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Review

Update on antiretroviral therapy in paediatrics

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ABSTRACT

This review provides an update on the most relevant issues concerning the current management of HIV infection in infants and children.

Tremendous progress has been made over the last few years to diagnose and treat infants and children with HIV infection, yet much remains to be done. Every day there are nearly 1150 new infections in children under 15 years of age, more than 90% of them occurring in the developing world and most being the result of transmission from mother-to-child (WHO 2008).

The comprehensive approach to preventing mother-to-child transmission (MTCT) has clearly reduced the number of children acquiring the infection in Western countries; while a further reduction of mother-to-child transmission should be aimed for personalized setting, specific intervention needs to be put in place and new efforts are now required in order to optimise treatment and care in HIV-infected children. The prompt initiation of treatment and a careful selection of first-line regimen, which considers potency as well as tolerability remain central. In addition, occurrence and prevention of opportunistic infections, adherence as well as long-term psychosocial consequences are becoming more and more relevant in the era of effective antiretroviral therapy. This article forms part of a special issue of Antiviral Research marking the 25th anniversary of Antiretroviral Drug Discovery and Development, vol. 85, issue 1, 2010.

Contents

An estimated 2.1 million (1.9–2.4 million) children younger than 15 years of age were living with HIV in 2007, and more than 90% of them were infected through mother-to-child transmission (UNAIDS/WHO, 2007). Children account for 6% of all HIV infections, 17% of new infections and 14% of all HIV-related mortality. About 90% of children living with HIV are in sub-Saharan Africa (WHO, 2009). However, while tremendous progress has been made towards universal access to antiretroviral therapy for children in many countries, most children living with HIV who need antiretroviral therapy globally are still not receiving treatment. This is resulting in high mortality rates among children younger than 5 years of age, which are directly attributable to HIV. Efforts must be made to continue to expand early infant diagnosis and the provision of treatment and care for children.

Zidovudine (ZDV) given prenatally, at delivery and postnatally has reduced perinatal transmission by 67% (Connor et al., 1994; Wade et al., 2004), and a further reduction in transmission to 2% or less has been achieved with more effective antenatal and perinatal combination antiretroviral therapy (Wade et al., 2004; Magder et al., 2005).

Disease progression is more rapid in vertically infected infants than in older children and adults. Perinatal HIV infection progresses in 2 patterns: early, with a median age of onset at 4 months, or late with a median age of onset at 6 years (MaWhinney et al., 1993; Blanche et al., 1990; Duliege et al., 1992; Auger et al., 1988). In the absence of highly active antiretroviral therapy (HAART) about 20% of children born in developed countries will develop AIDS or die in the first year of life. Laboratory markers for high risk of rapid disease

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progression perform poorly, although children with positive PCR at birth (presumed to be infected in utero) appear to be at higher risk (The European Collaborative Study, 1994; Blanche et al., 1997).

The impact of treatment on progression of perinatal HIV infection remains poorly characterized at the population level, however it has been shown that earlier diagnosis and treatment has improved the prognosis of perinatal HIV infection (PENTA, 2001; Abrams et al., 2003; de Martino et al., 2000; Faye et al., 2004).

Nowadays two paediatric HIV epidemics have been recognized. The first one in the west, where new perinatal infection is rare and antiretroviral drugs are widely available. The other in developing countries where more than 1000 infants are newly infected every day, early diagnosis is a major issue, drug supply is problematic and early treatment is often started late. On top of this, background mortality and lack of resources make HIV management completely different in developing countries. Due to the very high mortality in resources limited settings (RLS), that according to unpublished data has its highest peak around the 4th month of age, early treatment needs to be considered an ethical obligation (Bourne et al., 2009).

In developed countries this approach has been questioned due to the availability of strict monitoring and the possibility of unnecessary treatment to long-term non-progressors. However, data from observational studies in Europe and the US show that starting treatment early is of benefit even where narrow monitoring is already provided. This is true particularly in terms of viral suppression, disease progression, growth and neurological development, avoidance of long-term neurological sequelae (Faye et al., 2004).

As a result US and European guidelines have also been modified in this direction. Several studies have confirmed that even though the level of viral replication in perinatally infected infants is very high, early initiation of HAART can result in sustained viral suppression and normalization of immunologic responses to non-HIV antigens (Faye et al., 2004; Chiappini et al., 2006b; Van der Linden et al., 2007). In infants with persistent control of plasma viremia, there has also been lack of detection of extra-chromosomal replication intermediates, suggestive of a near-complete control of viral replication. Some of these infants have become HIV seronegative and have lost HIV-specific immune responses. Indeed, early treatment in infants modifies the natural course of infection by controlling HIV-1 replication and reducing viral load to below the threshold levels required for onset of HIV-1 immune response, but does not prevent the establishment of a reservoir of latently infected cells that precludes virus eradication (Zanchetta et al., 2008).

As expected, early therapy, however, is not curative: proviral HIV-1 DNA continues to be detectable in peripheral blood lymphocytes and viral replication resumes if therapy is discontinued (Saitoh et al., 2002; Walker et al., 2004).

