monotherapy, particularly in high risk scenarios such as lack or inconsistent use of prenatal and/or intrapartum ART, unsuppressed maternal viral load at delivery, and a history of maternal HIV resistance. While in practice the use of different combinations of ARV drugs in newborns postpartum is widely used for the described scenarios, very few studies have prospectively evaluated the use of combination ART in neonates. Most of the studies published to date evaluated the following combinations of ARV drugs in newborns^(6, 26):

- AZT plus 3TC
- AZT plus NVP

- AZT plus 3TC plus NVP
- AZT plus 3TC plus NFV

Recent data from a large international trial has shown higher rates of neutropenia and anemia associated with dual (AZT plus 3TC) and triple (AZT plus 3TC plus NFV) ART when compared to AZT monotherapy.⁽³⁷⁾ In addition, high variability of NFV exposure with potential for subtherapeutic exposure in newborns has been reported.^(37, 38) As a result of this study, NFV and 3TC are no longer recommended in the neonatal period in the US, and a dual ART prophylaxis with an addition of three doses of NVP (birth-48 hrs, 48 hrs, 96 hrs postpartum) in the first week of life has been recommended to be considered in cases of a high risk for MTCT.⁽⁶⁾ Monotherapy with NVP remains an equitable alternative to AZT neonatal prophylaxis in WHO guidelines.⁽⁸⁾

As described above, postnatal ARV prophylaxis is discontinued after 4–6 weeks in exclusively formula fed children. Breastfed infants, who represent the majority of newborn children in HIV epidemic areas in the world, remain at risk for MTCT for the duration of the breastfeeding. Due to multiple economical and logistical obstacles, most importantly the lack of clean water and high infant morbidity and mortality associated with formula feeding, complete elimination of breastfeeding and substitution with exclusive formula feeding has not proven to be a safe or feasible alternative in resource-limited settings.^(8, 26) With continued breastfeeding, the ongoing need for PMTCT generates consideration for ART in breastfeeding women and/or their nursing infants.

For resource-limited settings WHO recommends daily NVP in infants from birth until 1 week after cessation of all breastfeeding as option A.⁽²⁶⁾ Under the same option, 4–6 weeks of daily NVP is recommended for infants without breastfeeding or those breastfed by women on ART.⁽⁸⁾ As option B (including B+), daily AZT or NVP therapy for 4–6 weeks is recommended for neonates independent of infant feeding (breastfed or formula fed), while triple maternal ART is recommended until 1 week after cessation of all breastfeeding.⁽⁸⁾ Due to the availability and cost considerations, ART regimen with 2 NRTIs (ZDV, 3TC, TDF) in combination with one NNRTI (EFV, NVP) or co-formulated boosted PI (LPV/RTV) are most frequently considered for maternal ART during breastfeeding.⁽⁸⁾

During breastfeeding maternal ART continues playing a dual role of treating maternal HIV disease and preventing MTCT. The goal of treatment is to maximally suppress the maternal HIV viral load and to significantly diminish the risk of the viral passage through the breast milk. ARV drugs ingested by the infant during breastfeeding may equally provide some protection against HIV acquisition. Due to low breast milk/plasma ratio and rapid renal elimination, breastfed infants exposed to maternal AZT do not have detectable plasma AZT concentrations. NRTIs (3TC, TDF), NNRTIs (NVP, EFV) and PIs (NFV, indinavir (IDV)), however, have all been detected in breast milk at different ratios with maternal plasma concentrations of lactating women on ART.^(39–43) With low penetration of some of these ARV drugs into the breast milk (TDF, EFV, NFV) subtherapeutic infant plasma ARV concentrations may generate the development of viral resistance in HIV-infected infants.⁽⁴²⁾

Pharmacokinetics of antiretroviral drugs in infants

Compared to older children, neonates and young infants had delayed absorption, reduced liver metabolism and renal elimination of drugs.^(44–48) Rapid changes in renal function occur in the first days of life, making the dosing of ARV in neonates a challenging task. Despite wide use of ART in non-infected and HIV-infected neonates, the PK data on neonatal ARV exposure and the dosing guidelines are limited to the handful of ARV drug used for PMTCT: AZT, ddI, d4T and 3TC for NRTIs, NVP for NNRTIs, and NFV and

