From infanthood to adolescence across the globe: **growing-up with HIV**

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To my wife, Caroline

There can be no keener revelation of a society's soul than the way in which it treats its children

Nelson Mandela

ABBREVIATIONS

cART: combination antiretroviral therapy
CE: cost-effective(ness)
CEA: cost-effectiveness analysis
CHAPAS: children with HIV in Africa – pharmacokinetics and adherence/acceptability of simple antiretroviral regimens
CHER trial/study: children with HIV early antiretroviral therapy
CROI: conference on retroviruses and opportunistic infections
DALY: disability adjusted life year
ddI: didanosine
d4T: stavudine
DR: drug resistance
DRV: darunavir
DWB: doctors without borders
EID: early infant diagnosis
EFV: efavirenz
EMA: european medicines agency
FDA: food and drug administration
FDC: fixed-dose combination
FTC: emtricitabine
HAART: highly active antiretroviral therapy
ICER: incremental cost-effectiveness ratio
IDV: indinavir
IMPAACT: international maternal pediatric adolescent AIDS clinical trials
IP: intrapartum
IRIS: immune reconstitution inflammatory syndrome
LMIC: low-and middle-income countries
LPV/r: ritonavir-boosted lopinavir
MSOC: minimum standard of care
MTCT: mother-to-child transmission
ND: no data
NEVEREST: nevirapine resistance study trial
NFV: nelfinavir
NNRTI: non-nucleoside reverse transcriptase inhibitor
NRTI/NtRTI : nucleoside/nucleotide reverse transcriptase inhibitors
NFV: nelfinavir
NVP: nevirapine
OD: once-daily
OIs: opportunistic infections
PCR: polymerase chain reaction
PENPACT: paediatric european network for treatment of AIDS (PENTA) and pediatric AIDS Clinical Trials Group (PACTG/IMPAACT)
PENTA: paediatric European network for treatment of AIDS
PEPFAR: president's emergency plan for AIDS relief
PI: protease inhibitor
PMTCT: prevention of mother-to-child transmission
PP: post-partum

PTI: planned treatment interruption
RAL: raltegravir
RCT: randomized control trial
RLS: resource-limited setting
RF: Rwandan franc
RTV: ritonavir
SA: sensitivity-analysis
sdNVP: single-dose nevirapine
SQV: saquinavir
TAMs: thymidine-associated mutations
TDF: tenofovir
UNAIDS: joint United Nations programme on HIV/AIDS
US/USA: United States of America
VL: viral load
WTP: willingness to pay
ZDV: zidovudine
3TC: lamivudine

INTRODUCTION

This thesis has its origin in my personal background. In 2006, after being trained in the HIV field by Pr Jack Levy in CHU Saint-Pierre, I worked for nearly 2 years in Pietermaritzburg (PMB) Metropolitan Hospitals Complex (including Grey's Hospital, Edendale Hospital and Northdale Hospital) in South Africa. At this time, more than 1500 children were on follow-up and treatment at the Edendale Family Clinic, the busiest HIV clinic of Pietermaritzburg (Picture 1).

Picture 1. *Edendale Family Clinic, Pietermaritzburg*

I was shocked to discover that babies aged less than 6 months had no access to combination antiretroviral therapy (cART), the lifesaving treatment for HIV-infected patients. The rationale for this practice was that mortality and morbidity was too high in this age group and that efforts were being focused on treating older infants who had a better prognosis. Moreover, it was felt that there were inadequate resources to treat and save all infants. Coming from Belgium, where early initiation of cART was the rule since 1996 with excellent outcome[1], I was disturbed by what I discovered in KwaZulu Natal. After some negotiation we finally got the authorization to start cART in young infants. Later on, when evidence for early treatment came out in a randomized trial[2], we decided to perform an operational study to evaluate if early initiation of cART (under the age of 1) was as effective outside an academic setting[3].

By contrast, after returning back to Europe and during my fellowship in paediatric infectious diseases in Canada, the reality of paediatric HIV was totaly different. In high-income countries (HIC), such as Belgium and Canada, paediatric HIV cohorts are aging with the majority of patients being adolescents[4]. Data from USA (2008) showed that 62.4% of people living with perinatal HIV were aged 13-24 (75% 13-19 and 25% 20-24)[5]. This demographic shift is the result of two major advances during the past 17 years: effective prophylaxis and treatment in HIV-infected pregnant women, with virtual elimination of mother-to-child transmission (MTCT); and administration of effective cART to the infected children who now survive into adulthood. But considering that some HIV-infected adolescents are on treatment since birth we aim to study their health status at the time of transfer into adult services.

Two parts of the world, two extremes. Two different life periods.

CHAPTER I

1. EPIDEMIOLOGY OF HIV/AIDS IN CHILDREN

1.1 THE GLOBAL PICTURE

In 2011, there were an estimated 3.3 million children living with HIV and 230 000 deaths from HIV-related complications[6]. The last UNAIDS report states that, in 2011, 330 000 children were newly diagnosed with HIV[6]. This represents a considerable reduction compared to previous years with 560 000 new infections in 2003 (43% drop) and 430 000 in 2009 (24% drop). The number of paediatric HIV infections also decreased dramatically in the Caribbean (32%) and in Oceania (36%), with a less marked decline in Asia (12%). Modest decline has been observed in Latin America (24%), Eastern Europe and Central Asia (13%) but important progress has been previously made in those regions[6]. Between 2009 and 2011, the number of children acquiring HIV infection increased in 4 countries (Angola, Congo, Equatorial Guinea and Guinea Bissau)[6]. This considerable global decline comes from the collaborative effort including ambitious international initiatives[7-9] to strengthen prevention of MTCT (PMTCT) in many parts of the world. An indirect effect of the AIDS epidemic on children's health and survival is that numerous children (infected or not) have lost one or both parents. The Joint United Nations Program on HIV/AIDS (UNAIDS) estimated that 17.3 million children have been orphaned[6].

1.2 IN LOW-AND MIDDLE-INCOME COUNTRIES

In low-and middle-income countries (LMIC) children represent 14% of new HIV infections and close to a fifth of annual HIV deaths[6]. Sub-Saharan Africa has been heavily affected by the pandemic. In 2011, more than 90% of the children who were infected with HIV were living in this part of the world. From 2009 to 2011, 6 countries (Burundi, Kenya, Namibia, South Africa, Togo and Zambia) achieved significant progress by decreasing the number of new infections by 40-59%. From 2009 to 2011, 409 000 new paediatric infections were prevented by PMTCT in LMIC[6].

1.3 IN HIGH INCOME COUNTRIES

Thanks to the effectiveness of PMTCT programs (prenatal and obstetrical care, access to cART and safe formula-feeding), few children are infected at birth with HIV or die from HIV-related illness in Western-Europe[10, 11]. In 2010, 6000 children were living with HIV in Western and Central Europe[12]. In 2011, in Europe, only 1% of new HIV infections (adults and children) were due to MTCT. This represents a total of 222 new infections (8 in Belgium) in 2011 (46.4% of those cases coming from countries with generalized epidemics) and 2242 from 2004 to 2011 (68 in Belgium)[12]. After reviewing those numbers it appears that 14 out 68 cases diagnosed in Belgium between 2004 and 2011 were born in Belgium, 45 of the newly diagnosed children came from sub-Saharan Africa with 37 aged 5-20 years old at the time of diagnosis in Belgium (André Sasse, Scientific Institute of Public Health, Belgium, personal communication).