On the other hand, there are potential problems with treatment of asymptomatic infants. The rates of virologic failure reported seem to be higher with therapy started earlier rather than later. In studies addressing the effect of early therapy, the proportion of infants with viral levels remaining below quantification after 12–24 months of therapy is lower than observed in older children and adults, ranging from 18% to 62% (Walker et al., 2004; Luzuriaga et al., 2000; Aboulker et al., 2004). Incomplete viral suppression can lead to the development of drug resistance and compromise future treatment options (Aboulker et al., 2004). Virologic suppression, however, may take longer in young children given their higher viral load at the time of initiation of therapy than in older children or adults (Chadwick et al., 2008).

1. When to start ART in infants and children

When HAART became available in the mid-1990s, initiation of combination therapy in the first months of life was advocated as a possible approach to avoid rapid progression of disease (Luzuriaga et al., 2000; Hainaut et al., 2000). However, this remained controversial: the limited knowledge of the pharmacokinetics of antiretroviral (ARV) drugs in early life and the lack of appropriate formulations for infants complicated their administration, and there were concerns about the longer term toxicities and the risk of development of resistance, thereby limiting future treatment options. Data emerging from recent studies in resource constrained settings confirm that for infants acquiring HIV at or around delivery, disease progression occurs very rapidly in the first few months of life, often leading to death. In addition over 80% of infected infants become eligible to start antiretroviral therapy before 6 months of age (Luzuriaga et al., 2000; Violari et al., 2008).

Several observational studies in the United States and Europe had previously suggested that initiation of HAART before 6 months of age reduces the occurrence of early-onset severe disease (Faye et al., 2004; Prendergast et al., 2008; Chiappini et al., 2006b). Furthermore, initiating HAART before the age of 3 months had been reported to maintain CD4 cell count and percentage at adequate level despite low rates of HIV RNA viral load suppression (below limits of detection) (Luzuriaga et al., 2000; Aboulker et al., 2004; Chiappini et al., 2006b; Van der Linden et al., 2007).

Among 360 HIV-infected children included in a prospective study in the United States (Perinatal AIDS Collaborative Transmission Study—PACTS), infants who received early treatment with HAART (prior to 2 years of age, with nearly half starting in the first year of life) were considerably less likely to progress to AIDS or death compared with those who received no therapy, adjusting for year of birth and maternal disease factors (Abrams et al., 2003).

The French Perinatal Cohort reported a 70% reduction in the incidence of AIDS-associated events before the age of 24 months among infants born since 1996, and earlier initiation of HAART (before 6 months of age) appeared to be associated with a superior clinical outcome. No opportunistic infections or encephalopathy during the first 2 years of life were reported among 40 infants who started HAART before the age of 6 months, whereas 6 out of 43 infants who started HAART after age 6 months had 7 AIDS-defining events, 3 of which were encephalopathy (Faye et al., 2004).

The European Infant Collaboration reports data on 124 infants who commenced treatment before 3 months of age, and 86 who deferred the treatment. The risk of AIDS/death was considerably higher in infants with deferred treatment compared to those initiating antiretroviral therapy (ART) early (21.5% vs. 4.6% at 5 years; 11.7% vs. 1.6% at 1 year; $P < 0.001$). Starting ART after 3 months of age was associated with a five-fold increased risk of AIDS/death (crude hazard ratio HR, 5.0; 95% CI, 2.0–12.6; $P = 0.001$) (Goetghebuer et al., 2009).

The California Pediatric HIV Study Group and the Italian Register for Children both reported a reduction in HIV progression to AIDS and improved survival with early initiation of HAART (Chiappini et al., 2006a,b; Berk et al., 2005). While very early initiation (before 2 months of age) of mono/dual therapy resulted in decreased progression to AIDS compared to early initiation (age 3–4 months) of such therapy, the Italian Register did not find a difference in progression between children with very early versus early initiation of HAART. Similar to the French Cohort, however, initiation of therapy under the age of 6 months was superior to starting at >6 months (Faye et al., 2004; Chiappini et al., 2006a). In an analysis from the European Collaborative Study cohort, children who initiated potent therapy before 5 months of age were more likely to achieve CD4 recovery (defined as 20% increase in CD4 z-score) than children initiating therapy at older ages (Newell et al., 2006).

Criteria for initiation of HAART in HIV-infected infants have varied over time and between countries and centers. So far the recommendations about starting treatment have been based on analyses of CD4% and viral load from the large longitudinal HIV Paediatric Prognostic Markers Collaborative Study (HPPMCS, 2006)

of untreated infected children from US and Europe. However, these laboratory markers are poor predictors of disease progression in infancy, moreover, poorly applicable for different settings such as low and middle income countries.

More recently, the Cross Continents Collaboration for Kids (3Cs4kids) Study (2008), collecting individual longitudinal data from children has pooled data from approximately 2500 untreated vertically HIV-infected children from African studies, and evaluated the prognostic value of selected laboratory and growth markers on the 12-months risk of mortality.

Although infants <12 months have not been included, prognosis was shown to be poorer at younger ages for a given CD4% or CD4 cell count value while the predictive value of both markers improved with age across childhood in a similar manner to children from Europe and US in HPPMCS. Moreover, both CD4% and absolute cell count were shown to be less effective in discriminating between low and high mortality levels for children in RLS.