LPV/RTV for PIs. (Table 1) For premature infants AZT is the only drug with available PK and dosing data.⁽⁴⁹⁾

The immaturity of the glucuronide conjugation and glomerular filtration in the early neonatal period affects elimination and clearance of NRTIs. Elimination of orally administered AZT in infants increases rapidly during the first days of life and reaches adult levels by 4–8 weeks of life.^(50, 51) The clearance of AZT is even more decreased in premature infants requiring a significant increase in dosing interval to avoid potentially toxic exposure.^(49, 52, 53) Similar to AZT, 3TC clearance is prolonged immediately after birth requiring 50% dose reduction in younger (<1 month) infants and for ddI the recommended dose in newborns is 50 mg/m²/dose, compared to 90–150 mg/m²/dose in older infants and children.^(4, 54–56) Similar dose reduction is required for d4T with 50% of a pediatric dose in the first 13 days of life compared to the full pediatric dosing starting at 14 days postpartum.⁽⁵⁷⁾

Among all ARV drugs used in neonatal period, NVP has the longest elimination half life ($t_{1/2}$).⁽²¹⁾ Following administration of a sdNVP to infants at 48–72 hrs after birth, median $t_{1/2}$ is 43.6 hours (range: 23.6 hours – 81.6 hours). Since NVP is a substrate and inducer of hepatic metabolism by enzymes of the CYP450 family (primarily CYP3A4 and CYP2B6), chronic (not single dose) maternal NVP use prior to delivery may produce *in utero* induction of NVP metabolism and accelerate NVP elimination in the infant after birth.⁽⁵⁸⁾ Additional NVP doses postpartum (48 and 96 hrs) should allow, however, to maintain adequate NVP concentrations in infants born to mothers with chronic NVP therapy especially when used secondary to unsuppressed viral load and inconsistent use of NVP.⁽⁶⁾

Similar mechanism of the increased CYP450 metabolism in newborns might be responsible for the lower PIs exposure in neonatal period. While NFV is no longer recommended for the use in neonatal prophylaxis, its PK has been known to be significantly lower in neonatal period.⁽⁵⁹⁾ PK studies of LPV/RTV in neonates suggest that higher (300 mg/m²/dose) than pediatric dose (230 mg/m²/dose) is required in younger infants, and frequent dose adjustments are necessary to assure adequate LPV exposure throughout the first 12 months of life.⁽⁶⁰⁾ The liquid formulation of the LPV/RTV, however, contains high amounts of ethanol and propylene glycol, that may be potentially toxic to preterm and very young infants. Recent reports of the LPV associated neonatal cardiac (atrioventricular block, bradycardia, cardiomyopathy), metabolic (lactic acidosis), renal (renal failure), and central nervous system (CNS) (depression) toxicity have led to FDA and Department of Health and Human Services (DHHS) US guidelines limiting the use of LPV/RTV to the term (>42 weeks gestation) and older (postnatal age ≥ 14 days) neonates.^(6, 61)

TREATMENT OF HIV IN CHILDREN

Pediatric antiretroviral drugs

Development and maturation of organ systems involved in absorption, metabolism, and elimination of ARV drugs produce significant changes in the PK and pharmacodynamics (PD) of ART throughout childhood. Faster clearance of ARV drugs by children compared to adults requires significantly higher per weight or body surface area dosing of ARV drugs in younger children in order to achieve similar systemic ARV exposures.

In addition to the developmental changes in the PK of ARV drugs, multiple factors such as nutritional status and co-morbidities have the potential to influence the PK and PD of ART in children. In resource-limited settings significant anemia, decreased weight and delayed growth among HIV-infected children represent common challenges to ART.^(62–64) Concomitant illnesses, such as hepatitis, malabsorption and diarrhea, have the potential to

alter absorption of ARV drugs. Metabolic and endocrine abnormalities associated with malnutrition have the potential to influence the volume of distribution and the total body clearance of lipophilic ARV drugs such as PIs.⁽⁶⁵⁾ Moreover, therapeutic interventions for co-morbidities such as tuberculosis with significant potential for drug-drug interactions further complicate the choice of ART in children.