In Eastern Europe, Ukraine accounts for more than half of all cases of MTCT in non-EU/EEA countries with 169 new cases in 2011 (1115 cases since 2007). In a country with the same population as Belgium, Belarus had 23 MTCT infections in 2011 (175 since 2004). In 2011, non-EU/EEA cases exceeded those in the EU/EEA region by 88[12]. The Centers for Disease Control and Prevention (CDC) estimates that the number of infants born with HIV each year in the United States dropped from 1650 in 1991 to fewer than 200 in 2004[13]. In 2011, 192 children under 13 years of age were newly diagnosed with HIV, 127 through MTCT[13]. In Oceania, about 4600 [3600–5800] children were living with HIV in 2010, 500 of whom were newly diagnosed in 2010. In Australia, between 2002 and 2011, 311 children were perinatally exposed to HIV and 13 were infected; MTCT dropped from nearly 7% in 2002-2003 to 1.2% in 2010-2011[14].

1.4 ACCESS TO ANTIRETROVIRAL TREATMENT

1.4.1 Antiretroviral therapy for PMTCT

PMTCT is paramount in the struggle to eliminate paediatric HIV. Recently, UNAIDS declared that the elimination of mother-to-child-transmission (MTCT) of HIV is possible[15]. Simultaneously, the World Health Organization (WHO) published a strategic vision for 2010-2015 (picture 2) on the prevention of MTCT (PMTCT)[16]. The bold new vision of the 'Three Zeros' articulated by UNAIDS, WHO and other international institutions such as the Global

Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) includes the elimination of MTCT of HIV, the reduction of child mortality and improvement of maternal health (Millenium Development Goals 4 and 5) by 2015[17].

Picture 2. Eliminate new HIV infections among children by 2015

However, many pregnant women still have no access to cART, the most effective intervention in preventing vertical infection to their children. In 2011, cART coverage to prevent MTCT attains 57% [51–64%] in low- and middle-income countries[6]. Compared to high-income country, only the Caribbean has reached comparable levels of coverage at 79% [67–97%][6]. In sub-Saharan Africa, the current coverage is now 59% [53–66%]. Reported coverage is lower in South and South-East Asia (18% [13–23%]), in the Middle East and in North Africa (7% [6–9%])[6]. In 2013, the first systematic review on uptake of integrated PMTCT programs

(implemented between 1997 and 2006) in low- and middle-income countries was published. It showed overall low uptake of PMTCT with a median proportion of 55% HIV-infected women provided with cART in antenatal care and attending labour word. Overall, 79% of infants were tested for HIV and 11% (range 3-18%) were infected[18].

1.4.2 Antiretroviral therapy for treating HIV-infected children

Children have much poorer access to ART compared to adults, and attrition at each step in the cascade of care urgently requires attention to strengthen links within HIV services. In the 2012 WHO report one can read that globally, only 28% [25-31%] of children eligible for cART were effectively receiving treatment, which lagged significantly behind the 58% coverage for adults[6]. However, important progress has been achieved in some countries such as South Africa where the number of children starting cART each year has risen from 4200 in 2004 to 152000 in 2011[19]. Like PMTCT, scale-up of access to antiretroviral for children is the result of global efforts with an estimated 450 000 children now benefiting from cART in LMIC[15].

2. NATURAL HISTORY OF HIV IN CHILDREN

Mother-to-child transmission is the way of transmission in 95% of the cases, occurring during pregnancy, at the time of delivery, or postnatally through breastfeeding. High HIV-1 viral load (VL) and low CD4 count are recognized as the most important risk factors determining transmission from the mother to the child[20, 21]. Without specific interventions, HIV-infected women will transmit the virus to their infants during pregnancy or delivery in about 15-25% of cases; and an additional 5-20% of infants may become infected postnatally during breastfeeding, for an overall risk of 30-45%. Breastfeeding may thus be responsible for one third to one half of HIV infections in infants when interventions are not available[22]. In high-income countries (HIC), the risk of transmission through breastfeeding is virtually absent as all HIV-infected women are strongly encouraged to give formula-milk to their babies. However, postnatal transmission of HIV during breastfeeding is a major concern in LMIC[23], particularly in sub-Saharan Africa where breastfeeding remains the only feasible,

safe and culturally acceptable infant feeding choice[24]. WHO recommends HIV-infected exclusive breastfeeding for the first six months of life, unless replacement feeding is acceptable, feasible, affordable, sustainable and safe for them and their infants before that time. When those conditions are met, WHO recommends avoidance of all breastfeeding by HIV-infected women[22]. Pooled data from 2 cohorts in Western Africa and South Africa showed that longer duration of breastfeeding is associated with increased risk of MTCT. The overall risk of postnatal HIV infection was 3.9% among children breastfed for <6 months and 8.7% among children breastfed for > 6 months[25]. In this study, infants exposed to solid food during the 2 first months of life were 2.9 times more likely to be infected postnatally than children never exposed to solids this early[25].

In the past few years, there has been remarkable progress in the discovery of effective antiretroviral drug regimens to prevent postnatal transmission of HIV during breastfeeding[26]. Non-randomized interventional cohort study[27] and randomized trials have shown that maternal or infant antiretroviral regimens during breastfeeding can significantly reduce postnatal transmission of HIV during breastfeeding[28, 29]. In AMATA study, a study performed in Rwanda, 532 infants were born to HIV-infected women. Breastfeeding was given to 227 infants (43%) and 305 (57%) were formula fed. MTCT was 1.3%, 6 in utero infections and one child who became infected in the breastfeeding group, corresponding to a 9-month cumulative risk of postnatal infection of 0.5% with breastfeeding[27].

However, in HIC, where formula feeding is safe and affordable, and despite recent changes in British guidelines[30] allowing breastfeeding in some conditions (mothers with undetectable VL) and monthly monitoring of both mother and child), most experts still strongly discourage this practice when alternatives are available. Indeed, it would be questionable to take supplementary risk of transmission during the breastfeeding period and to expose an uninfected child to potential toxicities linked to antiretrovirals taken by the mother.

Other ways of transmission include sexual transmission among adolescents, sexual abuse of children, transfusion of infected blood or blood products, unsterile injection procedures, pre-mastication of food and scarification.

In the absence of treatment with cART, more than 50% of HIV-infected children living in Sub-saharan Africa will die by the age of 2 years[31]. In contrast, data from Europe show that after 6 years, 75% of infected children are still alive but rapid progression to U.S. Centers for Disease Control and Prevention (CDC) group C disease or HIV-related death will occur in an estimated 20% of infants during the first year of life[32].

The natural history of the infection differs greatly from infected adults. In children, the clinical progression is bimodal[33]. Fifteen to 25% of vertically infected children will progress rapidly to AIDS and death within the 2 first years of life while 75% to 85% will have a much slower progression (similar to adults) and will remain asymptomatic for 2 to more than 10 years[33]. Higher VL in infants compared to adults is associated with early disease progression[34]. Risk factors for rapid progression include high VL during the 6 first months of life and low CD4 in both infants and mothers[35].

The risk of mortality differs between HIC and LMIC. The mortality rate at 2 and 5 years is 25-54% and 62% for LMIC and much lower for HIC with a mortality rate of 10-20% and 28% at 2 and 5 years respectively. The difference in mortality rate between HIC and LMIC was attributed to worse maternal health status such as advanced disease, anaemia, death, and delivery complications as well as early failure to thrive, absence of breastfeeding and progression to severe immunosuppression before 6 months of age. All those factors were predictors of death before 2 years of age in one study[36].