Recently, a randomized controlled trial performed in South Africa, the CHER study (Children with HIV Early antiRetroviral therapy) has demonstrated a 76% reduction in mortality in infants initiating HAART before 12 weeks of age compared to those deferring therapy (Luzuriaga et al., 2000) (Fig. 1). In this trial 252 asymptomatic infants with CD4% >25 were started on antiretroviral therapy as soon as possible after diagnosis of HIV. These infants showed a decrease in disease progression when compared to infants who were started on treatment based on immunological or clinical criteria (as recommended by WHO guidelines). In addition, infants initiated on early ART have significantly better Locomotor and General Scores on the Griffiths Mental Development Scales at a median age of 11 months compared to infants on deferred ART, despite careful monitoring and ready access to ART in the latter (Laughton et al., 2009).

On the basis of these strong results treatment is now recommended both in developed and resource constraints settings for all HIV-infected infants in the first year of life (PENTA, 2008; Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, 2009; WHO, 2008) (Table 1).

In children older that 12 months of age there are no randomized trials on when to start ART and evidence is based predominantly on analysis of paediatric and adult cohort data and extrapolation from the adult SMART trial (HPPMCS Group, 2005, 2006; Dunn et al., 2008; SMART, 2006; Dunn, 2003; Emery et al., 2007).

Starting ART is recommended in all children with significant symptoms, and in asymptomatic children with CD4 counts or percentages below recommended age-related thresholds. Starting ART should also be considered in those with a high HIV RNA viral load as they are more likely to progress rapidly to symptoms or rapid fall of CD4 values. Children with AIDS or significant symptoms (CDC Clinical Category C or B or WHO stage 3 or 4) have a higher mortality risk (Galli et al., 2000) and should start ART as a matter of urgency. The evidence for clinical benefit of ART in children with AIDS is so strong, that complete parental refusal to treat is now a child protection issue in Europe. CDC clinical category B covers a wide range of disease severity, and it is recognized that some children with milder stage B disease may have treatment deferred if their CD4 count allows this.

Data from the SMART trial (2006) clearly showed that adults with CD4 counts between 250 and 350 have significantly better outcomes on ART than off ART. This remains true in a sub-analysis of

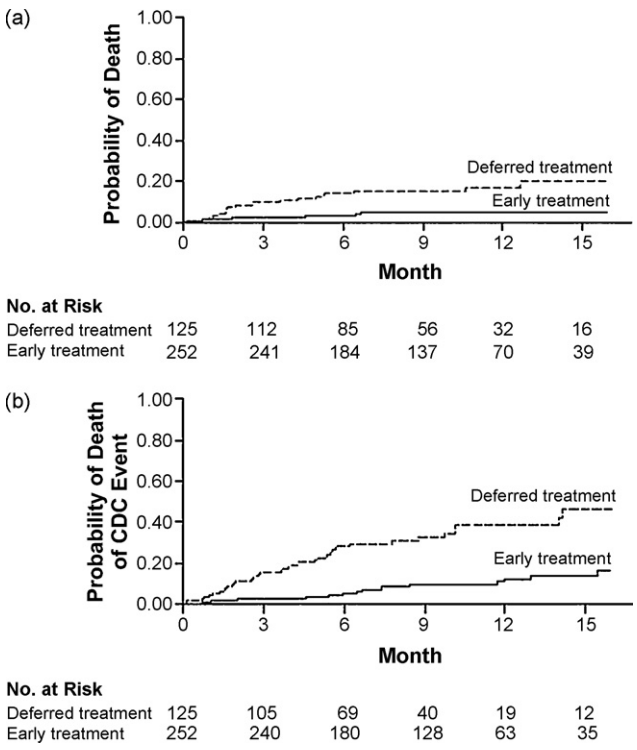

Fig. 1. CHER Study: Probability of Death or a First Event, According to Treatment Group. (Panel A shows the probability of death. Panel B shows the probability of death or onset of a CDC stage or severe stage B event) (Violari et al., 2008).

Table 1
Comparison of current international guidelines on when to start ART in infants and children.

		PENTA (2008) (Paediatric European Network for Treatment of AIDS—PENTA, 2008)	US 2008 (Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, 2009)	WHO, 2008 (WHO, 2008)	
0–11 months	Clinical Immunological Virological	Treat all	Treat all	Treat all	0–11 months
12–35 months	Clinical	Treat CDC stage B or C	Treat CDC stage B or C	Treat WHO Stage IV and severe III	12–35 months
	Immunological CD4%/count	Treat <25% or <1000	Treat <25%	Treat <20% or <750	
	Virological	Consider >100 000 copies/mL	Consider >100 000 copies/mL		
36–59 months	Clinical	Treat CDC stage B or C	Treat CDC stage B or C	Treat WHO Stage IV and severe III	36–59 months
	Immunological	Treat <20% or <500	Treat <25%	Treat <20% or <350	
	Virological	Consider >100 000 copies/mL	Consider >100 000 copies/mL		
5 years+	Clinical	Treat CDC stage B or C	Treat CDC stage B or C		5 years+
	Immunological	Treat <350	Treat <350	Treat <200 or <15%	
	Virological	Consider >100 000 copies/mL	Consider >100 000 copies/mL		

patients who had not received previous ART, confirming the benefit of starting treatment at these thresholds (Emery et al., 2007). Adult (US and European) guidelines have been changed to recommend ART initiation at CD4 cell counts below 350 cells/mm^3 (Gazzard, 2008). This is supported by data from the UK Collaborative HIV Cohort (CHIC) showing that in untreated adults, mortality is related to CD4 cell count at values <500 cells/mm^3 (Phillips et al., 2007).