While an important success has been achieved in the development of the pediatric ART dosing guidelines, the data on the developmental changes in the ARV PK/PD are still limited in children. Therapeutic drug monitoring (TDM) of ARV drugs needs to be considered in pediatric patients with drug-drug interactions and ART failure, particularly in scenarios when adherence failure had not been established.⁽⁶⁶⁾ The use of the PK data in combination with viral resistance may provide grounds for a successful individualized dosing of ARV drugs in children and adolescents.⁽⁶⁷⁾

Currently out of 22 FDA-approved marketed ARV drugs for treating HIV-infected adults and adolescents, 19 drugs are approved for use in children and 16 are available in pediatric formulations.⁽⁶⁸⁾ (Table 1) In addition to the single drug ARV preparations, following a successful development and utilization of the fixed dose co-formulations (FDCs) of ARV drugs in adults, five 2-in-1 and four 3-in-1 pediatric FDCs have been developed and received quality certification by WHO and FDA.⁽⁶⁹⁾ (Table 2) A recent rise in the certification and pooled purchasing of high quality generic drugs produced in Brazil, India, South Africa and Thailand has increased the availability of pediatric ART in resource-limited settings.⁽⁶⁹⁾ Despite significant global progress in scaling up the access to the ART among children and adolescents in recent year, children continue to have limited access to antiretroviral therapy than adults, with only 23% of children (20–25%) receiving ART in 2010.^(10, 70)

Even with availability of the pediatric formulations of the ARV drugs, serious challenges to an efficient pediatric ART remain across the countries and continents. Among those are specific pediatric adherence barriers such as palatability and high dosing volumes of the liquid ARV formulations, pill swallowing capacity of the child, dispensability of the pediatric ARV preparations, bioavailability of the FDC ARV components, parental and child behavior modification skills, disclosure of HIV status, handling and delivery of pediatric ART to the caregivers, and, most importantly, caregiver's experience and capacity to administer ART to younger patients and to serve as a supplier of ART, encouragement and support for older children.^(71–82)

Current approach to pediatric antiretroviral therapy

Following the introduction of new ARV drugs in adults and accumulation of new data on the PK and PD of ARV drugs in children, the pediatric HIV treatment guidelines have significantly evolved throughout the years. The most recent WHO and US (DHHS) pediatric guidelines updates were released in the summers of 2010 and 2011, respectively.^(3, 4) European (Pediatric European Network for Treatment of AIDS (PENTA)) pediatric guidelines were updated in the fall of 2009 and had a letter with the statement position on the age of initiation of ART in children presented at the International AIDS conference in Vienna in summer of 2010 (available at: <http://www.pentatrials.org>).⁽⁸³⁾

Both US and European guidelines recommend universal treatment of all HIV-infected children <12 months of age.^(4, 83) The 2010 WHO pediatric guidelines have increased the age of universal initiation ART to 24 months with obligatory recommendation for infants <12 months and conditional recommendation for children >12 months and <24 months of age.⁽³⁾ The increase of the threshold for universal ART from 12 months to 24 months of age in WHO guidelines is based on the statistics of the higher infant and young children

mortality from HIV in resource-limited settings (particularly in sub-Saharan Africa) when compared to European and American cohorts of HIV-infected peers. Moreover, limited ability to monitor clinical, CD4+ cell counts and HIV viral load progression of the disease in resource-limited settings dictates the need for the ART coverage in the years when the pediatric mortality from HIV is the highest.⁽³⁾

The choice for the initiation of ART for asymptomatic children >12 (>24 months for WHO) months and <5 years of age is guided by the age appropriate CD4+ cell count percentage (US, WHO, Europe) and absolute CD4+ cell number (WHO, Europe) thresholds.^(3, 4, 83) While using similar percentage of CD4+ cell for the treatment initiation threshold in younger children (<36 months of age), European guidelines set lower CD4+ cell percentage and lower absolute CD4+ cell number in older children (>36 months<59 months of age) as a threshold for the initiation of ART in compared to the US and WHO guidelines for this age group.^(3, 4, 83) High viral load (HIV RNA PCR >100,000 copies/mL) is also used as a criterion for the initiation of the pediatric ART in children >12 months of age in the US and Europe, but is not included into the WHO guidelines due to limited access to the HIV PCR in resource-limited settings. In children older than 5 years of age lower CD4+ cell counts (350 cells/mm³ for WHO and <350 cells/mm³ for Europe) as compared to the US (500 cells/mm³) are used. Finally, the presence of the array of clinical co-morbidities, including opportunistic infections and acquired immune deficiency syndrome (AIDS) defining conditions, or the clinical stage of the HIV infection are used to guide the initiation of ART in symptomatic children in all three sets of pediatric guidelines.

