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Developments in early diagnosis and therapy of HIV infection in newborns

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1. Introduction

The use of antiretroviral drugs as prophylaxis in HIV-infected pregnant women has resulted in a dramatic decrease in the rate of HIV transmission to infants in high-income countries [1-3].

The identification of perinatal HIV exposure prior to pregnancy or as early in pregnancy as possible provides the best opportunity to prevent infant infection. However, despite the effectiveness of antiretroviral drugs in pregnancy, the global coverage of services to prevent mother-to-child HIV transmission (PMTCT) remains below 80\% [2] and the number of children newly infected with HIV reached 150,000 (110,000–190,000) in 2015 [4]. Even when services to PMTCT exist, residual infant HIV infections may occur among women with poor drug adherence, or in those who were HIV-uninfected at first antenatal visit and who subsequently acquired the infection during pregnancy or postpartum. Congenital and perinatal hematogenous transmission from mother to child may occur during pregnancy or during labor, or by breastmilk during breastfeeding. In most cases, transmission is thought to occur near or during delivery [2]. Perinatal transmission is a multifactorial process in which maternal viral load seems to be the strongest predictor of HIV transmission [5,6]. Therefore, achieving and maintaining virological suppression during pregnancy and at the time of delivery is paramount to PMTCT. Although most perinatal transmission events in pregnant women without antiretroviral therapy (ART) occur late in pregnancy or during delivery, it should be noted that mother-to-child transmission of HIV can occur during pregnancy (\textit{in utero}), and early control of viral replication may be important in preventing transmission. A recent report from the French Perinatal Cohort found that, in addition to maternal viral load at delivery, timing of ART initiation was independently associated with the risk of perinatal transmission [7]. The perinatal transmission rates were 0.2\%, 0.4\%, 0.9\%, and 2.2\%, for women starting ART before conception, in the first, second, or third trimesters, respectively. No cases of perinatal transmission were documented in infants born to women who started ART before conception and maintained viral suppression throughout pregnancy and at the time of delivery [7]. In treatment-naive pregnant women, ART should thus be initiated as soon as possible, with the goal of suppressing plasma viremia throughout pregnancy. Ensuring that women who started ART prior to pregnancy are virologically suppressed throughout pregnancy may be an important component to PMTCT often neglected due to issues around viral load testing, particularly in low-resource setting.

Combined ART has dramatically reduced morbidity and mortality in HIV-infected people, including HIV-infected children [8,9]. Since 2000, AIDS-related mortality among children under the age of five has fallen by approximately 60\% globally [2]. In high-income countries, mortality in
Infants and young children who acquire HIV have an exceptionally high risk of morbidity and mortality if they do not receive antiretroviral therapy. Identification of perinatal HIV exposure provides the best chance to prevent neonatal infection by using antiretroviral drugs as prophylaxis in pregnant women, and to early detect neonates who become infected. Accurate early infant diagnosis by nucleic acid amplification tests is crucial: virologic testing should ideally be performed as soon as possible, particularly in HIV-exposed infants at high risk of perinatal transmission. Prompt initiation of antiretroviral therapy in every child infected with HIV is now considered the standard of care. The potential benefits of very early treatment—close to birth—include the possibility of prolonged remission in infected neonates, require further investigation.

This box summarizes key points contained in the article.

### Article Highlights
- Infants and young children who acquire HIV have an exceptionally high risk of morbidity and mortality if they do not receive antiretroviral therapy.
- Identification of perinatal HIV exposure provides the best chance to prevent neonatal infection by using antiretroviral drugs as prophylaxis in pregnant women, and to early detect neonates who become infected.
- Accurate early infant diagnosis by nucleic acid amplification tests is crucial: virologic testing should ideally be performed as soon as possible, particularly in HIV-exposed infants at high risk of perinatal transmission.
- Prompt initiation of antiretroviral therapy in every child infected with HIV is now considered the standard of care.
- The potential benefits of very early treatment—close to birth—include the possibility of prolonged remission in infected neonates, require further investigation.

Children with perinatal HIV infection has decreased by more than 80–90% [8–10].

At the present time, prompt initiation of ART is recommended for all HIV-infected adults and adolescents, regardless of CD4 cell count, to reduce the morbidity and mortality associated with HIV infection, and to prevent HIV transmission [11]. Although available data on the risks and benefits of immediate therapy in asymptomatic HIV-infected children are weaker than in adults, ART is also recommended for all HIV-infected children [12,13]. Infants and young children who acquire HIV have an exceptionally high risk of morbidity and mortality and half will die before their second birthday if they do not receive a treatment [14]. A systematic review of randomized controlled trials that evaluated treatment strategies in perinatally HIV-infected infants and young children (aged < 3 years) concluded that ART initiation reduces morbidity and mortality [15]. However, prompt initiation of ART remains uncommon in infants, particularly in neonates [16–18]. Obstacles to use ART in neonates include the need for virologic testing for early diagnosis of HIV infection, and safety concerns by pediatricians arising from limited knowledge and experience regarding the use of antiretroviral drugs in this setting.

Over the last few years, there have been significant advances in HIV virologic testing that have improved accuracy and reduced performance time of laboratory-based assays for early diagnosis of HIV infection in neonates. In addition, the report of a prolonged remission in an HIV-infected child treated with combined ART at approximately 30 h of age [19] has generated discussion and enthusiasm about very early initiation of therapy in HIV-infected infants.

This article aims to review recent developments in early diagnosis and therapy of HIV infection in neonates and propose recommendations for managing HIV-infected infants. Data were obtained from literature searches from PubMed, abstracts from International AIDS Conferences, and authors' files, based on the pertinent key terms that identified the articles about diagnosis and therapy of HIV infection in newborns.