Hopefully, the natural history of this disease has changed dramatically in children and in adults since 1996 with the access to cART. However, in 2008, an American federal report still showed a 10–30-fold higher mortality rate in HIV-infected children compared to similarly aged uninfected paediatric populations[37].

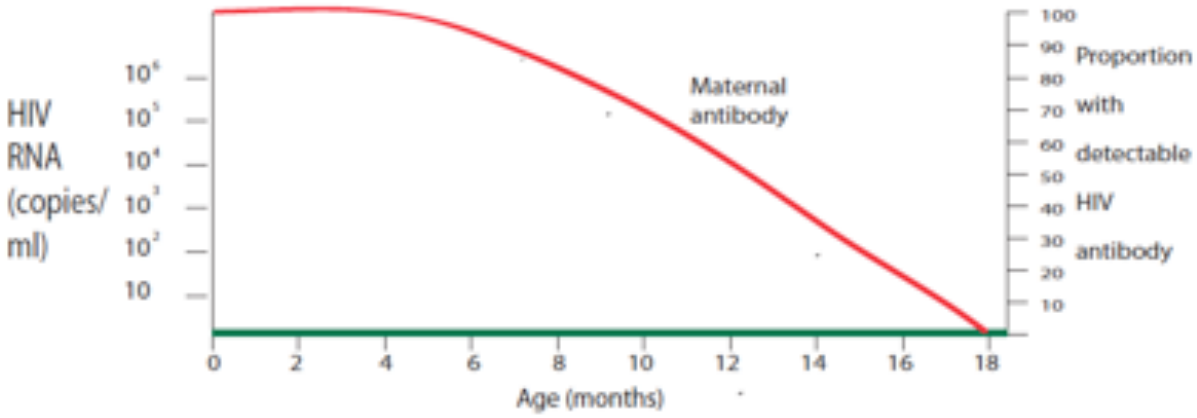
3. HIV DIAGNOSIS IN CHILDREN

HIV infection cannot be solely diagnosed with antibody assays in infants until at least 18 months of age. This is due to the fact that maternal antibodies are transplacentally transmitted to the fetus. Antibodies will progressively decrease and all uninfected infants will become seronegative by 18 and rarely by 24 months (in case of using an ultrasensitive serological method) (Figure 1a)[38]. However, in children older than 18 months of age, HIV-1 antibodies assays can be used for diagnosis. HIV diagnosis in young infants requires the use of polymerase chain reaction (PCR), either HIV-DNA PCR (qualitative method) or HIV-RNA PCR (quantitative method)[39].

A definitive diagnosis of HIV infection is made after obtaining 2 positive PCR on 2 different blood samples. A positive HIV-1 DNA PCR within the first 48h of life is suggestive of in-

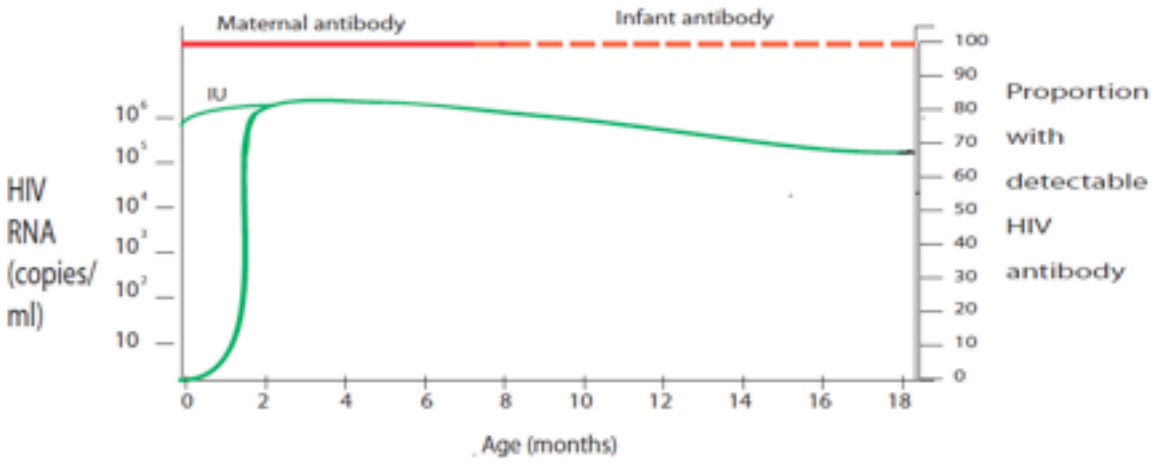
utero transmission (Figure 1b)[38]. The specificity of the HIV DNA PCR is 99.8% at birth and 100% at 1, 3, and 6 months. The sensitivity HIV DNA PCR done at birth is 55% but increases to more than 90% by 2 to 4 weeks of age, and 100% at 3 months and 6 months of age. The specificity of the HIV RNA PCR (if > 5000 copies/mL) has been shown to be 100% at birth, 1, 3, and 6 months of age and is comparable to HIV DNA PCR. HIV RNA PCR sensitivity goes from 25% to 58% during the first weeks of life, 89% at 1 month of age, and increases to 90% to 100% by 2 to 3 months of age[40]. To presume that the infant is not infected, proviral HIV-1 DNA PCR should be negative at 2 and 3 months with at least one test performed one month after ending neonatal antiretroviral prophylaxis. A recent study shows that neonatal prophylaxis with zidovudine (ZDV) can lead to false negative PCR results in 11% of infected infants at 1 month but all had positive PCR at 3 months[40].

Figure 1a. Clearance of maternal antibodies in HIV-exposed but uninfected infants[38]



This figure represents progressive clearance of maternal antibodies in HIV-exposed infants. By 18 months most uninfected infants have cleared maternal antibodies.

Figure 1b. Maternal and infant antibodies in HIV-infected infants[38]



This graph shows clearance of maternal antibodies but production of HIV-infected infant's own antibodies. Viral load (VL) is high from birth in in-utero infected children. IU= in-utero.

- **More than 90% of HIV-infected children are living in sub-Saharan Africa**
- **In high income countries, new paediatric HIV infection is a rare event due to the efficacy and effectiveness of PMTCT**
- **WHO global target for 2015 is to decrease MTCT by 90% compared to 2009**
- **Early diagnosis of HIV in infants requires the use of PCR**
- **In absence of early combination antiretroviral therapy, 50% of HIV-infected children will die by the age of 2 years**

In the next chapter we will review current recommendations for prevention of mother-to-child transmission as well as comparison of cost-effectiveness between different strategies.