All three (WHO, European, US) pediatric ART guidelines recommend the first line treatment of choice for HIV-infected children to be comprised of two NRTIs plus a third potent agent from a different class, either an NNRTI or a RTV-boosted PI.^(3, 4, 83) (Table 3) In European and US guidelines 3TC and abacavir (ABC) are the recommended NRTIs backbone of choice with pre-screening for HLA-B *5701 prior to the administration of ABC.⁽⁸³⁾ In the WHO guidelines the choice of NRTI backbone start with the combination of AZT plus 3TC, followed by 3TC plus ABC and 3TC plus d4T.⁽³⁾ (Table 3) Among NNRTIs, in all guidelines NVP is the preferred drug in children <3 years of age without previous exposure to NVP as part of maternal or neonatal PMTCT. After 3 years of age EFV becomes a preferred NNRTI in the US and Europe, while NVP and EFV remain as equitable choices in the WHO guidelines.^(3, 4, 83) Among boosted PI-based LPV/RTV is the first line choice in the US until the age of 6 years, when ATV/RTV becomes more preferable and LPV/RTV and other boosted PIs (darunavir (DRV) and fosamprenavir (FPV)) are considered as alternatives. LPV/RTV is also listed as preferred boosted PI in WHO guidelines for the infants born exposed to NVP as part of maternal or neonatal PMTCT. (Table 3)

The development of significant clinical morbidity, unsuppressed or rebound viral load, incomplete recovery or newly detected decline in CD4+ cell count can all serve as indicators of the first line ART failure. Thorough investigation of the ART practices including assessment of adherence, unidentified ARV drug toxicities, ARV drug-drug and drug-food interactions needs to take place prior to considering stopping or switching ART in children. Evaluation of HIV resistance is warranted in settings where it can be obtained. Moreover, administration of the second line ART usually requires switching some or all of the first line ARV drugs with an introduction of at least one new drug from a different class, and requires pediatric HIV expertise in combination with enhanced adherence support.

Adherence remains one of the most important factors in the success of ART in children. Incomparable to any other pediatric morbidity, this lifelong disease universally affects one or more family members of an infected child, making the large majority of the caregivers for

HIV-infected children patients themselves. Due to the high mortality of HIV and AIDS in resource-limited settings, many perinatally infected children become orphans and are placed in remote family or institutional settings. The ability of the caregiver and the child to maintain an adequate level of adherence needs to be addressed prior to initiating and throughout continuation of ART in HIV-infected pediatric patients.

TREATMENT OF HIV IN ADOLESCENTS

Antiretroviral therapy in adolescents

HIV-infected adolescents represent a heterogeneous group of pubertal children and young adults with vertically and horizontally transmitted HIV infection and diverse demographic and socio-economic status, sexual and substance abuse history, and different stages of psychosocial development.⁽⁸⁴⁾ With growing access to pediatric ART an increasing number of children with perinatally acquired HIV infection are surviving into adolescence. These children are usually highly treatment experienced and might be on their second and third line regimen by the time they enter puberty. In addition, per WHO statistics, out of 6000 estimated new HIV infections/day among adults and adolescents >15 years of age, 42% affected youth between the ages 15 and 24 years old in 2010.⁽⁸⁵⁾

Currently, the choice of ART during puberty is represented in both pediatric and adolescent guidelines. The choice of ARV drugs dosing is usually based on the sexual maturation stages (Tanner stages I through V reflecting transition from a child to an adult body). Such an approach presumes that national and ethnic standards for sexual maturation are identical to Tanner stages developed in Europe and that the local providers are familiar with them. For children in Tanner Stages I through III, the WHO pediatric guidelines recommended using pediatric weight band dosing of ARV drugs, whereas for adolescents in Tanner Stages IV and V adult dosing guidelines are used.⁽³⁾ In the US, pediatric dosing of ARV drugs is reserved for children in Tanner stages I and II and adult dosing is automatically applied for the youth in Tanner stage V, while ARV dosing in Tanner stages II and IV is left to provider discretion.⁽⁴⁾ Continued use of higher (weight- or surface-based) pediatric doses during adolescence can result in increased and potentially toxic drug exposure, while early introduction of lower adult doses can lead to suboptimal therapeutic exposure and development of drug resistance and subsequent virologic failure.⁽⁸⁴⁾