### 2. Identifying perinatal HIV-exposed infants to stop transmission

As stated earlier, identification of perinatal HIV exposure provides the best chance to prevent neonatal infection, by using antiretroviral drugs as prophylaxis in pregnant women, and to early detect neonates who become infected, allowing prompt initiation of ART. Health systems gaps in HIV diagnosis in pregnant women or late diagnosis testing in exposed infants will likely worsen the prognosis of HIV-infected infants [20].

Universal voluntary HIV testing early in pregnancy is now the standard of care in high-income and in many low- and middle-income countries. Pregnant women not tested for whatever reason earlier in pregnancy should be offered testing during the third trimester. Maternal HIV acquisition following initial negative test has been reported to occur in up to 46% of the newly infected infants [20]. Thus, a second HIV test during the third trimester should also be considered for all HIV-seronegative pregnant women, particularly for those known to be at high risk of acquiring HIV or reporting symptoms consistent with acute HIV infection [21]. In those cases, a fourth-generation combination immunoadsorbent assay should be used, as these combined antigen/antibody tests show a higher sensitivity for the detection of primary HIV infection than conventional tests [22]. Rapid HIV testing in labor or delivery should be performed in all women with undocumented HIV status. When HIV testing is positive, intrapartum and infant postnatal antiretroviral drug prophylaxis should be initiated, and additional virologic test be performed in the newborn.

Postnatal antiretroviral drug prophylaxis should be started in all HIV-exposed infants as soon as possible, preferably within 6–12 h of delivery [12]. According to the risk of perinatal transmission, infants exposed to HIV are considered at low risk of HIV acquisition when they are born to mothers who received ART during pregnancy with sustained viral suppression and no concerns related to maternal adherence. Infants considered at high risk of HIV acquisition are those born to HIV-infected women who have not received antepartum or intrapartum prophylaxis with antiretroviral drugs, received intrapartum antiretroviral drugs only, were diagnosed with acute HIV infection during pregnancy, have received prophylaxis but had detectable HIV viral loads near delivery, or did not have sustained viral suppression. A drug combination regimen during 6 weeks is recommended in infants at higher risk of HIV acquisition [12]. There is no clear consensus on the specific regimen to use in these infants. In the HPTN 040/PACTG 1043 study, a large clinical trial enrolling 1684 formula-fed neonates whose mothers did not receive ART during pregnancy, prophylaxis with two-drug ART regimen (zidovudine for 6 weeks plus three doses of nevirapine during the first 8 days of life), or three-drug ART regimen (zidovudine for 6 weeks plus nelfinavir and lamivudine for 2 weeks) was not superior to zidovudine alone for 6 weeks for the prevention of in utero HIV transmission, but intrapartum transmissions were reduced by half in the drug combination groups, as compared with the zidovudine-alone group; the two-drug regimen had less toxicity than the three-
drug regimen [6]. Although the ease of use, reduced toxicity, availability, and low cost make zidovudine plus nevirapine an attractive option, following the prolonged remission of HIV in an infant reported in 2013 [19], many clinicians prefer a three-drug regimen for prophylaxis in infants at high risk for perinatal infection [12]. A three-drug regimen may be particularly indicated in infants who could be at the highest risk of HIV acquisition, such as those born to mothers diagnosed with acute HIV infection during pregnancy or who had very high HIV viral loads near delivery. An ongoing clinical trial is investigating a three-drug prophylaxis regimen containing zidovudine, lamivudine, and nevirapine shortly after birth in infants at high risk of HIV infection (IMPAACT P1115, ClinicalTrials.gov identifier NCT02140255). Safety and pharmacokinetic (PK) data from this study will guide future recommendations. It is worth noting that the benefits of postnatal enhanced prophylaxis have only been formally proven in untreated mothers during pregnancy. For full-term infants with low risk of perinatal transmission, a 4-week zidovudine regimen is recommended [23,24]. For the prevention of in utero HIV transmission, nevirapine is an alternative to zidovudine monotherapy with potent antiretroviral effect but low barrier to resistance.

The World Health Organization (WHO) recommends that breastfeeding women with HIV receive ART throughout breastfeeding or lifelong [13]. Maternal ART dramatically reduces but does not eliminate breast milk transmission. Some studies of infants breastfed by women with chronic HIV infection have shown that extending postnatal antiretroviral prophylaxis can reduce the risk of infection [25–27].

3. Virologic testing in the management of perinatal HIV exposure

In order for HIV-infected neonates to receive ART as soon as possible, accurate early infant diagnosis of HIV is crucial. Antibody testing does not allow the diagnosis of HIV infection in infants and children younger than 18 months with perinatal HIV exposure due to transplacental transfer of maternal antibodies; therefore, a virologic assay that directly detects HIV should be performed [22] and it is strongly recommended by the WHO [28].

The preferred assays to detect HIV-1 directly are the nucleic acid amplification tests. These tests include RNA- and DNA-based polymerase chain reaction (PCR) assays and related RNA quantitative assays. RNA-based PCR assays detect extracellular HIV-1 RNA in plasma whereas DNA-based assays detect specific HIV-1 DNA in peripheral blood mononuclear cells. Although both techniques are considered to be highly specific, HIV-1 RNA levels <5000 copies/mL may not be reproducible and should be repeated before they are interpreted as documenting HIV infection in an infant [29–32]. The specificity of both HIV RNA-based (for results ≥5000 copies/mL) and DNA-based PCR assays has been shown to be 100% at birth and at 1, 3, and 6 months of age [29–32]. The effect of maternal or infant exposure to combination ART on the sensitivity of infant virologic diagnostic testing – particularly using HIV RNA assays – remains largely unknown. Some experts prefer to use HIV DNA PCR assays in this setting.