Comparison of the short-term risks of disease progression in the pre-HAART adult CASCADE cohort collaboration and in children 5 years and older in the paediatric HPPMCS cohort showed that the short-term risk of disease progression was very similar in young adults (around 20 years) and children aged 5 years and older (Dunn et al., 2008). Therefore, absolute CD4 cell count, rather than percentage, should be used to determine treatment thresholds in children 5 years or older, for whom the same CD4 threshold recommendations as adults should be followed.

New analyses from the HPPMCS cohorts (2006) show that CD4 cell count is highly prognostic at ALL ages after infancy, and specific cut offs have been sat for different age bands. As CD4 cell count thresholds change more with age than CD4 percent thresholds in young children, the child's age within age bands 1–3 and 3–4 years also needs to be taken into account. The treatment thresholds have been identified in order to keep the risk of mortality below 2% and the AIDS progression risk below 5% in older children, even though progression risk is higher and more variable in the first few years after infancy. The level of plasma HIV RNA provides some useful information in terms of risk of progression, although its prognostic significance is weaker than CD4 count or percent (HPPMCS Group, 2005; Palumbo et al., 1998). Consideration may be given to starting ART in asymptomatic children with HIV viral load values persistently above 100 000 copies/mL even if they do not meet CD4 count criteria.

Table 2
Antiretroviral drugs approved in adults and in children.

	Adults	Children
N(t)RTI		
Abacavir (ABC)	+	+[1]
Didanosine (ddI)	+	+[1]
Emtricitabine (FTC)	+	+[2]
Lamivudine (3TC)	+	+[1]
Stavudine (d4T)	+	+
Tenofovir (TDF)	+	
Zidovudine (AZT, ZDV)	+	+
NNRTI		
Efavirenz (EFV)	+	+[3]
Nevirapine (NVP)	+	+[4]
Etravirine	+	
Protease inhibitors		
Atazanavir (ATV)	+	
Darunavir (DRV)	+	+[5]
Fosamprenavir (fAPV)	+	+[5]
Indinavir (IND)	+	
Lopinavir/ritonavir (LPV/r)	+	+[6]
Nelfinavir (NFV)	+	+[3]
Saquinavir (SQV)	+	+[7]
Tipranavir (TPV)	+	
Ritonavir (RTV)	+	+[6]
Entry/fusion inhibitors		
Enfurvitide (T20)	+	+[5]
Integrase inhibitors		
Raltegravir	+	+[7]

(1) >3 months old; (2) >4 months old; (3) >3 years old; (4) >2 months old; (5) >6 years old; (6) >2 years old; (7) >16 years old.

2. What to start with?

Growth and development in the paediatric patient can significantly affect drug absorption and disposition. Immature renal function, developing hepatic enzyme activity (particularly for Cytochrome P450 involved in the metabolism of several ARVs) and differences in drug absorption lead to variations in systemic exposure of ARVs among children (Kearns et al., 2003).

The lack of specific paediatric studies for several ARVs limit the number of drug registered in children as well the formulation available (Table 2).

While efficacy of non-nucleoside reverse transcriptase inhibitor (NNRTI) based and protease inhibitor (PI) based regimens are well established in older children, appropriate data is still missing for young infants.

The advice on choice between NNRTI- and boosted protease inhibitor-based regimens as first-line therapy has been limited by the lack of head-to-head comparisons between these regimens in controlled clinical trials.

The preferred dual nucleoside reverse transcriptase inhibitor (NRTI) combinations for initial therapy in children consist of a primary NRTIs (abacavir, ABC; didanosine, ddI; or ZDV) combined with either lamivudine (3TC) or emtricitabine (FTC). ABC in combination with 3TC has been shown to be well tolerated and more potent than ZDV in combination with 3TC in both children and adults (Green et al., 2007).

The choice of whether to add a PI or NNRTI to the dual NRTI backbone is being addressed in PENPACT 1, a 4-year randomized trial of 263 children with a viral load endpoint; results will be available in early 2010. Currently either an NNRTI or a PI is acceptable. Issues to consider include: age appropriate formulations; palatability, which may be a particular problem with ritonavir (RTV)-containing syrups; frequency of daily dosing; and likely adherence (Table 3).

New treatment approaches in infancy have raised new challenges in terms of drug choice, especially considering lifelong treatment and the related need to identify an efficacious drug sequencing and keeping a good toxicity and tolerability profile.

Advantages of protease inhibitor-based regimens include excellent virological potency, a high barrier for the development of drug resistance (requires multiple mutations), and the sparing of the NNRTI drug class; however, the drugs have potential for multiple drug interactions due to metabolism via hepatic enzymes, and long-term use may be associated with metabolic complications such as dyslipidaemia, fat maldistribution and insulin resistance (Panel on Antiretroviral Guidelines for Adult and Adolescents, 2007).

Results of pharmacokinetics and 24-week safety and efficacy studies of LPV/RTV therapy in very young infants (6 weeks–6 months) were recently reported (Chadwick et al., 2008). Although half of the subjects demonstrated delayed achievement of full virological suppression, most were able to sustain HIV-1 RNA at 400 copies/mL with longer follow up, implying that treatment-limiting resistance to the study medication did not occur. In addition all infants remained clinically and immunologically stable, with preservation or improvement of CD4 cell percentage at an age when CD4 cell values usually show a natural decline (Chadwick et al., 2008).