CHAPTER II

1. PREVENTION OF MOTHER-TO-CHILD TRANSMISSION

Soon after the epidemic emerged, different strategies were deployed to decrease MTCT and some of the major randomized control trials selected from a recent Cochrane review are summarized in Table I [41]. First, systematic formula feeding was introduced in countries where it was believed to be safe and feasible. In 1994, in PACTG 076, administration of ZDV during pregnancy, at delivery and to the newborn reduced the risk of MTCT by approximately two thirds[42]. In 1998, obstetrical practices contributed to decrease MTCT with the introduction of elective caesarean section[43]. Currently, there is a strong body of evidence showing that treating pregnant women with cART is the most effective strategy to prevent transmission of HIV from mother to child[41, 44]. Most of the studies assessing different PMTCT regimens and length of treatment were carried out in resource-limited settings (RLS) in order to choose the most adapted strategy according to existing resources[45-47]. In RLS, the efficacy of short-course antiretroviral therapy has been demonstrated with the reduction of MTCT to <1%-10% compared with HIV transmission rates of 12%-40% without any intervention[48]. However, combination antenatal prophylaxis taken over a longer duration is more effective than a short-course single drug regimen in reducing perinatal transmission[44]. Combination antiretroviral therapy reduce perinatal transmission by different mechanisms, including decreasing maternal antepartum VL and providing infant pre- and post-exposure prophylaxis. Therefore, combined antepartum, intrapartum, and infant ARV prophylaxis is recommended by international guidelines (National Institute of Health, European AIDS Clinical Society, British HIV Association) to prevent perinatal transmission of HIV (strong level of evidence)[30, 44, 49].

Table I. Overview of major PMTCT interventions (randomized control trials) [41-43, 45, 50-54]

Intervention	Author	Year	Setting	Breastfeeding	Intervention	Results (MTCT%)	n	*p*
Caesarean section	European Mode of Delivery Collaboration	1999	Europe	no	201 C/S delivery vs 235 vaginal delivery	3.4% at 18 m vs 10.2% at 18 m	***436***	*P*<0.001
Zidovudine	Connor, E. et al PACTG 076	1994	USA/France	Only 1 mother in the placebo group (baby was not infected)	ZDV pregnancy & IV ZDV labour, oral ZDV baby 6 w vs Placebo	8.3% at 18 m vs 25.5% at 18 m	***402***	*P*=0.00006
	DITRAME	2000	Ivory Coast	yes	ZDV mothers 36 to 38 w gestation, labour & 7 days post delivery vs Placebo	19.8% at 18m vs 29.75% at 18m	***431***	*P*=0.03
	RETRO-CI	1999	Ivory Coast	yes	ZDV mothers from 36 w + labour vs Placebo	12.2% at 4w vs 21.7% at 4w	***280***	*P*=0.05
	Thai-CDC Shaffer, N. et al	1999	Thailand	no	ZDV mothers from 36w + labour vs Placebo	9.4% at 6 m vs 18.9% at 6 m	***1140***	*P*=0.006
ZDV+3TC	PETRA	2002	Tanzania-Uganda-South-Africa	yes	arm1 ZDV-3TC mothers from 36w+labour+7days PP AZT-3TC newborns 7 days arm2 as arm 1 without prepartum component arm3 only intrapartum AZT-3TC	arm1 5.7% & 15% at 6w & 18 m arm2 8.9% & 18% at 6w & 18 m arm3 14.2% & 20% at 6w & 18 m	***1797***	*P*=0.001* 6w NS 18m (vs placebo) *P*=0.025 6w NS 18m (vs placebo) *P*=0.74 6w NS 18m (vs placebo)
Long ZDV vs Short ZDV	PHPT Lallemand, M. et al	2000	Thailand	no	ZDV mothers from 28w ZDV newborns 6w vs ZDV mother from 35w ZDV newborns 3d	4.1% at 6m vs 10.5% at 6m	***1437***	*P*=0.004
sdNVP vs IP and PP ZDV	HIVNET 012	2003	Uganda	yes	sdNVP mothers labour sdNVP newborns vs ZDV mothers labour ZDV newborns 7d	15.7% at 18 m vs 25.8% at 18 m	***616***	*P*=0.0023

*Efficacy of arm 1 and 2 disappeared at 18 months due to MTCT through breastfeeding

Table I (next). Overview of major PMTCT interventions (RCTs) [28, 29, 41, 55, 56]

Intervention	Author	Year	Setting	Breastfeeding	Intervention	Results	n	*p*
sdNVP vs Short ZDV	Chung, M.H. et al	2005	Kenya	Yes	sdNVP mothers labour sdNVP newborns vs ZDV mothers from 34w +labour	6.8% at 6w** vs 30.3% at 6w	***76***	*P*=0.02
NVP vs NVP+ZDV	Taha, T.E. et al	2003	Malawi	Yes	sdNVP newborns after birth vs sdNVP newborns after birth + ZDV 7d	15.3% at 6-8w vs 20.9% at 6-8w	***1119***	*P*=0.03
Triple cART vs others	Kesho Bora	2011	Kenya, Burkina-Faso, South Africa	Yes (mixed feeding)	ZDV-3TC-LPV/r mothers from 28-36w until cessation breastfeeding (max 6.5m) sdNVP newborns + 7d ZDV vs ZDV mothers from 28-36w sdNVP mothers labor ZDV-3TC mothers 7d PP sdNVP newborns + 7d ZDV	5.6% at 12m (in breastfed infants) vs Shapiro et al[27] 10.7% at 12m (in breastfed infants)	***882***	*P*=0.02
Triple cART vs Triple Cart	Mme Bana Shapiro R.L. et al	2010	Botswana	Yes	ABC+3TC+ZDV mothers from 26-34w until 6 m PP sdNVP newborns after birth + 4w ZDV vs ZDV+3TC+LPV/r mothers from 26-34w until 6 m PP sdNVP newborns after birth + 4w ZDV	2.1% vs 0.4%	***560***	NP

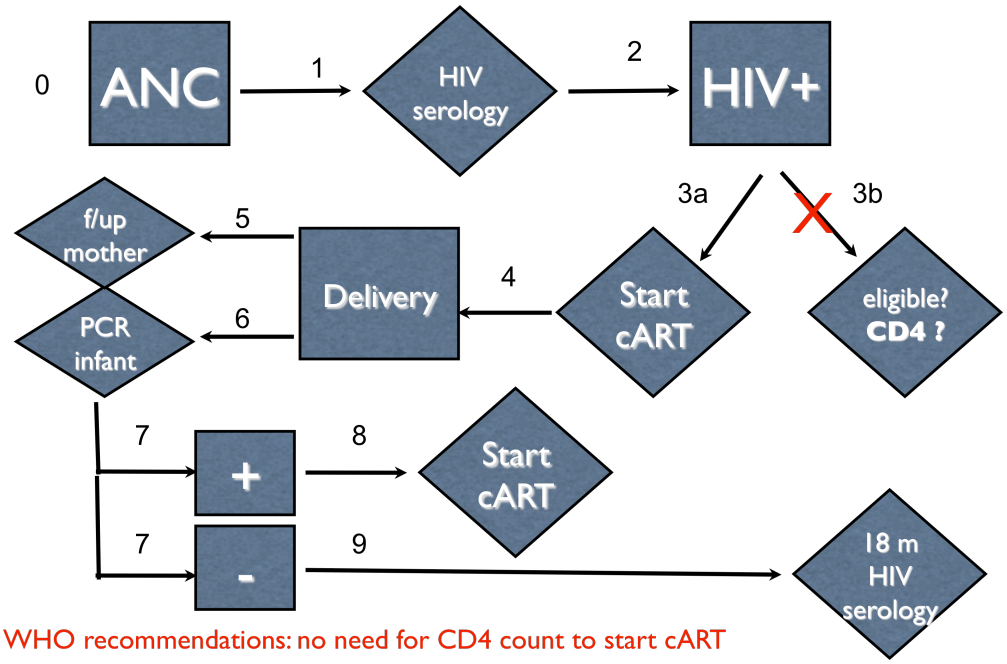
NP : not powered to compare difference in HIV-transmission