The main caveat of both HIV RNA and DNA assays is that testing at birth will detect infants who were infected in utero but not those who become infected from exposure during or immediately prior to delivery (i.e. in the intrapartum period) [30–33]. In a substudy of the French multicenter prospective cohort of neonates born to HIV-infected mothers, 1567 infants were tested simultaneously with HIV RNA and DNA assays. At birth, sensitivity was 58% for the RNA- and 55% for the DNA-based assays; and it was 89% at 1 month and 100% at 3 months for both assays. A high degree of concordance was found between HIV RNA and DNA assays [31]. Another study informing on accuracy of nucleic acid amplification tests for early diagnosis of HIV-infected infants at different time points was the NICHD HPTN 040/PACTG 1043 trial. In that trial evaluating different regimens of postpartum prophylaxis in neonates whose mothers did not receive ART during pregnancy, infant virologic testing was performed by HIV DNA PCR at birth, 10-14 days, 4-6 weeks, and 3 and 6 months [6]. The overall transmission rate in the trial was 8.5% (140 infants). Of the 140 infected infants, 93 (66.4%) were identified at birth. Of the 47 infected infants who had negative virologic testing at birth, 68% were identified at 4 to 6 weeks, and 100% by 3 months [6].

WHO recommends that infants exposed to HIV be tested with a nucleic acid amplification tests at the first postnatal visit or at the earliest opportunity, and that those who are infected start treatment immediately [13]. Virologic testing should ideally be performed at 14-21 days of life and at ages 1-2 months and 4-6 months. For settings where it is available, virologic testing at birth should be considered for HIV-exposed infants at high risk of perinatal transmission, especially in women who have not received antepartum or intrapartum prophylaxis, have not had good virologic control during pregnancy, or if adequate follow-up of the infant cannot be assured. A positive HIV virologic test should be confirmed as soon as possible with a second HIV virologic test on a different specimen. Although perinatal transmission of resistant virus appears to be unusual, if feasible, any newly diagnosed infant should undergo HIV drug-resistance testing.

WHO and its partners have also been examining the feasibility of testing at birth in low-resource settings, which may provide an adjunct to the earlier detection and treatment of infected infants worldwide [2,34]. According to the Joint United Nations Programme on HIV/Acquired Immune Deficiency Syndrome, of an estimated 1.2 million (1.1–1.3 million) HIV-exposed infants among the 21 priority countries in sub-Saharan Africa participating in the Global Plan toward the elimination of new HIV infections among children [35], only 49% received a virologic test to determine their HIV status within the first two months of life (compared to 40% in 2013) [2]. In many settings, access to virologic testing remains poor, leading to delayed infant diagnosis of HIV and high rates of children’s lost-to-follow-up, demonstrating the importance of improving availability and affordability of these tests if infants are to benefit from early ART [2].
Early infant diagnosis is particularly challenging in resource-limited settings and remote areas. Efforts to place infant testing capabilities in small health facilities and innovative point-of-care virologic tests are needed to allow for instituting early therapy in those settings.

4. Treating HIV infection in neonates

As stated earlier, prompt initiation of ART in every child infected with HIV should now be considered the standard of care [12,13]. The recommendation for early onset of treatment in HIV-infected children is justified by the rapid progression of HIV disease reported in younger children [14] and supported by data from cohort studies and clinical trials suggesting that earlier initiation of ART may reduce the risk of mortality and progression to AIDS [15,36–39] and improve neurodevelopment and motor development compared to late treatment [40].

4.1. Potential benefits of early ART in neonates

The benefit of immediate ART in children under 1 year of age was clearly demonstrated in the Children with HIV Early Antiretroviral Therapy (CHER) trial [41]. In this trial, HIV-infected infants 6–12 (median 7.4) weeks of age with a CD4 lymphocyte percentage of 25% or more were randomly assigned to receive ART (lopinavir-ritonavir, zidovudine, and lamivudine) when the CD4 percentage decreased to less than 20% or clinical criteria were met (the deferred ART group) or to immediate initiation of limited ART until 1 year of age or 2 years of age (the early ART groups). Early ART reduced infant mortality by 76% and HIV progression by 75% [41]. Of interest, a considerable number of children could not enroll in the main CHER trial (Part A) due to severity of illness or low CD4 that emphasizes the rapid progression of HIV infection and suggests that achieving virologic control very early in infancy can be associated with a low proviral reservoir size that may be maintained for over a decade on long-term effective ART. However, it should also be noted that the clinical benefits of reducing viral reservoir remain speculative and, to date, the only proven benefit of very early treatment is the reduction in early mortality and progression found in the CHER trial [41]. The benefit of a very early treatment for children with less severe illness not at risk of early mortality is less obvious. In addition, there are no good predictors of progression in young children. The so-called "Mississippi Child," who received ART between 30 h of life and 18 months of age and remained free of replicating HIV without treatment for more than 2 years, has generated hope on the potential long-term benefits of very early ART in perinataly infected infants [19].

4.2. Initiating ART in neonates

While there is considerable interest in moving treatment initiation closer to birth, there are challenges to start ART in early life, including a paucity of drug choices, uncertain dosing for some medications, concerns about toxicities, and adherence. In addition, the poor palatability of many of the existing formulations often leads the children to refuse taking them. Compared to older children, neonates and young infants have delayed absorption, reduced liver metabolism, and reduced renal elimination of drugs; therefore, it is important to obtain data on PK and safety of antiretroviral drugs in this particular population. Changing PK as a result of rapid growth and continuous development and maturation of the organs involved in drug metabolism, and in the activity of the isoforms of drug metabolizing enzymes, makes dosing even more complex. Although routine evaluation of plasma concentrations of antiretroviral drugs is not generally recommended for managing infants with HIV infection, targeted
therapeutic drug monitoring can be considered when using drugs with limited PK data and/or therapeutic experience, in cases of significant drug–drug and food–drug interactions, or when suspecting suboptimal absorption, distribution, metabolism, or elimination of the drug.