In this study as well as in the CHER study and other observational studies the toxicity pattern of LPV/RTV based regimen in young infants reported was not a concern: grade 3 or higher adverse events considered possibly or definitively related to the treatment occurred in a range of 0–14% of the infants and were transient, confirming a general good tolerability of LPV/RTV at this age.

Nevirapine (NVP) based regimens have also been proven to be safe and efficacious, and as NVP is the only NNRTI registered so far for use in young infants, a lot of data has been collected to support a safe and effective use of this drug.

Table 3
PENTA/CHIVA treatment grid for children with HIV – 1st and 2nd line antiretroviral choices – 2009 (Paediatric European Network for Treatment of AIDS—PENTA, in press).

First-line antiretroviral therapy		
<3 years	>3 years but <40 kg	>40 kg
nevirapine + lamivudine + abacavir (+zidovudine[f])[a] or lopinavir/ritonavir + lamivudine + abacavir (+zidovudine[f])	efavirenz + lamivudine + abacavir[a] or lopinavir/ritonavir + lamivudine + abacavir	efavirenz + (emtricitabine + tenofovir[b]) or (lamivudine + abacavir[b])[a] or lopinavir/ritonavir[c] + (emtricitabine + tenofovir[b]) or (lamivudine + abacavir[b])
At failure undertake: review of adherence and resistance testing. Ideally children should not remain for prolonged periods on failing regimens, because of the risk of accumulating resistance mutations. Second line ART choices should always be guided by resistance test results.		
Most likely second line antiretroviral therapy—when 1st line NNRTI based		
<30 kg	>30 kg	>40 kg
lopinavir/ritonavir + zidovudine + didanosine[d]	lopinavir/ritonavir + zidovudine + tenofovir	previous (emtricitabine + tenofovir)[c] lopinavir/ritonavir[c] + didanosine + abacavirprevious (lamivudine + abacavir)[c] lopinavir/ritonavir[c] + zidovudine + tenofovir
Most likely second line antiretroviral therapy—when 1st line PI based[e]		
<3 years	>3 years but <30 kg	>30 kg	>40 kg
nevirapine + zidovudine + didanosine	efavirenz + zidovudine + didanosine[d]	efavirenz + zidovudine + TDF	previous (emtricitabine + tenofovir)[c] efavirenz + didanosine + abacavir previous (lamivudine + abacavir)[c] efavirenz + zidovudine + tenofovir

[a] Where there are concerns about optimal adherence, it is advisable to start with a boosted PI regimen and monitor drug levels. When the HIV VL is consistently <50, then change to OD NNRTI regimen can be offered.
[b] Fixed dose combinations ("Truvada" – emtricitabine + tenofovir, "Kivexa" – lamivudine + abacavir).
[c] Alternative PIs include atazanavir/r, fosamprenavir/r, saquinavir/r and darunavir/r.
[d] TDF may be substituted for didanosine.
[e] Failure of a boosted PI regimen is particularly likely to be due to adherence rather than resistance, and this must be addressed before switching to an NNRTI.
[f] Some clinicians use 4 drug combination therapy (zidovudine + lamivudine + abacavir + nevirapine) for starting treatment in infants with very high HIV viral loads, not all clinicians agree that this is necessary, a randomized controlled trial is underway which will help to address this further (the arrow trial http://www.arrowtrial.org/).

3. Does the preventing mother-to-child transmission (PMTCT) approach affect treatment choice?

Efficacy in young infants might be affected by drug resistant virus acquired from the mother, either from multidrug exposure in high-income countries or due to simple PMTCT interventions such as single-dose NVP (sdNVP) in low/middle income countries.

The prevalence of transmitted primary ARV drug resistance in new perinatal HIV Infections has been reported by a few studies in western countries showing a relevant rate of detection of resistance, increasing by 58% between 1998 and 2002 (Panel on Antiretroviral Guidelines for Adult and Adolescents, 2007; Karchava et al., 2006). Clearly the availability of ARVs has modified the circulating "wild type" virus and a much wider access to ARVs is likely to enhance the issue of drug resistance, extending it to resource-limited settings where ART is being rapidly scaled up. Occurrence of drug resistance needs to be carefully weighed up in the choice of any 1st line treatment regimen.

Data from a meta-analysis and from observational studies (Arrivé et al., 2007; Shapiro et al., 2006; Jourdain et al., 2004; Moorthy et al., 2008; Church et al., 2008; Barlow-Mosha et al., 2008; Musiime et al., 2009) confirm that HIV-infected infants exposed to NVP through infant or maternal treatment or prophylaxis has demonstrable viral resistance (Fig. 2). Another observational study (Lockman et al., 2007) from Botswana also suggests that in infants who acquire HIV despite intra- or peri-partum exposure to NVP the response to NVP-containing first-line treatment regimens be may compromised.

The NVP-resistance issue therefore needs to be addressed and considered in the choice of first-line regimens. The new WHO recommendations for resource-limited settings suggest that where a previous exposure to NVP is known the infant should be started on a PI based regimen. Clinicians should keep a flexible approach and should apply these recommendations where such drugs are constantly available and when for the single patient in question adherence and storage requirements do not represent a major concern.