** sustained viral suppression in breastmilk in single dose nevirapine (sdNVP) group

2. BARRIERS TO ACHIEVE EFFECTIVE PMTCT

Despite demonstrated efficacy from clinical studies, there are many challenges in RLS to achieve effective PMTCT. Interventions to assure PMTCT have been exposed in the PMCT cascade (Figure 2). PMTCT cascade is a tool used to assess program coverage, defined as the final product of a crucial pathway of events that must be put in place to assure prophylaxis and access to treatment in HIV infected/exposed mother/infant pairs. One of the main challenges is to reach sufficient coverage and uptake of HIV testing for pregnant women after getting them into antenatal care (Figure 2 step 0 -1). In 2010, an estimated 35% of pregnant women in LMIC were tested for HIV compared to 8% in 2005[14]. This is an improvement but it is far from optimal. To increase HIV testing uptake rates, WHO is promoting the integration of HIV prevention, care and treatment services within maternal health programmes. In 2010, only 63% of pregnant women were tested in Uganda[57]. In this study, barriers for testing include lack of onsite testing facilities, lack of male partner support and distance to health facilities[57]. Retesting during pregnancy is another important issue and potential barrier to efficient PMTCT (Figure 2 step 4-5). At first HIV testing some women will be tested negative because they are in the serological window period. Other seronegative women will get infected during late pregnancy or during breastfeeding[58]. Retesting strategy during late pregnancy or at labour has been shown to be CE in comparison to a single test in endemic countries[59, 60]. In the first study, 3482 infant infections were expected if only the initial HIV test was offered but retesting women at 34 weeks of gestation (after initial test at 20 weeks) would prevent 76 new paediatric infections and was CE if ART is available to treat children[59]. In the second study, different strategies were compared using one or 2 tests during pregnancy and/or using confirmatory HIV-RNA testing by PCR[60]. The strategy of repeating HIV serology at delivery was considered CE with 415 765 life years saved and an incremental cost-effectiveness ratio (ICER) of 379 USD[60]. Once diagnosed, pregnant women need to access to appropriate care including cART (Figure 2 step 3a). Although PMTCT is well implemented in HIC, some gaps still exist. For example, in USA, important obstacles to elimination of MTCT include constant increase in HIV infection in women of childbearing age, absent or delayed antenatal care, especially in women using drugs; acute infection in late pregnancy and in during breastfeeding; lack of adherence to ARV regimens in pregnant women; and poor implementation of routine, universal prenatal HIV counseling and testing[44].

Figure 2. *PMTCT cascade*



X 2013 WHO recommendations: no need for CD4 count to start cART

ANC : antenatal care

0. Barriers of getting pregnant women into antenatal care
1. Barriers of testing women for HIV
2. Barriers of delivering HIV rapid test result to the patient

3a. Barriers of starting cART in pregnant women (all of them according to 2013 WHO guidelines)

3b. Barriers of getting CD4 count prior to start cART (in settings where ex-option A is still practiced (starting cART in pregnant women with less than 350 CD4/mm^3 and starting AZT from the 14th week of gestation in those women with more than 350 CD4/mm^3)

4-5 Barriers of adherence to cART and retetion to care of HIV-infected women

4-5 Barriers of retesting pregnant women at the time of delivery in endemic settings

6. Barriers of early infant diagnosis
7. Barriers of getting PCR results
8. Barriers of starting early cART in HIV-infected children
9. Barriers of confirming serostatus of children at 18 months

3. WHO PMTCT OPTIONS

In their last update on PMTCT, WHO is now recommending to start cART in all pregnant women irrespectively of CD4 count[61]. The goal is to facilitate scaling-up of PMTCT especially in settings where access to CD4 count is limited. Issues regarding those options and arguments in favour to one option over the other will be discussed in the point 4.4 of this chapter.

Table II. WHO options for PMTCT (2013 update)[61]

<table>
<tr><th rowspan="2">National PMTCT programme option</th><th colspan="2" rowspan="2">Pregnant and breastfeeding women with HIV</th><th colspan="2">HIV-exposed infant</th></tr>
<tr><th>Breastfeeding</th><th>Replacement feeding</th></tr>
<tr><td rowspan="2">Use lifelong ART for all pregnant and breastfeeding women ("Option B+")</td><td colspan="2">Regardless of WHO clinical stage or CD4 cell count</td><td rowspan="3">6 weeks of infant prophylaxis with once-daily NVP</td><td rowspan="3">4–6 weeks of infant prophylaxis with once-daily NVP (or twice-daily AZT)</td></tr>
<tr><td colspan="2">Initiate ART and maintain after delivery and cessation of breastfeeding</td></tr>
<tr><td rowspan="2">Use lifelong ART only for pregnant and breastfeeding women eligible for treatment ("Option B")</td><td>Eligible for treatment[a]</td><td>Not eligible for treatment[a]</td></tr>
<tr><td>Initiate ART and maintain after delivery and cessation of breastfeeding [b]</td><td>Initiate ART and stop after delivery and cessation of breastfeeding [b c]</td></tr>
</table>

a CD4 count ≤500 cells/mm3 or clinical stage 3 or 4 disease at the time of ART initiation or in accordance with national guidelines.

b Patients who develop clinical or laboratory criteria indicating failure during pregnancy or the breastfeeding period should be assessed for second-line therapy.

c In the case of breastfeeding stop ART one week after breastfeeding ends. In the case of replacement feeding stop ART after delivery

4. PMTCT WHO STRATEGIES : REVIEW OF COST-EFFECTIVENESS STUDIES

4.1 SETTINGS AND METHODS

Eight studies on PMTCT CE were published in the last 5 years (2008-2013) with a large spectrum of results[62-69]. Heterogeneity comes from various factors like the area of intervention, the level of the country's health expenditure and the urban/rural environment. All except one study was conducted in sub-Saharan Africa. All but one study used sensitivity analysis; Schmidt et al. made a cost-comparison but not using common variables such as ICER or Disability Adjusted Life Year (DALY)[64]. Number of HIV-infected babies at birth was only reported in 2 studies for the year 2009 with 67000 to 125 000 and 110 000 new infections per year for Nigeria and Uganda respectively.

All except one study[64] were comparing WHO option B to other PMTCT strategies. In this last study, the objective was to see if costs of cART given during second and third trimester of pregnancy might be offset by the hypothetical lower costs of treating a decreased number of perinatally HIV-infected infants[64]. Two studies included option B+ in their CE analysis (CEA)[65, 69]. Table III includes the settings, methods and objectives or those 8 studies.