Puberty produces a remarkable increase in growth velocity and changes in body composition which vary between genders with a significant increase in lean body mass in boys and accumulation of fat in girls.^(86, 87) Girls are generally a year or two more advanced in pubertal maturation than boys, and the African-American race has been associated with an earlier age at onset of menarche.^(87, 88) Very limited information on the potential differences in the PK and PD of ARV drugs in adolescents is available to date with some suggesting potentially higher dose requirement for certain ARV drugs during puberty.⁽⁸⁹⁾ None of the available adolescent studies have investigated the effects of pubertal changes on the metabolism and disposition of ARV drugs, and the information on failure of ART therapy in adolescents is limited.

Compared to younger children, adolescents are more frequently exposed to antidepressants, hormonal contraceptives, anabolic steroids, alcohol and illicit drugs. A limited number of studies is available to date on the effect of psychotropic drugs, and substance abuse on drug disposition and effect of ART in adolescence.⁽⁸⁴⁾ The potential drug interaction between PIs and NNRTIs with oral contraceptives has been reported in adults and need to be addressed when prescribing ART to young female patients.^(4, 5)

As adolescents with perinatally acquired HIV infection approach adulthood, the attention to long term consequences of ART exposure is renewed. While significant knowledge has been accumulated concerning the metabolic and cardiovascular complications of ART in adults in recent years,^(90, 91) the data on the prevalence of pediatric ART associated metabolic complications is just starting to emerge. The significance of childhood ART associated lipodystrophy, dyslipidemia, insulin resistance, hyperlactatemia, renal insufficiency and osteopenia in the development of the cardiovascular, renal and bone disease of adulthood is not known and the management of these complications during childhood is under investigation.⁽⁹²⁾ To date, very few studies have evaluated the impact of ARV drug exposure on the development of those complications.^(93–96) A recent report of high rates of coronary artery abnormalities on cardiac magnetic resonance imaging (MRI) in adolescents and young adults with a long standing history of HIV exposure suggested possible early atherosclerosis in this population.⁽⁹⁷⁾ Although not associated with coronary artery disease in adults, coronary irregularities were seen in youth with increased cumulative exposure to tenofovir disoproxil fumarate (TDF) and 3TC.⁽⁹⁷⁾ Based on the potential risks of long-term associated ART toxicity and delayed onset in their clinical presentations, accumulation of new data and development of the biomarkers to facilitate early identification of children at high risk for ARV associated toxicities are urgently needed.

Adherence in adolescents

In addition to the described pediatric adherence barriers, HIV-infected adolescents face many new obstacles related to the psychological and social changes during the transition from childhood to adulthood. Among most important adolescent adherence challenges in perinatally infected youth are the following:

- growing independence
- change in schedules and lifestyle
- increased amount of time away from home
- rebellion against parental involvement
- increased risk-taking behavior
- increased peer pressure
- previous history of poor adherence
- delay in disclosure of HIV status
- premature transition of ART responsibility to an adolescent

For the newly infected youth, denial and fear of HIV infection, lack of disclosure with the family, partners and peers, lack of support system and confidentiality issues are among most challenging to address. Common for both groups are psychiatric problems (depression) and alcohol and substance abuse.^(98, 99) Finally, the issues of reproductive health and potential for family planning become important considerations and need to be addressed.

A comprehensive assessment of adherence should be incorporated into the design and maintenance strategy of the ART regimen of every adolescent patient with HIV infection.⁽¹⁰⁰⁾ Multiple interventions to improve long term adherence in adolescents have been proposed, but little evidence-based data are available to date. A once daily ART regimen is frequently a preferred choice by adolescents and their caregivers, particularly those who are involved in supervision of the ARV dose intake, and should be considered when possible.^(4, 101) Among the currently applied methods to improve adherence to ART of adolescents with HIV are^(102–104):

- reminder systems (calendars, medical diaries, text messaging and reminders via cell phones, beepers and alarm systems)
- pill boxes
- directly observed therapy

Most important is the involvement of a multidisciplinary team of providers involving medical doctors, nurses, pharmacists, behavioral and mental health specialist and other support systems such as peer groups and involvement of the partners. Efforts to support, evaluate and maximize adherence should begin prior to the start of ART and should continue throughout the transition of the youth to adult care.