New information provided by ongoing studies may in the future modify or clarify this approach (WHO, 2008).

The use of PI-containing regimens is under evaluation in HIV-infected children despite exposure to NVP for PMTCT in developing countries (PACTG 1060 study) (Giaquinto et al., 2008). In this trial infants with and without prior sdNVP exposure (aged 6–36 months) and ART-eligible by WHO criteria were randomized to AZT/3TC + either NVP or LPV/RTV. Preliminary results have shown that infants exposed to sdNVP respond better to LPV/RTV than NVP-based therapy (Palumbo et al., 2009). This data clearly reinforces the current recommendation and LPV/RTV is becoming a more strongly recommended key component in any first-line treatment regimen in most developing countries, creating the worrisome issues of procurement.

However, strategies may be considered in order to reduce treatment cost without compromising treatment efficacy; for instance NEVEREST study (NEVirapinE Resistance STudy) was designed with the aim of testing if NVP prophylaxis-exposed children could switch to NVP-based therapy after initial suppression on a LPV/RTV-based regimen. HIV-infected children under the age of 2 years exposed to NVP prophylaxis and who met immunologic and clinical criteria for antiretroviral therapy were started on LPV/RTV, D4T and 3TC. 65.6% of children in the switch group consistently tested <50 copies/mL through 24 weeks post-randomization compared to 49.5% of children in the control group ($p = 0.02$). In contrast, fewer children in the switch group than in the control group consistently maintained <1000 copies/mL

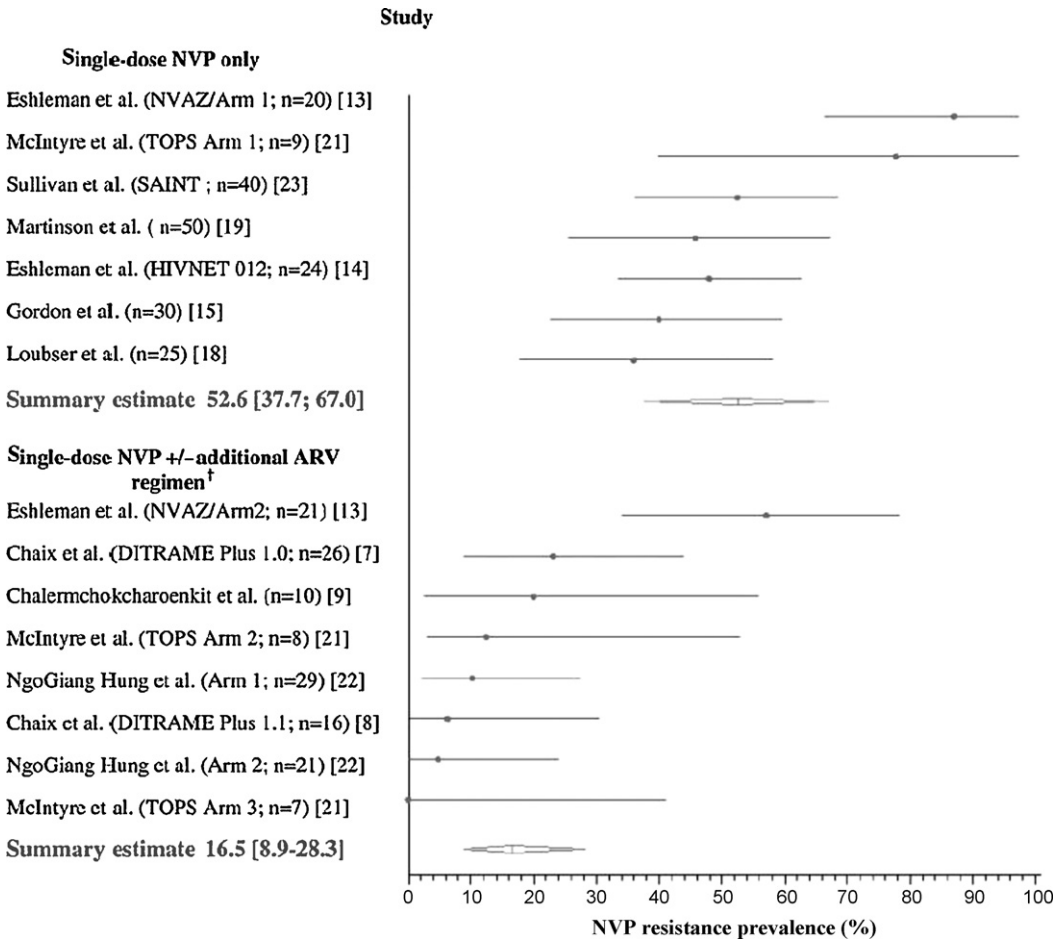

Fig. 2. Forest plot of viral resistance prevalence of resistance to neviparine (NVP) in children at 4–8 weeks postpartum after single-dose exposure, grouped according to whether mothers and children received single-dose NVP or received additional antiretroviral therapy (univariable random effect model). Antenatal/intrapartum zidovudine ± lamivudine and/or postpartum zidovudine and lamivudine and/or postnatal zidovudine ± lamivudine. TOPS: Treatment Options Preservations Study. SAINT: South African Intrapartum Nevirapine Trial. NVAZ: Nevirapine-AZT (zidovudine). HIVNET: Network for Prevention Trial. DITRAME: Diminution de la Transmission Mere-Enfant. PHPT: Perinatal HIV Prevention Trial (Arrivé et al., 2007).

through 24 weeks post-randomization ($p = 0.007$) (Coovadia et al., 2009).