4.2.1. Antiretroviral drugs that can be used safely in neonates

Unfortunately, dosing and safety data to provide appropriate recommendations for the treatment of HIV infection in neonates have been generated only for a few antiretroviral drugs. Data on which to base a firm recommendation for treatment doses from birth in full term neonates exist only for four antiretroviral drugs: zidovudine, lamivudine, emtricitabine, and stavudine; in preterm infants, data are available only for zidovudine. From age 2 weeks in full-term neonates, there are data to allow recommendations for safe doses for another three antiretroviral drugs: didanosine, nevirapine, and lopinavir-ritonavir [12]. Two (stavudine and didanosine) of the seven antiretroviral drugs are rarely used in adults due to the high risk of mitochondrial toxicity. The use of other nucleoside reverse transcriptase inhibitors like abacavir or tenofovir is not recommended due to the lack of data in neonates. Even with the considered “safe medications,” close monitoring is needed when ART is initiated very early after birth. The experience with the use of lopinavir-ritonavir oral solution in infants highlights the risk of using antiretroviral drugs during the first weeks of life without neonatal PK and safety data. Life-threatening toxicity, including cardiovascular, renal, and central nervous system severe adverse events, has been reported in 10 infants (8 preterm) receiving lopinavir-ritonavir oral solution during the first weeks of life [47]. After this report, the use of lopinavir-ritonavir oral solution is only recommended in full-term neonates of 2 weeks or older [47].

Integrase strand transfer inhibitors have become a cornerstone of antiretroviral combination regimens in adults [11] and there is considerable interest in the use of these drugs in children and neonates, especially after the recent approval of an oral granule raltegravir formulation which is suitable for use in young infants. After preliminary data from a cohort of 15 infants receiving two single doses of raltegravir during the first week of life [48], PK results and 6-week safety data from 25 newborns (full-term infants aged ≤48 h of age; gestational age at birth at least 37 weeks & weight ≥2 kg) have been recently reported [49]. In this study, daily raltegravir given at the study-specified dosing regimen (as described in Table 1) was safe and well tolerated during the first 6 weeks of life, meeting the PK targets and the safety guidelines [49]. As raltegravir is primarily metabolized by the UGT1A1 enzyme, it may compete with bilirubin for elimination through glucuronidation. Indeed, in vitro data suggest that raltegravir plasma concentrations 50–100 times greater than typical peak concentrations (~5000 ng/mL) may lead to increased plasma concentrations of free unconjugated bilirubin, leading to an increase risk of bilirubin encephalopathy and kernicterus [52]. Therefore, caution should be taken in neonates with elevated bilirubin, particularly in preterm infants.

4.2.2. Summary of antiretroviral drugs recommended for initial therapy in neonates

4.2.2.1. Zidovudine. Therapeutic indication and usage: recommended for HIV treatment from the first day of life. Zidovudine is the only antiretroviral drug currently recommended for premature infants.

Pharmaceutical form: it is available in syrup form with concentration of 10 mg/ml [12].

Metabolism: zidovudine is metabolized in the liver to zidovudine glucuronide and then renally excreted. The enzymes responsible for glucuronidation increase dramatically during the first 4–6 weeks of life in full-term neonates, and hence dose adjustment after this age is required.

Dose: an initial dose of 4 mg/kg orally twice a day during the first 4 weeks of life is recommended in infants with at least 35 weeks of gestation, and this dose has to be increased to 12 mg/kg twice daily after the fourth week of life. In premature infants, the clearance of zidovudine is reduced, and adjustments should therefore be done [53]. In neonates with gestational age between 30 and 35 weeks, the initial recommended dose is 2 mg/kg twice a day, increasing to 3 mg/kg twice a day after 2 weeks of life and then to 12 mg/kg twice a day from 6 to 8 weeks of life. In case of premature infants born before the 30th week of gestation, an initial dose of 2 mg/kg twice a day is recommended for the first 4 weeks of age, increasing to 3 mg/kg twice a day from 4th to 8th or 10th week of life, and thereafter to 12 mg/kg twice a day [54].

For infants unable to tolerate oral agents, intravenous zidovudine, at a concentration of 10 mg/mL, may be used, although this formulation is not available in many settings. If the intravenous formulation is used, the dose of zidovudine should be reduced by 25%, maintaining the same dose interval [53].

Recommendations for administration: this drug can be given without regard to food, and it is recommended to be discontinued in case of substantial granulocytopenia or anemia due to its association with both hematologic side effects [12].

Adverse events are shown in Table 1. Treatment-limiting adverse events with zidovudine has been described in <10% of the children receiving this drug in Europa and Thailand [54].

4.2.2.2. Lamivudine. Therapeutic indication and usage: lamivudine is recommended for HIV treatment from the first day of life in full term infants.

Pharmaceutical form: it is available in oral solution in concentration of 10 mg/mL [11].

Metabolism: this drug is eliminated by renal excretion. It is recommended to double the starting dose after the fourth week of life for infants with normal maturation of renal function.