An adolescent patient who has been treated in the settings of a family-centered pediatric/ adolescent HIV clinic is frequently unprepared to face the busy adult individual-centered care. Transition of the perinatally infected adolescent with HIV to the adult care is complicated by the high rates of the viral resistance following 10–15 years course of ARV drug exposure. Currently, the most treatment-experienced adolescents and young adults are residing in the areas of North America and Europe with guaranteed access to ARV drugs.⁽¹⁰⁵⁾ In a European cohort of 654 perinatally infected youth, 52% and 12% of the 166 patients have been reported to have dual- or triple class resistance mutations, respectively.⁽¹⁰⁶⁾ The ongoing increase in ART coverage of the pediatric population in resource-limited settings has certainly the potential to generate significant number of treatment-experienced adolescents and to lead to the global rise in ARV drug resistance among perinatally infected youth.

Multiple issues such as insurance coverage, access to ARV drugs, different expectations from the patient and different adult-oriented support systems are all unfamiliar and can be intimidating after having a long-standing family style relationship with a pediatric provider.⁽¹⁰⁷⁾ Communication between programs and medical providers, and establishment of a transition process within the participation of multidisciplinary team of social workers, mental health providers, and nurses is crucial in assuring uninterrupted ART for the many years ahead.

CONCLUSION

Over the last decades great successes have been achieved in the prevention, diagnosis and therapy of pediatric HIV disease. While not providing a cure, modern ART is capable to significantly reduce the MTCT allowing international community to generate an ambitious goal of creating an HIV-free generation. Close international collaboration involving multiple resources and continuous advocacy efforts are necessary to make this goal a reality within the next decade.

ART has also significantly decreased morbidity and mortality and provided high quality survival to children and adolescents with HIV-infection. Significant efforts have been devoted to the development, approval and increased access to pediatric ARV drugs. Despite an obvious success of PMTCT and pediatric ARV therapy, millions of children remain affected by the disease worldwide. HIV-infected children and their caregivers are faced with the difficult challenge of preserving long term adherence to ART, avoiding ARV drug resistance and ARV associated toxicities throughout the different stages of child's growth and development. Multiple factors including age-specific adherence barriers, changes in social and economical surroundings, and psychological and sexual maturation affect the choices of ART in infants, children and adolescents. Maintaining flexibility and focus on the therapeutic goals for this highly dynamic antiretroviral treatment process is the key to success in improving the outcome of pediatric HIV disease worldwide.

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KEY POINTS

- HIV infection represents one of the most serious pediatric morbidities in the world with an estimated 3.4 million children infected with HIV globally.
- Important etiological, physiological, psychological and social differences between children and adults create unique consideration for antiretroviral therapy in pediatric patients.
- Antiretroviral therapy significantly decreases HIV-associated morbidity and mortality, assures normal growth and development, and improves survival and quality of life in children and adolescents.
- Limited data on the long-term effects of antiretroviral drugs exposure *in utero*, infancy and throughout childhood warrants further investigation.
- With only 23% of HIV-infected children currently with access to antiretroviral therapy, development and delivery of pediatric antiretroviral formulations needs to continue.

Table 1

Available pediatric dosing and formulations of antiretroviral drugs.