Table III. Settings and methods of studies on PMTCT cost-effectiveness (2008-2013)

	Setting	ANC HIV preval (%)	ANC PMTCT (%)	Interventions/objectives
Shah, M. (2011)	Nigeria	4	10%	Compare MSOC vs option B at 3 different levels of PMTCT coverage : 10-58-100%
Schmidt,NC. (2012)	Dom.Republic (Capital + La Romana)	2.5	ND	Could extra-cost of cART (vs sdNVP) be offset by reduced infant HIV infection?
Orlando S. (2010)	Malawi DREAM study	25.07	ND	Compare option B with no intervention*
Ciaranello, AL. (2012)	Zimbabwe	16	56	Compare 5 options : no intervention, sdNVP, option A, B and B+#
Kuznik, A. (2012)	Uganda (single rural hospital)	ND	51.6	Compare 4 options : no intervention, sdNVP, dual therapy or option B. Assessment for 18 months cART & lifelong cART**
Binagwaho A. (2013)	Rwanda	4.3	68 (year 2009)	Compare dual therapy with option B##
Robberstad, B. (2010)	Tanzania	2	ND	Compare PMTCT+ (option B) with sdNVP***
Fasawe, O. (2013)	Malawi	ND	23-31 (year 2010)	Compare option B+ with current practice###, option A and B

CEA : cost-effectiveness analysis, ND : no data ; SA : sensitivity analysis, CC : cost-comparison, MSOC : minimum standard of are (zidovudine + lamivudine from 34 weeks of pregnancy until 7 days post- partum and sd-NVP at delivery for mother and baby)

*Option B in this study: cART : stavudine/zidovudine + lamivudine + nevirapine (from 25th week of gestation until weaning breastfeeding at 6 months

= 10 months cART) ; # Clinical outcomes :HIV-infection risk at weaning, Maternal LE from delivery, Infant LE from birth ; economic outcomes: ANC costs, maternal HIV-related costs, infant healthcare costs. ** Clinical outcome : MTCT ; 1st study to evaluate CE for lifelong cART ; ##Children HIV infections averted and 18 months HIV free survival. *** Child infection averted = primary outcome ; ### Depending on availability and setting, sdNVP or dual-drug regimen or cART prophylaxis until cessation of breastfeeding.

4.2 COST-EFFECTIVENESS ANALYSIS RESULTS

In all studies including option B in their model, this strategy was more CE than simpler or no PMTCT intervention (table IV). For example in Nigeria, if option B is implemented at 58% ANC coverage instead of minimal standard of care (MSOC), this will prevent 3203 new vertical infections per year with an ICER/DALY averted of 113 USD. In 2 out of the 8 studies, option B+ was also included in the sensitivity analysis and was superior to all other options[65, 69]. In one of those studies, the 3 options (A, B and B+) were in fact similarly CE in preventing new paediatric infections compared to the practice they were using at the time but

option B+ had the advantage to increase maternal ten-year survival by more than four-fold. Option B+ will save more than 250,000 maternal life years compared to mothers receiving only option A or B[69].

Table IV. Results of cost-effectiveness of PMTCT studies (2008-2013)

Authors (years)	Infant HIV infection averted	ICER/DALY averted	ICER/HIV infection averted	DALY averted	Discount rate (%)	Cost-year currency	GDP per capita	Cost-effectiveness
Shah, M. (2011)	7680*	113*	3203*	230400*	3	2010 USD	1191** (year 2010)	Option B CE compared to MSOC
Schmidt,NC. (2012)	698	ND	ND	ND	ND	ND	ND	cART CE compared to sdNVP
Orlando S. (2010)	370	35	998	10449	3	2007 USD	667	Option B CE compared to no intervention
Ciaranello, AL. (2012)	ND#	ND****	ND	ND###	3	ND	400## (year 2008)	Option B+ CE compared to no interevention, sdNVP, option A and B.
Kuznik, A. (2012)	ND¶	46, 99, 34¶¶	ND	5.21, 3.22 and 8.58¶¶	3	2011 USD	490 (year 2009)	Option B CE compared to simpler interventions
Binagwaho A. (2013)	3863§	ND	11882§§	ND	3	570 RF= 1USD	ND	Option B CE compared to dual therapy
Robberstad, B. (2010)	0,0027/ pregnancyπ	162	4062	0,0067/ pregnancyπ	3	2007 USD	NDππ	Option B CE compared to sdNVP
Fasawe, O. (2013)	15606-15997ß	38-68-64ßß	844-1331-1265ßß	ND	ND	ND	310ßßß (year 2010)	Option B+ CE compared to simpler interventions

Compared with MSOC if implemented at 58% (current ANC coverage) ; ** per DALY averted ; # 18-month infant HIV infection risk 5.7% for option B+ compared to 7.5%, 14.2%, 24.8% for option A, sdNVP and no intervention respectively ; ## per year life saved (YLS); **** ICER/YLS : 1370 USD option B+ compared with option B ; ### Option B+ increases combined mother-infant LE to 39.04 y (from 36.03 without intervention) ; ¶ MTCT 3.8% with option B compared to 17.4%, 25.8% and 40% for dual therapy, sdNVP and no intervention respectively ; ¶¶ 18 months ART compared with sdNVP, dual therapy and no intervention for a cost per DALY averted of US$ 46, US$99 and US$34 ; § Number of infection averted with Sc HAART + replacement feeding compared to no intervention ; §§ Sc-HAART with 12 months breastfeeding (BF) : more children alive HIV-uninfected by 18 months than Sc-HAART with 6 months BF for ICER/child alive and uninfected of 11,882 USD ; π 5.2 times more effective than sdNVP (0.00051 infection and 0.013 DALYs averted per pregnancy) ; ππ if WTP is superior to 162 USD/DALY, the option B is CE ; ß Option A, B and B+ averted the same amount of new infant HIV infections ; ßß ICER/DALY averted and ICER/ HIV-infection averted for option A, B and B+ respectively (ICER/DALY averted compared to current practice) ; ßßß Option A, B or B+ have ICER/DALY averted less than 3x GDP per capita and are CE compared to current practice.

4.3 LIMITATIONS

There are several limitations in the comparison of those studies.

- One study was limited to a single rural hospital[68] limiting generalizability to other contexts.
- The model developed in Malawi may not be applicable to low prevalence setting, using replacement feeding or with low fertility[69].
- Two important factors were considered to influence CE in some studies; HIV prevalence and PMTCT coverage. If coverage is low, some more complex PMTCT interventions become less CE (MSOC more CE than option B in Nigeria)[63]. Similarly, in Zimbabwe, in mothers with high CD4 counts, poor adherence or loss to follow-up after delivery, projected maternal life-expectancy is superior with option A compared to option B[65]. In area with lower HIV prevalence, CE was improved when simulating higher prevalence such in Tanzania comparing sdNVP with option B. If HIV prevalence increases from 2% to 6.6%, ICER improves from 162 to 60 USD/DALY[68].
- Adherence was not taken into account in most of the studies [66, 67, 69].
- Estimating life-expectancy of HIV-infected children and the lifetime costs for ART was also challenging[63, 65].
- Another limitation is that studies do not account drug resistance (DR) and needs for 2nd or 3rd line treatment, important factors that could influence CE[65, 69].

4.4 DISCUSSION ON PMTCT COST-EFFECTIVENESS

Our review includes studies comparing option B with other PMTCT interventions. In light of those studies, it clearly appears that option B is CE compared to simpler strategies such as sdNVP or dual-therapy. In 2 studies including option B+ in their CEA, this last option pretends to be superior. The authors claim that B+ should be strongly considered for its numerous advantages.

Arguments pro option B+compared to option B

- Positive impact on retention in care with decreased risk for opportunistic infections (OIs) and prevention of maternal deaths with positive effect on child survival,

reduction of AIDS orphans and reduction of HIV transmission within discordant couples[70, 71].

- Simplicity as there is no need for CD4 testing to judge woman's eligibility to start cART (Figure 2 step 2b). This could improve PMTCT uptake in some countries such as Malawi where access to CD4 count is limited[72].
- Clear message for the community: once cART is started, it is for life. In Malawi, option B^+ was recently launched by the Ministry of Health in order to provide the best public-health approach adapted to their setting[73]. The chosen ARV regimen is the fixed-dose combination of tenofovir (TDV), 3TC and efavirenz (EFV). The efficacy of this regimen for hepatitis B-HIV coinfection is an added value as 10-15% of HIV-infected patients in Malawi are coinfected with hepatitis B.