Dose: Studies made with oral solution of lamivudine set the recommended dose at 2 mg/kg twice a day for neonates, increasing to 4 mg/kg twice a day from the fourth week of life [55]. Bioavailability of oral solution is lower than tablets of lamivudine, and this is reflected in the differences in the response rate between...
Table 1. Antiretroviral drugs recommended for initial therapy in neonates.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Presentation for neonate</th>
<th>Dose</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>Syrup 10 mg/mL</td>
<td>≥35 weeks of gestational age</td>
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<td>Intravenous 10 mg/mL</td>
<td>Birth to age 4 weeks:</td>
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<td>- 4 mg/kg twice a day</td>
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<td>- Aged &gt;4 weeks:</td>
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<td>- 12mg/kg twice a day</td>
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<td>≥ 30 to &lt;35 weeks of gestational age</td>
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<td>- Birth: age 2 weeks:</td>
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<td>- 2 mg/kg twice a day</td>
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<td>- Aged 2 weeks to 6–8 weeks:</td>
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<td>- 3 mg/kg twice a day</td>
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<td>- Aged &gt;6–8 weeks:</td>
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<td>- 12 mg/kg twice a day</td>
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<td>&lt;30 weeks of gestational age:</td>
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<td>- Birth: age 4 weeks:</td>
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<td>- 2 mg/kg twice a day</td>
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<td>- Aged 4 weeks to 8–10 weeks:</td>
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<td>- 3 mg/kg twice a day</td>
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<td>- Aged &gt;8–10 weeks:</td>
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<td>- 12 mg/kg twice a day</td>
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<td>Lamivudine</td>
<td>Oral solution 10 mg/mL</td>
<td>Birth to age 4 weeks:</td>
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<td>- 2 mg/kg twice a day</td>
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<td>- Aged &gt;4 weeks:</td>
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<td>- 4 mg/kg twice a day</td>
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<td>Emtricitabine</td>
<td>Oral solution 10 mg/mL</td>
<td>Birth to age 3 months:</td>
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<td>- 3 mg/kg once a day</td>
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<td>Aged ≥3 months:</td>
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<td>- 6 mg/kg once a day (maximum dose 240 mg)</td>
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<td>Stavudine</td>
<td>Powder for oral solution:</td>
<td>Birth to age 13 days:</td>
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<td>1 mg/mL</td>
<td>- 0.5 mg/kg twice a day</td>
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<td>Aged ≥14 days:</td>
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<td>- 1 mg/kg twice a day</td>
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<td>Didanosine</td>
<td>Powder for oral solution:</td>
<td>Aged ≥ 2 weeks to &lt;3 months:</td>
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<td>10 mg/mL</td>
<td>- 50 mg/m² twice a day</td>
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<td>Aged ≥ 3 months to 8 months:</td>
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<td>- 100 mg/m² twice a day</td>
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<td>Nevirapine</td>
<td>Suspension 10 mg/mL</td>
<td>Aged &lt;14 days:</td>
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<td>- Term infant: 6 mg/kg twice a day: No lead-in</td>
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<td>- Preterm infant(**):</td>
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<td>- 1st week: 4 mg/kg twice a day:</td>
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<td>- Aged &gt;7 days:</td>
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<td>- 6 mg/kg twice a day</td>
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<td>Aged &gt;14 days (or &gt;14 days of adjusted gestational age) to 8 years:</td>
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<td>- Term infant: 200 mg/m² twice a day:</td>
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<td>Body weight &lt; 2 kg</td>
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<tr>
<td>Ritonavir</td>
<td>Oral solution:</td>
<td>Aged ≥ 14 days to 6 months:</td>
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<tr>
<td>boosted lopinavir (LPV/r)</td>
<td>80 mg LPV / 20 mg ritonavir /mL</td>
<td>- 300mg/m² LPV/75 mg/m² ritonavir twice a day</td>
<td>- Frequent: hyperlipidemia, headache, diabetes, nephrotic syndrome with potential for multisystem organ involvement and shock</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1–2 Kg: 40 mg every 12 h</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>2–6 Kg: 80 mg every 12 h</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>6–10 Kg: 120 mg every 12 h</td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Granules: 100 mg</td>
<td>Birth – age 7 days(**):</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 1.5 mg/kg once a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aged 8 –28 days(**):</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- 3 mg/kg twice a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aged ≥ 4 weeks(**):</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 6 mg/kg twice a day</td>
<td></td>
</tr>
</tbody>
</table>

* 34–37 weeks of gestational age.
**Investigational dose, not FDA-approved.

pediatric patients treated with oral solution compared with pediatric patients treated with tablets at the same dose. There are no identified causes to justify this, and further research is needed [56].

Recommendations for administration: lamivudine oral solution can be given without regard to food and can be kept at room temperature.

Adverse events are shown in Table 1.

4.2.2.3. Emtricitabine. Therapeutic indication and usage: as well as lamivudine, emtricitabine is recommended for HIV treatment in full-term neonates since birth.

Pharmaceutical form: it is available in oral solution at concentration of 10 mg/mL [12].

Metabolism: emtricitabine is excreted 86% through urine [57].
**Dose:** recommended dose is 3 mg/kg once a day for the first three months of life, increasing to 6 mg/kg once a day from then on, to a maximum dose of 240 mg per day until the child’s weight is over 33 Kg. It is recommended to escalate the dose after the third month of life because of the increasing clearance of the drug with increasing age.

**Recommendations for administration:** oral solution can be given regardless of food intake and it can be kept at room temperature if used within 3 months after opening [12]. Adverse events are shown in Table 1.

4.2.2.4. Stavudine. **Therapeutic indication and usage:** stavudine is no longer a drug of choice and its use is limited in adults and children because of the risk of serious adverse events associated with mitochondrial toxicity. It could exceptionally be considered in selected cases of full-term neonates from the first day of life, and only for a short period of time.

**Pharmaceutical form:** it is available for neonates in powder for oral solution to get a concentration of 1 mg/mL.

**Metabolism:** This drug is eliminated by renal excretion to about 50%, so it is recommended to reduce the dose in case of renal dysfunction.

**Dose:** in the first two weeks of life, the recommended dose is 0.5 mg/kg twice a day, and it must be increased to 1 mg/kg twice a day from the 14th day of life [58].

**Recommendations for administration:** this solution must be shaken before use and kept refrigerated [12]. Adverse events are shown in Table 1. The combination of stavudine with didanosine should never be used due to a higher risk of hepatotoxicity, pancreatitis, or lactic acidosis [59]. Combination of antiretroviral drugs with stavudine showed higher risk of clinical and analytical toxicity than combinations with zidovudine [60].