Drug (abbreviation)	FDA licensed in children	Age restriction	Formulations available	Dosing regimen in children and adolescents <18 years old
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)				
Zidovudine (AZT, ZDV)	Yes	No	Tablets: 60 mg, 300 mg Capsules: 100 mg, 250 mg Liquid: 10 mg/ml	Twice daily
Stavudine (d4T)	Yes	No	Capsules: 15 mg, 20 mg, 30 mg Liquid: 1 mg/ml	Twice daily
Abacavir (ABC)	Yes	3 months	Tablets: 60 mg, 300 mg Liquid: 20 mg/ml	Twice daily *
Lamivudine (3TC)	Yes	No	Tablet: 150 mg Liquid: 10 mg/ml	Twice daily *
Didanosine (ddI)	Yes	2 weeks	Chewable tablets: 25 mg, 50 mg, 100 mg, 200 mg Capsules (delayed release): 125 mg, 200 mg, 250 mg, 400 mg Liquid: 10 mg/ml	Twice daily Once daily delayed-release capsules with weight ≥20 kg
Emcitritabine (FTC)	Yes	No **	Capsule: 200 mg Liquid: 10 mg/ml	Twice daily *
Tenofovir Disoproxil Fumarate (TDF)	Yes	2 years	Tablets: 150 mg, 200 mg, 250 mg, 300 mg Powder: 40 mg/gm	Once daily
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)				
Efavirenz (EFV)	Yes	3 years ****	Tablets: 200 mg, 600 mg Capsules: 50 mg, 100 mg, 200 mg Liquid: 30 mg/ml	Once daily
Nevirapine (NVP)	Yes	>2 weeks old	Tablets: 50 mg, 100 mg, 200mg Liquid: 10 mg/ml	Twice daily 400 mg extended release (XR) NVP currently not approved in children
Etravirine (ETV)	Yes	6 years and 16 kg	Tablets: 25 mg, 100 mg	Twice daily
Protease Inhibitors (PIs)				
Atazanavir (ATV)	Yes	6 years ****	Capsules: 100 mg, 150 mg, 200 mg, 300 mg	Once daily RTV boosting preferred *****
Darunavir (DRV)	Yes	3 years and 10 kg	Tablets: 75 mg, 150 mg, 400 mg, 600 mg Liquid: 100 mg/ml	Twice daily Should be boosted with RTV Once daily dose can be used if therapy-naïve and >12 years
Fosamprenavir (FPV)	Yes	2 years if therapy-naïve and 6 years if therapy-experienced	Tablet: 700 mg Liquid: 50 mg/ml	Twice daily Should be boosted with RTV if therapy-experienced and may be boosted with RTV if therapy-naïve *****
Indinavir (IDV)	No	N/A	Capsules: 100 mg, 200 mg, 400 mg	N/A
Nelfinavir (NFV)	Yes	2 years	Tablets: 250 mg, 625 mg	Twice daily

Drug (abbreviation)	FDA licensed in children	Age restriction	Formulations available	Dosing regimen in children and adolescents <18 years old
			Oral powder: 50 mg/gm (50 mg/scoop)	
Lopinavir/ritonavir (LPV/r)	Yes	>42 weeks gestation and >14 days old	Co-formulated tablets with RTV: 100 mg LPV+25 mg RTV 200 mg LPV+50 mg RTV Co-formulated capsule with RTV: 133 mg LPV+33 mg RTV Liquid: 80 mg LPV/ml + 20 mg RTV/ml	Twice daily
Ritonavir (RTV)	Yes	No	Co-formulated with LPV (see lopinavir) Tablet: 100 mg Liquid: 80 mg/ml	Used to boost other PIs
Saquinavir (SQV)	No	N/A	Tablets: 500 mg Hard gel capsule: 200 mg	N/A
Tipranavir (TPV)	Yes	2 years	Capsule: 250 mg Liquid: 100 mg/ml	Twice daily Should be boosted with RTV
Fusion and Entry Inhibitors				
Raltegravir (RAL)	Yes	2 years and 10 kg	Chewable tablet: 25 mg Tablet: 400 mg	Twice daily
Maraviroc (MVC)	No	NA	Tablets: 150 mg, 300 mg	N/A
Enfuvirtide (ENF)	Yes	6 years	Lyophilized powder for subcutaneous injection: 108 mg/vial (90 mg/ml when reconstituted with water)	Twice daily

Information on the drug formulation, dosing and approval were obtained from FDA, DHHS and WHO pediatric guidelines.^(4, 26, 108)

* Once-daily dosing not approved, but PK data encouraging

** Limited PK data in children <3 months

*** Limited PK data for children <3 years of age or weighing <10 kg

**** Limited PK data available for children 3 months to 6 years old

***** Specifics on RTV boosting outlined in 2012 labeling revision (available at: <http://www.accessdata.fda.gov>)

Table 2

Selected FDA-approved fixed dose combinations (FDCs) of antiretroviral drugs for children ^{*}.