This study provides proof of concept that re-use of NVP following successful suppression on LPV/RTV-based therapy is possible under some circumstances for HIV-infected children exposed to NVP prophylaxis. NEVEREST study results give hope but further research is necessary to determine the circumstances and interventions required to safely re-use NVP.

4. Treatment strategies

An adequate balance between efficacy and mid/long-term toxicity of ARV regimen is often hard to find in the context of long-life treatment. It is possible that some patients are treated overly aggressively, and would be equally effectively treated with an easier, which would be more convenient, may spare toxicity and be less costly. Several studies have identified pill burden as well as lifestyle issues (not carrying medication, change in schedule) as barriers to optimal adherence (Ryan et al., 2008; Belzer et al., 1999). Adherence is also affected by the relationship between care provider and child. Children receiving therapy from foster parents are more adherent than those receiving drugs from biological parents or relatives (Giacomet et al., 2003).

The potential benefits of an induction maintenance strategy with the current more potent drugs available are mainly preserving future therapeutic alternatives, minimizing the exposure to potentially toxic drugs and decreasing the risk of adverse events or resistance selection.

Controlled clinical trials in adults have shown that LPV/RTV monotherapy maintains virological suppression in most patients at 144 weeks (OK 04 study). In those few patients with virological rebound, re-intensification with triple therapy may successfully lead back to virological suppression without development of PI-resistance (Pulido et al., 2008).

Two prospective, open label, multicentre, randomized trials, PENTA 17 and 18, will soon explore the efficacy of two different simplification strategies looking at the potential use of LVP/RTV once-daily administration and induction maintenance strategy with LPV/RTV monotherapy in the paediatric population.

The role of Short-Cycle Therapy (SCT) in the management of HIV-infected young people who have responded well to ART still needs to be investigated outside adulthood (Cohen et al., 2007). A new trial (PENTA 16 or BREATHER study), starting soon and involving Europe and Uganda, will inform on this option and address the advantages and disadvantages of SCT (five days on ART and two days off) strategy, the incidence of toxicities, immunological control, resistance mutations, acceptability, quality of life and adherence. Data from adult studies evaluating the strategy of 5 days on,−2 days off are promising and low rates of virological rebound were reported (Cohen et al., 2007, 2008; Reynolds et al., 2008); however, the use of this kind of approach remains controversial and should be carefully evaluated accounting for the ART regimen in use as more applicable

in regimens containing drugs – such as efavirez (EFV) or NVP) – for the longer half-life rather than PIs.

Whether treatment interruption within strategies where therapy is begun in early infancy and stopped after a defined period of treatment (e.g., 1–2 years) allowing the child to be protected during the period at greatest risk for HIV disease progression and mortality, and restarting of therapy when the child meets standard age-related criteria, is valid is under evaluation in clinical trials in South Africa and Kenya.

Currently, planned treatment interruption (PTI) is not recommended in children outside of a clinical trial setting; trials evaluating treatment interruptions in adults have reported higher rates of AIDS events/deaths and non-AIDS serious cardiovascular, renal and hepatic events in those stopping ART (Ananworanich et al., 2006; Danel et al., 2006; SMART Study Group, 2008; Marchou et al., 2007; DART Trial Team, 2008). However, PTIs may have a role in the future management of paediatric HIV as reassuring data have been reported by PENTA 11 (TICCH - Treatment Interruption in Children with Chronic HIV infection) trial, where a CD4-guided PTI in chronic HIV has been piloted; no deaths or serious clinical events occurred in the PTI group, while more minor clinical events (but not infections) were recorded. Although CD4 levels and HIV RNA suppression were inferior at 72 weeks in the PTI group, some PTI children were off ART at 72 weeks and CD4 recovery after PTI was significantly better in younger children. In addition further reassurance comes from the high proportion of children, in the PTI group, with suppressed viral load after 24 weeks back on ART, among whom no evidence of more resistance than the continuous treatment group was found (Castro et al., in press). Long-term consequences of planned treatment interruptions in PENTA 11, including neurocognitive assessment and immunology sub-studies, are now under investigation. Therefore, available results provided by this trial provide useful information for children who may undergo unplanned interruptions of ART for a variety of reasons, but cannot be used to advocate PTIs.

5. Monitoring

Even though the increasing antenatal ART use (Cooper et al., 2002; Dorenbaum et al., 2002; European Collaborative Study, 2004a), particularly during organogenesis, has raised questions relating to the short and longer term safety for exposed children, to date there appears to be no increased risk of congenital malformations associated with ART exposure in pregnancy (Public Health Service Task Force, 2004) for most ARVs.

The short term risks associated with ZDV are limited to anaemia, which is reversible at the end of treatment (Public Health Service Task Force, 2004; Le Chenadec et al., 2003; European Collaborative Study, 2004b). However, a longer term haematological impact of in utero exposure to ART has been reported by several European studies (PEP Study Group, 2005; Townsend et al., 2009; Noguera et al., 2004; Ekouevi et al., 2006). Severe mitochondrial toxicity was reported in a few infants and children exposed to NRTI in pregnancy in the French Collaborative Study (Blanche et al., 1999). Although asymptomatic lactic acidosis reflecting possible mitochondrial damage was also reported by others (Alimenti et al., 2003; Giaquinto et al., 2001), these findings were not confirmed in large observational studies. Finally use of ART and particularly PI in pregnancy has been associated with a 1.5 fold increased risk of premature delivery (Townsend et al., 2009).