4.2.2.5. Didanosine. **Therapeutic indication and usage:** didanosine is no longer a drug of choice and its use is limited in adults and children because of the risk of serious adverse events associated with mitochondrial toxicity. It could exceptionally be considered in selected cases of neonates from two weeks of life and only for a short period of time.

**Pharmaceutical form:** it is available in powder for oral solution, at concentration of 10 mg/mL when reconstituted [12]. This solution contains antacids that may interfere with the absorption of other drugs.

**Metabolism:** like other antiretroviral drugs, didanosine is partially excreted through the kidneys, and that justifies increasing the dose according to maturation of renal function.

**Dose:** from 2 weeks of life to 3 months of age, the recommended dose is 50 mg/m² twice a day, and from 3 months, dose should be doubled to 100 mg/m².

**Recommendations for administration:** didanosine absorption is decreased when given with food, and that is why it is recommended to be given 30 min before or 2 h after a meal. In neonates, it is impractical due to the need of frequent oral intake. The effect of food on didanosine was studied in adults, showing that the administration of food did not interfere with the antiviral activity of didanosine [61]. Adverse events are shown in Table 1.

4.2.2.6. Nevirapine. **Therapeutic indication and usage:** nevirapine is approved by the Food and Drug Administration (FDA) of US for HIV treatment in full-term neonates aged >1 month.

**Pharmaceutical form:** nevirapine is available in suspension at concentration of 10 mg/ml.

**Metabolism:** nevirapine is metabolized by cytochrome P450 and 80% excreted in urine. Prematurity is associated with immature drug metabolism and nevirapine safety; efficacy and PK data in preterm and low-birth weight infants are limited. Nevirapine auto-induces its metabolism and it is traditionally initiated at a lower dose and increased after 2 weeks to allow induction of cytochrome P450 metabolizing enzymes. This stepwise fashion results in increased drug clearance and it is believed that it may reduce drug toxicity, but has the potential for under-dosing with an increased risk of resistance. The extent of autoinduction on immature enzyme systems is unknown, and preliminary data suggest that full-dose nevirapine at ART initiation should be considered in infants and younger children [62–65]. No dose adjustment is required in renal insufficiency. When given with ritonavir-boosted lopinavir, higher dose of lopinavir may be needed because of the increase of lopinavir metabolism caused by nevirapine.

**Dose:** based on PK modeling for full-term newborns diagnosed as infected in the first few days of life, a nevirapine investigational (not FDA-approved) dose of 6 mg/kg administered twice daily (without lead-in dose) is recommended for full-term newborns [66]. For late preterm newborns between 34 and 37 weeks of gestational age, the traditional stepwise fashion of administering the drug is still recommended with an initial dose if 4 mg/kg twice a day for the first week of life, followed by an increase to 6 mg/kg twice day after the first week, which have shown to get an adequate therapeutic plasma concentration of nevirapine (3 µg/mL) [62]. For infants <2 kg, the Health Organization guidelines recommend nevirapine 2 mg/kg/day, but in a recent study carried out in low-birth-weight infants, doubling the dose to 4 mg/kg/day at 2 weeks achieved adequate plasma concentrations without significant toxicity [67]. Single nevirapine dose of 2 mg/kg within 72 h of birth to prevent mother-to-child transmission is no longer recommended due to the potential risk for resistance with single-dose nevirapine.

**Recommendations for administration:** this suspension must be shaken before use and can be given without regard to food [12]. Adverse events are shown in Table 1. Skin rash has been observed in between 7.5% and 20% of the children receiving nevirapine as part of first-line antiretroviral regimen; it can occasionally be severe, needing hospitalization [68]. Hepatic toxicity, including fatal hepatic necrosis, or severe hypersensitivity syndrome with potential for multisystem organ involvement and shock, are less common. Severe nevirapine-related toxicity, according to the criteria of the Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases [69] when given as treatment, occurred in 6.8% of the children [70]. In the HPTN 046, a randomized, double-blind, placebo-controlled trial, comparing three different regimens with once-daily infant nevirapine for prevention of postnatal HIV transmission, 16% of the children had a serious adverse events [71].
Most cases of nevirapine-associated toxicity occur during the first 6–12 weeks of therapy; frequent clinical and laboratory monitoring, including liver function tests, is important during this period.

4.2.2.7. Lopinavir/ritonavir. Therapeutic indication and usage: lopinavir/ritonavir is indicated to treat HIV infection in full-term neonates aged 2 weeks or older. Lopinavir/ritonavir has demonstrated being superior to nevirapine, reducing mortality and achieving higher degree of virological suppression [70,72].

Pharmaceutical form: lopinavir/ritonavir oral solution is available at concentration of 80 mg of lopinavir and 20 mg of ritonavir per milliliter. Oral solution contains 42% of alcohol and 15% of propylene glycol [12].

Metabolism: lopinavir/ritonavir is primarily metabolized by the liver and it is a cytochrome P 3A4 inhibitor and substrate. Newborn immature hepatic metabolism and renal excretion can lead to an accumulation of lopinavir, ritonavir, and propylene glycol. Adverse events, including cardiac, renal, metabolic, or respiratory problems, have been described in neonates receiving lopinavir and have been related to accumulation of the drug or the inactive ingredients. Adrenal dysfunction was also observed in newborns treated with lopinavir/ritonavir, but life-threatening symptoms compatible with adrenal insufficiency were only present in premature infants [73].

Dose: dose recommended for infants from 14 days to 6 months of age is 300 mg/m² of lopinavir and 75 mg/m² of ritonavir twice a day, this approximates 16 mg of lopinavir and 4 mg of ritonavir per kg body weight twice daily. Lopinavir/ritonavir population PK in 96 neonates and infants from birth to less than 2 years (1.16–10.4 kg) showed that clearance and distribution volume were dependent on body weight on an allometric basis and post-menstrual age [70]. According to this model, optimal dosing regimens would be 40 mg every 12 h for children from 1 to 2 kg, 80 mg every 12 h for children from 2 to 6 kg, and 120 mg every 12 h to children from 6 to 10 kg [74].