Drugs (abbreviations)	FDCs available	Dosing frequency
2-in-1 FDCs		
Stavudine/lamivudine (d4T/3TC)	Pedi tabs: d4T 6 mg + 3TC 30 mg d4T12 mg + 3TC 60 mg Adult tabs: d4T 30 mg + 3TC 150 mg	Twice daily
Zidovudine/lamivudine (3TC/AZT)	Pedi tabs: AZT 60 mg + 3TC 30 mg Adult tabs: AZT 300 mg + 3TC 150 mg	Twice daily
Abacavir/lamivudine (ABC/3TC)	Pedi tabs: ABC 60 mg + 3TC 30 mg Adult tabs: ABC 600 mg + 3TC 300 mg	Twice daily
Tenofovir/emtricitabine (TDF/FTC)	Pedi tabs: N/A ^{**} Adult tabs: TDF 300 mg + FTC 200 mg	Once daily ^{**}
3-in-1 FDCs		
Zidovudine/lamivudine/nevirapine (AZT/3TC/NVP)	Pedi tabs: AZT 60 mg + 3TC 30 mg + NVP 50 mg Adult tabs: AZT 300 mg + 3TC 150 mg + NVP 200 mg	Twice daily
Stavudine/lamivudine/nevirapine (d4T/3TC/NVP)	Pedi tabs: d4T 6 mg + 3TC 30 mg + NVP 50 mg d4T12 mg + 3TC 60 mg + NVP 100 mg Adult tabs: d4T 30 mg + 3TC 150 mg + NVP 200 mg	Twice daily
Abacavir/zidovudine/lamivudine (ABC/AZT/3TC)	Pedi tabs: ABC 60 mg + AZT 60 mg + 3TC 30 mg Adult tabs: ABC 300 mg + AZT 300 mg + 3TC 150 mg	Twice daily

Information on the drug formulation, dosing and approval were obtained from FDA, DHHS and WHO pediatric guidelines. (4, 26, 108)

^{*} LPV is routinely co-formulated with RTV and is included in Table 1

^{**} TDF/FTC restricted for adolescents >12 years and >35 kg

Table 3Summary of current pediatric ART guidelines.^(3, 4, 83)

Recommended Initial ART regimens for infants and children^a		
Source/Year	First-Line Regimen	Alternative Regimen
International (WHO)^b 2010	< 24 months old 2 NRTIs ^d + NVP without ARV exposure ^c 2 NRTIs + LPV/RTV with ARV exposure ^c >24 months < 3 years 2 NRTIs + NVP 3 years 2 NRTIs + NNRTI (NVP or EFV)	(AZT or d4T) ^d + 3TC + ABC or if 3 months old (AZT or d4T) + FTC + ABC
European (PENTA)^b 2009	< 3 years old 2 NRTIs ^d + NVP 2 NRTIs + LPV/RTV > 3 years 2 NRTIs + EFV 2 NRTIs + LPV/RTV	< 3 years old^e 3 NRTIs + NVP 3 NRTIs + LPV/RTV > 40 kg 2 NRTIs + ATV/RTV 2 NRTIs + FPV/RTV 2 NRTIs + DRV/RTV 2 NRTIs + SQV/RTV
US (DHHS)^b 2011	< 3 years old 2 NRTIs ^d + LPV/RTV 3 years old 2 NRTIs + EFV 2 NRTIs + LPV/RTV 6 years old 2 NRTIs + ATV/RTV 2 NRTIs + EFV 2 NRTIs + LPV/RTV	Any age 2 NRTIs + NVP 6 years old 2 NRTIs + DRV/RTV 2 NRTIs + FPV/RTV

^aThis table serves as a summary of recommended ART in international guidelines. Please see complete guidance for specific information at related sources^(3, 4, 83)

^bWHO recommends universal treatment for all HIV-infected children <24 months. PENTA and DHHS guidelines recommend universal initiation of ART in all HIV-infected infants <12 months.

^cARV exposure in younger infants <12 months includes exposure to maternal PMTC (including sdNVP)

^dAZT and d4T are both thymidine analogues and cannot be co-administered

^eSome clinicians consider using 3 NRTIs (AZT+3TC+ABC) in combination with NVP

^dThe most preferred combination of NRTIs across all guidelines include:

- ABC plus 3TC or (FTC) (if 3 months old)
- AZT plus 3TC or (FTC) (if 3 months old)
- TDF (if 12 years and Tanner stage 3) plus 3TC or FTC
- 3TC plus d4T (alternative in the US and one of the preferred choices in WHO guidelines)