Arguments against option B+ compared to option B

- Serious objections have been raised against option B+[74]. For those authors, current evidence for superiority of option B+ is lacking and this option could potentially disorganize HIV program by increasing workload and interfering with existing activities (eg : treatment of medically eligible HIV-infected patients).
- Current or future resources, including scarce health personnel, may be insufficient[74].
- Retention rates and adherence are unknown in pregnant women with no need of cART for their own health and long-term consequences on HIV DR could be negative (Figure 2 step 5)[74]. A meta-analysis shows that only 73.5% of pregnant women achieved optimal adherence to cART (adherence >80%) and that adherence was significantly lower during postpartum[75]. More recently a South African study showed that 57.5% (95% CI 51.6–63.3%) were lost between HIV testing and 6 months post-delivery[76]. However a recent report from Malawi shows a 12 months retention rate (77%) similar to the rate for all adults in the national program[77]. This represents a huge improvement compared to a previous study, showing that despite the fact that 9 on 10 women were tested for HIV in rural Malawi, more than three-quarters of this cohort was lost to follow-up by the 6-month postnatal visit[78].

Option B or Option B+?

A randomised trial (PROMISE study) comparing option B and B+ is ongoing and first results are expected for early 2016[79]. For the time being, each country will have to choose its own strategy according to existing resources and feeding practices. Option B+ is probably the best option for countries like Malawi and Mozambique with high fertility and long breastfeeding

period but not for South Africa where fertility is lower and breastfeeding is a less common practice.

During the last 10 years, we found 2 systematic reviews on PMTCT CE[80, 81]. In the first study, 9 studies were included. The quality of reporting was found to be lacking regarding amounts of resources required for interventions, and the methods for estimating health outcomes and unit costs. In this systematic review, more recent studies were showing more CE ratios than older studies due to lower drug costs and in some studies the use of shorter drug regimens[80]. In the second systematic review, the authors found 19 articles published from 1996 to 2010. Sixteen articles concluded that PMTCT intervention was CE compared to no intervention. Divergent results were found by 1 study, which analyzed long course AZT and reflected older (higher) drug costs, and 2 other studies, which considered very low HIV prevalence settings[81]. The authors conclude that in low HIV prevalence settings, PMTCT may offer a low relative value as compared to competing interventions to improve population health. In those 2 reviews, such as in ours, comparison of those studies was hampered by heterogeneity. The contexts are very different and the costs were contemporaneous to each study period and now outdated.

5. SAFETY ISSUES AND SURVEILLANCE AFTER ANTIRETROVIRAL EXPOSURE IN HIV-UNINFECTED CHILDREN

Despite the numerous advantages of PMTCT, surveillance of side effects in exposed infants is warranted in order to recommend the safest antiretroviral regimen during pregnancy allowing normal growth and development of HIV-exposed but uninfected (HEU) children. Growing evidence suggests that antiretrovirals are generally safe for both mother and baby[82]. Known side-effects are usually outweighed by the benefits of preventing HIV transmission. In a recent Cochrane review, no serious life threatening was observed in infants exposed to any of the ART regimen[41]. Mild anaemia was observed in infants exposed to ZDV, no case of lactic acidosis nor severe hepatoxicity were found in the different trials. The trials did not find a difference in growth patterns, occurrence of cancer or congenital defects although length of follow-up was not long enough in most of the trials to evaluate those outcomes[41]. In the USA,

the Antiretroviral Pregnancy Registry Report (01/01/1989-31/07/2012) on 14612 life births exposed to any antiretroviral drug did not show a significant increased of overall birth defect with the exceptions of didanosine (ddI) and nelfinavir (NFV) (modest increase and unclear significance)[83]. There is currently not clear evidence of association between ART and birth defects.

However some side effects have been observed at shorter or longer term in infants exposed to antiretrovirals through PMTCT. Table V is summarizing the main adverse events.

Table V. Short-term side-effects in HEU infants associated with cART administered for PMTCT

	Molecule				**Side-effect**		
	Zidovudine				Neonatal anaemia[84] Association with CHD[85, 86]		
	Lamivudine				Not known		
	Abacavir				Not known		
	Stavudine				Not known		
	Tenofovir				Potential lower length-for-age and head circumference-for-age z-scores at age 1 year in a cohort of 449 infants[87] Those results were not confirmed in DART trial with longer follow-up (4 years)[88]		
	Didanosine				Head and neck birth defects[86]		
	Nevirapine				Well tolerated		
	Efavirenz				Initially associated with neural tube defect[89] in case reports but not confirmed in larger studies and meta-analysis[90-92] Association with other neurological defects (pachygyria, agenesis of CC, hydrocephalus, cerebral cysts)[86]		
	Lopinavir/r				Risk of cardiac toxicity[93], adrenal dysfunction in neonates[44]		
	Atazanavir				Safe, hyperbilirubinemia monitoring[94]		

CC: corpus callosum

One major concern is the possible association of EFV use and neural tube defects in monkeys[89, 95]. In one study birth defect was observed more significantly in children exposed to EFV during the first trimester versus children not exposed to EFV (aOR : 4.31)[85]. In

another study on 1112 infants enrolled in the International Maternal Pediatric Adolescent AIDS Clinical Trials Group protocol P1025 born between 2002 and 2007, EFV was associated with a significantly increased risk of congenital anomalies (OR 2.84)[96]. However a recent meta-analysis did not confirm this association and is reporting similar birth defect prevalence for women exposed to first trimester EFV-exposed (2%) compared to women who were not exposed to EFV (2.9%) with a low incidence of neural tube defect (0.07%)[92]. In light of those reassuring data, current US guidelines allow EFV use in pregnant women treated with EFV-based regimen who present for antenatal care in the first trimester, considering there is virologic control on this regimen[44]. WHO is promoting use of EFV during pregnancy due to reassuring data. Review by the WHO of the available data and programmatic experience provides reassurance that exposure to EFV in early pregnancy has not resulted in increased birth defects or other significant toxicities[97]. Recently, the largest prospective study of birth defects in ARV-exposed infants was presented at the Conference on Retroviruses and Opportunistic Infections (CROI) in Atlanta[86]. The aim of this prospective French study was to estimate the prevalence of birth defects in HEU exposed to any ARV during the pregnancy and to find association of birth defect with individual ARV molecules. They included 13124 live births between 1994 and 2010. EFV exposure during first trimester was not associated with overall birth defects but was significantly associated with neurological defects (aOR 3.2 [1.1-9.1]), one case of pachygyria, one case of agenesis of corpus callosum, one case of hydrocephalus and one case of cerebral cysts. Interestingly they did not find any neural tube defect. Following those finding, the French guidelines recommend not to use EFV (at least during the first trimester) when other options are available[86].

A possible association of antiretroviral use during pregnancy and congenital heart defect (CHD) has been raised[82]. Zidovudine during the first trimester of pregnancy was specifically associated with CHD[85]. In the French study, exposure to ZDV during the first trimester was also significantly associated with CHD, mostly ventricular septal defects (aOR = 2.34 [1.39-3.94])[86]. As other studies the limitations are that only live births were assessed and that no information was provided on intercurrent drugs used during pregnancy. Further studies are required to understand the exact physiopathology of ZDV and possible mitochondrial toxicity on heart defects. Results from NRTI sparing ART for PMTCT will certainly add more knowledge in this field. Mitochondrial toxicity was first described in neonates exposed to ZDV[98-101]. This was finally never confirmed in larger studies[102-104].