Recommendations for administration: lopinavir/ritonavir should be taken with food. The poor palatability of oral solution lopinavir/ritonavir is a problem, and it is difficult to mask. Future studies with pellets of lopinavir/ritonavir might increase adherence in infants younger than 12 months [75].

Adverse events are shown in Table 1.

4.2.2.8. Raltegravir. Therapeutic indication and usage: raltegravir is at present not approved for neonates [12]. Recent data from IMPAACT P1110 study support that raltegravir could be an alternative to lopinavir/ritonavir or nevirapine for full-term neonates providing elevated bilirubin requiring phototherapy and low-weight infants are excluded [48].

Pharmaceutical form: raltegravir is available in granules for oral suspension as a single use package of 100 mg.

Metabolism: the same as bilirubin, raltegravir is metabolized through glucuronidation by UGT1A1 (uridine diphospho-glucuronosyl transferase), and hence both of them are in clinical development in adults [76] and could represent a paradigm shift in the treatment of HIV infection.

4.2.2.9. Novel drugs and strategies under investigation. Clinical studies in neonates are characterized by ethical and logistic barriers complicating the development of new antiretroviral agents and strategies. Fixed-dose combinations and once-a-day medications have solved many issues of adherence in older children and adolescents who are able to swallow pills. Developing child-friendly pediatric drug formulations remains a challenge to improve ART in neonates. One of the most rapidly changing fields is the formulation of poorly water-soluble drugs in flexible solid dosage forms. A novel technology that produces in situ self-assembly nanoparticles is a promising platform to manufacture palatable and flexible pediatric granules of ritonavir [76] and fixed-dose combinations of lopinavir/ritonavir that can be used as sachets and sprinkles [77]. In addition to fixed-dose combinations, once-a-day formulations of extended-release nevirapine show promise as a way to simplify ART administration, decrease pill burden, and improve adherence in children [78]. Another area of innovation is the development of injectable long-acting formulations of antiretrovirals. These formulations may be a pharmacological alternative to oral drugs and an innovative clinical option to address adherence. Long-acting injectable nanosuspension formulations of cabotegravir and rilpivirine are in clinical development in adults [79] and could represent a paradigm shift in the treatment of HIV infection.

4.2.3. Recommended antiretroviral regimen options for neonates

Decisions around which ART regimen to start with in neonates are complicated by the lack of clinical trials in this particular setting, few drug choices, and potential toxicities. Despite lack of scientific evidence and concerns associated with initiation of effective ART within the first days of life, clinicians seems to be moving toward effective combination treatment from birth. Most information on trends in ART usage in newborns comes from drug prophylaxis of infants at high risk of HIV infection. Among 1105 infants at high risk of HIV infection receiving prophylaxis in eight European cohorts between 1996 and 2010, 13.5% received zidovudine plus lamivudine, 22.7% received zidovudine plus single-dose nevirapine, 55.8% received zidovudine plus single dose nevirapine plus lamivudine, and 4.4% received a regimen including a protease inhibitor [80].
Table 2. Recommended antiretroviral regimens in newborns.

<table>
<thead>
<tr>
<th>Length of gestation and age</th>
<th>Recommended regimen options</th>
<th>Alternative regimen options</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm neonates</td>
<td>Individual case assessment weighing the risks and benefits of treatment</td>
<td>PK and safety data available only for zidovudine</td>
<td></td>
</tr>
<tr>
<td>First 2 weeks of life</td>
<td>Zidovudine plus lamivudine (or emtricitabine) plus nevirapine</td>
<td>Zidovudine plus lamivudine (or emtricitabine) plus raltegravir</td>
<td></td>
</tr>
<tr>
<td>From 2 weeks of life onwards</td>
<td>Zidovudine plus lamivudine (or emtricitabine) plus lopinavir-ritonavir</td>
<td>Zidovudine plus lamivudine (or emtricitabine) plus nevirapine</td>
<td>Limited PK and safety data with raltegravir*</td>
</tr>
</tbody>
</table>

An standard three-drug antiretroviral regimen generally consists of two nucleoside reverse transcriptase inhibitors in combination with a third active drug from one of three drug classes: a non-nucleoside reverse transcriptase inhibitor, a boosted protease inhibitor, or an integrase strand transfer inhibitor. With regard to the third active drug, as mentioned earlier, PK and dosing data in neonates only exist for nevirapine and lopinavir/ritonavir and, to a lesser extent, for raltegravir, and sufficient safety data as to prescribe a complete three-drug regimen are only available for full-term newborns from 2 weeks of life onwards. Available evidence from clinical studies favors triple-drug combinations including lopinavir/ritonavir, recommendation supported by data obtained in older children showing that a lopinavir/ritonavir-based first-line regimen is more efficacious than a nevirapine-based regimen, regardless of PMTCT exposure status [70].

Table 2 provides guidance on choosing an antiretroviral regimen based upon length of gestation and age. Given the options for initial therapy, in full-term neonates from age 2 weeks onwards, a regimen consisting of zidovudine and lamivudine (or emtricitabine) in combination with lopinavir/ritonavir is recommended. Regimens using nevirapine or raltegravir as third active drugs may be alternative options for infants who cannot tolerate lopinavir-ritonavir. In term infants younger than 2 weeks, a regimen consisting of zidovudine and lamivudine (or emtricitabine) plus nevirapine is recommended, although there are no clinical trial data supporting that initiating treatment before 2 weeks improves outcome compared to starting after 14 days of age. Switching from nevirapine to lopinavir/ritonavir should be considered after 14 days of life based on the better outcomes of lopinavir/ritonavir in children aged <3 years. Existing safety information is insufficient for recommending ART in preterm infants, with PK data only available for zidovudine. If ART is considered in this setting, an individual case assessment of the risk/benefit ratio of treatment should be made, and the latest information on neonatal drug doses of the candidate drugs to be used thoroughly reviewed.