Therefore, a proper follow up of all children exposed to ARV therapy during pregnancy and/or postnatally in currently recommended in order to evaluate mid- and long-term events possibly associated with in utero exposure to ARV.

Clinical and laboratory monitoring should take place more frequently after initiating or changing therapy, and this needs to continue in infants who are growing rapidly and in children with adherence difficulties.

Once children are established on treatment, clinical and laboratory monitoring should be undertaken 3–4 monthly in the same way as before starting treatment, with the important additions of monitoring adherence, drug toxicities and interactions. More sophisticated methods of therapeutic drug monitoring (TDM) in children are not supported by clear evidence to inform recommendations for routine use of it. However, it may be useful in circumstances where drug doses are less well established or there is suspected toxicity, failure or likely drug interactions (PENTA, in press).

Monitoring capacity is often very difficult to implement in setting with resource constraints as in many high prevalence countries and the DART (Development of AntiRetroviral Therapy in africa) study has investigated the Impact of routine laboratory monitoring over 5 years after ART initiation on clinical disease progression of HIV-infected African adults. Results from this large trial show that the overall survival at 5 years (Clinically Driven Monitoring: 87%; Laboratory and Clinical Monitoring: 90%) was excellent, strongly reinforcing that ART should never be withheld due to lack of laboratory monitoring and that 3TC/AZT + ABC or TDF or NVP, can be given without need for routine toxicity laboratory monitoring, even in advanced disease (Mugyenyi et al., 2009).

Evidence to support this type of approach in the paediatric population will come from the ARROW (AntiRetroviral Research for Watoto) trial, which is now being carried out in Uganda and Zimbabwe to evaluate the best management and monitoring strategies in developing countries.

6. Outstanding issues and future challenges

Information on appropriate drug dosing particularly for infants less than 3–6 months of age is partially established. Hepatic and renal function are immature in the newborn, as these undergo rapid maturational changes during the first few months of life, leading to substantial differences in antiretroviral dose requirements between young infants and older children.

Inadequate dosing, poor absorption, or incomplete adherence, followed by sub-therapeutic drug concentration may result in ARV drug resistance, which can develop rapidly, particularly in young infants with high levels of viral replication. Frequent follow-up and continued assessment and support of adherence therefore are especially important in the treatment of young infants. The importance of adherence to treatment needs to be fully discussed with the caregivers, and potential problems must be identified and resolved prior to initiation of therapy, even if this might delay starting treatment.

The occurrence of toxicity such as lipodystrophy, dyslipidemia, glucose intolerance, osteopenia, and mitochondrial dysfunction with prolonged therapy is a concern (Leonard and Mc Comsey, 2003; Amaya et al., 2002). Moreover little is known about drug tolerability in young infants and additional data is needed. These concerns are particularly significant because life-long administration of therapy is currently the only option recommended.

Finally, the treatment sequencing needs to be addressed. The use of a highly potent drug such as LPV/RTV in the first-line treatment of those infants exposed to NNRTIs, emphasizes the current lack of a reliable 2nd line choice, in those setting where LPV/RTV is still the only PI available.

New drugs and 2 new classes of ARVs (integrase inhibitors and CCR5 inhibitors) have recently become available for adults. Data are available on the paediatric use of several RTV-boosted PIs. Some are licensed for use in older children, and more may soon follow. However, drugs from the 2 new classes are not yet licensed for use in children, although phase I/II studies are in progress. Even in adults, drugs from new classes have not been used long enough

to determine their best place alongside older drugs in the optimal sequence of first-line and subsequent ARV combinations.

Infant and child friendly formulations need to be available urgently where they are not and new drugs produced and distributed where necessary. New approaches require a new focus on infants by the pharmaceutical industries, that are now also required to improve formulation as well as make adequate Fixed Drug Combinations (Esté and Cihlar, 2010) suitable for HIV/AIDS management in RLS.

Of particular interest are issues related to adolescents and their transition to adult care; while newly diagnosed behaviourally infected adolescents are likely to face the same health concerns as adults with HIV infection, the group of adolescents who have lived with HIV all of their lives present different challenges to care providers (i.e. adherence, disclosure of diagnosis, sex education etc.), which require a specific expertise to be managed. Adherence is usually influenced by multifactorial events and bio-psycho-social factors, which interrelate and change over time. HIV-infected adolescents also face specific adherence challenges (Ryan et al., 2008; Belzer et al., 1999). Several studies have identified pill burden as well as lifestyle issues (not carrying medication, change in schedule) as barriers to optimal adherence (Ryan et al., 2008; Belzer et al., 1999). Transitioning treatment responsibility from the *care–giver* to the adolescent represents a critical point that could sensibly affect the drug efficacy, therefore any measure should be used in order to achieve and maintain a good virological control.

Careful surveillance of this population is essential to clarify long-term health outcomes including reproductive matter, and, as it is known that lymphomas increase over time in HIV, careful screening for such malignancies as well as cervical cancers must be carefully considered.

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