4.2.4. Challenges and needs for early initiation of therapy in neonates

Despite global recommendation to initiate ART in HIV-infected newborns as soon as possible, implementation of early treatments remains complex. An important barrier for early initiation of ART is the complexity of early infant diagnosis in low-resource settings. Conventional virological diagnosis requires sophisticated technology that is typically only available in urban, centralized laboratories. As a result, in resource-limited settings, access to early diagnosis may be difficult and the logistic challenges may lead to long turnaround times, thereby delaying the diagnosis. Point of care (POC) diagnostic technology has the potential to increase access to virological tests for early infant HIV diagnosis. Available data indicate that some POC assays perform well showing high specificity and positive predictive value, thus suggesting that a positive POC result may be adequate for immediate infant ART initiation [81,82]. Large clinical studies are under way to provide evidence for the incremental benefit of implementing a POC strategy in low-resource settings where only off-site services for virological early infant HIV diagnosis are currently available [83].

Additional challenges associated with early ART in neonates include concerns on the risk of emergence of early viral resistance and virological failure [84,85]. Antiretroviral drug-resistant virus can develop during ART due to ongoing viral replication in the presence of subtherapeutic drug concentrations caused by limited pediatric drug formulations, poor adherence, poor absorption, variable PK, a regimen that is not potent, or a combination of these factors. Concerns related to drug adherence should be addressed before initiating therapy and suboptimal regimens should be avoided particularly in those with high pre-ART viral loads. In settings where technology is available, any newly diagnosed infant should undergo viral resistance testing by genotype and/or phenotype to assess for susceptibility to ART. In addition, frequent monitoring of plasma viral load is needed to assess virologic response to therapy.

5. Conclusion

Early diagnosis and prompt initiation of ART in every infant infected with HIV should now be considered the standard of care. There is considerable interest in moving treatment initiation closer to birth, since very early ART appears to limit the size of the viral reservoir. However, there are challenges to start ART in early life, including a paucity of drug choices, uncertain dosing for some medications, and concerns about toxicities. Safety data and available evidence from clinical studies favor triple drug combinations in full-
term neonates. The risks associated with use of different ART regimens as well as the potential benefits of very early treatment within days of birth, including the possibility of prolonged remission in infected neonates, require further investigations before firm recommendations can be made.

6. Expert opinion

Although available data on the risks and benefits of immediate therapy in asymptomatic HIV-infected children are weaker than in adults, there is general consensus in initiating ART as early as possible in HIV-infected infants. In order for HIV-infected neonates to receive prompt treatment, accurate early infant diagnosis is crucial. Advances in HIV virologic testing have improved accuracy and reduced turnaround time, allowing diagnosis of HIV infection soon after birth.

The recommendation for early onset of treatment in HIV-infected children is justified by the rapid progression of HIV disease reported in younger children and supported by data from cohort studies and clinical trials suggesting that earlier initiation of ART may reduce the risk of mortality and progression to AIDS. The precise timing of initiation of ART in neonates remains undetermined. Whereas the benefit of starting therapy between 6 and 12 weeks of age has been clearly demonstrated in the CHER trial, it is not known whether initiating ART earlier (close to birth) would carry additional benefits. Very early effective ART in perinatal HIV infection appears to limit the size of the viral reservoir, which is considered one step in the pathway toward HIV cure. Initiation of therapy very early may also restrict replication-competent HIV and promote continuous decay of viral reservoirs during long-term effective ART.

Barriers to use ART in neonates include lack of access to virologic testing, insufficient data on which to base a firm recommendation for treatment doses, and safety concerns by pediatricians arising from limited knowledge and experience regarding the use of antiretroviral drugs in this setting. Compared to older children, neonates and young infants have delayed absorption, reduced liver metabolism, and reduced renal elimination of drugs; therefore, it is important to obtain data on PK and safety of antiretroviral drugs in this particular population. In addition, the poor palatability of many of the existing formulations often leads the children to refuse taking them.

Unfortunately, reliable dosing and safety data to provide appropriate recommendations for neonates have been generated for a few antiretroviral drugs, most of them old agents. In full-term neonates, reliable data exist only for seven drugs. Two ( stavudine and didanosine) of the seven antiretroviral drugs are rarely used in adults due to the high risk of mitochondrial toxicity. In preterm infants, data are available only for zidovudine. If ART is considered in neonates born to mothers with HIV infection, and currently PK and safety data in preterm newborns are only available for zidovudine. If ART is considered in preterm infants, an individual case assessment of risks and potential benefits should be made.

Improvement on palatability of antiretroviral drugs is another neglected field. Due to the impossibility to swallow pills, oral solutions have to be given and poor palatability can make the neonate reject the medication and affect to the treatment adherence.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.


This paper compares efficacy and safety of three antiretroviral regimens (zidovudine alone; zidovudine plus three doses of nevirapine; zidovudine plus nelfinavir and lamivudine) to prevent intrapartum HIV transmission. Combined regimens were superior to zidovudine alone.


- Randomized clinical trial comparing immediate initiation of antiretroviral therapy versus clinical-based or laboratory-based initiation in HIV-infected infants (median 7.4 weeks of age). Early therapy reduced infant mortality by 76% and HIV progression by 75%.


- Retrospective study comparing proviral reservoir between HIV-infected children with early initiation of antiretroviral therapy (within the first year of life) and HIV-infected children with very early initiation of antiretroviral therapy (within the first 12 weeks of life).