In the large prospective French study, there was no concern about TDF use and birth defect[86]. Tenofovir is now recommended as first-line ART by WHO[105] and is increasingly used. This molecule is known to cause renal and bone toxicities[88] and concerns exist about potential toxicity in newborns exposed to in utero TDF. It was demonstrated that TDF crosses the placenta exposing the fœtus to relatively high concentration in utero[106]. Finally, preterm delivery was associated with use of protease-inhibitors (PIs)[107]. It is also not recommended to use LPV/r in premature babies because of potential cardiac toxicity and adrenal dysfunction[93].

In countries where optimal cART option is not available for PMTCT, concerns have been raised about potential emergence of resistance mutations following different suboptimal PMCT options. Resistance mutations can compromise futur therapeutic options in settings where few antiretroviral molecules are available. In a study performed in seven African countries, 241 women infected with HIV-1 who either received or not received single-dose nevirapine (NVP) at least 6 months before enrollment were randomly assigned to receive antiretroviral therapy with TDF-emtricitabine plus NVP (n=121) or TDF-emtricitabine plus LPV/r (n=120). The women in the NVP group experienced more virological failure than women in LPV/r group (26% vs. 8%) (adjusted *P*=0.001). There was no difference in women not exposed to NVP if they were subsequently treated either with NVP or LPV/r regimen[108]. It was also demontrated that HIV-infected children previously exposed to sdNVP were more likely to fail NVP-based regimen (39.6% virologic failure or discontinuation of treatment at week 24) compared to those treated with LPV/r based regimen (21.7%)[109].

What is the role for resistance testing to identify infants who would require a non-NVP based regimen?[110]. Although it is feasible and recommended in high-income countries[111] and particularly in case of treatment failure in a mother exposed to several antiretrovirals with potential transmission of resistant strain to the baby, the costs of this exam are likely to limit its usefulness in LRS.

- **PMTCT can decrease mother-to-child transmission to less than 1%**
- **PMTCT interventions are cost-effective compared to no intervention**
- **Combination antiretroviral is strongly recommended in all pregnant women**
- **Lifelong combination antiretroviral therapy after delivery in women who don't need treatment for their own health, in LMIC, is still under debate but is strongly promoted by WHO**
- **PMTCT effectiveness depends on coverage and strengthening of the cascade of care**
- **Antiretrovirals are generally safe for both infants and mothers; benefits outweight risks but constant monitoring and large-scale surveillance are mandatory**

Despite increasing effectiveness of PMTCT and reduced number of new perinatal infections, many infants are still infected each year with the need of early diagnosis and treatment. In the next chapter we will review the evidence for early treatment and the different treatment strategies.

CHAPTER III

1. COMBINATION ANTIRETROVIRAL THERAPY IN CHILDREN

Over the last two decades, therapeutic strategies for the treatment of HIV-infected children have been developed[39]. ***In November 2012, 19 ARV drugs were Food and Drug Administration (FDA)-approved for use in HIV-infected children.*** The majority of those antiretrovirals are available in different formulations such as liquid, powder, chewable tablet, or small capsule or tablet suitable for paediatric use. Antiretrovirals are classified into several major drug classes: nucleoside/nucleotide reverse transcriptase inhibitors (N/NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), PIs, entry inhibitors (including fusion inhibitors and CCR5 antagonists), and integrase inhibitors. An exhaustive list of the antiretroviral (ARV) drugs – including paediatric dosing, toxicity and drug–drug interactions – can be found in the National Institute of Health (NIH) guidelines at http://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf[39].

Current WHO and US recommendations for first line regimen regimen in children are summarized below:

What to start - WHO recommendations (June 2013 update)[61]

Children < 3 years of age :

LPV/r based regimen regardless of NNRTI exposure. If not feasible (eg LPV/r not available), NNRTI-based regimen should be used (Strong recommendation, moderate quality of evidence)
The recommended WHO backbones are o ABC or ZDV + 3TC or o d4T + 3TC (Strong recommendation; low quality of evidence)
In settings where VL monitoring is available, LPV/r could be replaced by NNRTI after virological suppression is sustained 6 and 12 months after ARV initiation (Conditional recommendation, low quality of evidence)

Children 3-12 years of age :

EFV is the preferred NNRTI for first line ARV treatment and NVP is an acceptable alternative (Strong recommendation; low quality of evidence)
ABC, TDF or AZT + 3TC or FTC are equally preferred NRTIs (Conditional recommendation; low quality of evidence)

Children above 12 years of age :

TDF is the preferred NRTI in combination with 3TC or FTC and AZT is an alternative NRTI for first-line ARV treatment. (Strong recommendation; low quality of evidence)

What to start -US recommendations (last update : november 2012)[39]

2 N/NtRTIs backbone + 1 NNRTI (NVP at any age, EFV in ≥ 3 y old children) or 1 PI (LPV/r after 14 days post-birth, ATV/r in in ≥ 6 y old children
Preferred NRTI backbone : ≥3 months old infants: ABC + 3TC or FTC • HLA-B*5701 genetic testing should be done prior to initiate ABC-based therapy • ABC is contra-indicated in a child who tests positive for HLA-B*5701 •
At any age: ZDV + 3TC or FTC
For adolescents: TDV + 3TC or FTC
Alternative regimens or to be used in special circumstances are available at NIH guidelines (page 84)[39]

Over time one can expect to see new molecules and drug combinations with demonstrated efficacy and acceptable toxicity profiles, which will increase therapeutic options for children. Because of the lack of FDA-approved treatment options, unlicensed drugs are often used at experimental dosages. Access to drugs is much more limited in countries with limited resources. Previous WHO guidelines was recommending to start NNRI-based regimen in all HIV-infected infants not exposed to PMTCT and particularly not exposed to sd-NVP[112]. The new WHO guidelines (2013) are now recommending to start a PI-based regimen regardless of previous NNRTI exposure in settings where it is feasible[61].

Should we start PI-based regimen in all infants ?

Data pro

In a large randomized trial (IMPAACT 1060) conducted in 6 African countries and India, HIV-infected children aged 6-36 months with no prior exposure to NVP were treated with either ZDV-3TC-NVP versus ZDV-3TC-LPV/r[109]. The primary end-point was treatment failure or treatment discontinuation at week 24. Primary end-point was reached by significantly higher percentage of children in the arm receiving NVP-based regimen (39.6% vs. 21.7%). Because of this significant outcome difference, the study had to be early interrupted on the recommendation of the data and safety monitoring board[109]. In this study, several factors might explain those results such as high baseline VL and selection for NVP resistance. More than half (19/32) of the children treated with NVP-based regimen with virological failure (and for who resistance testing was performed) were harbouring resistant virus to NVP at the time of virological failure (4 children at both baseline and the time of virologic failure; and in 12 more children by the time of virologic failure)[109]. However, there is still an ongoing debate about first line therapy in NNRTI non-exposed infants.

Data contra

In the Paediatric European Network for Treatment of AIDS (PENTA) and Pediatric AIDS Clinical Trials Group (PACTG/IMPAACT) (PENPACT)-1 trial (PENTA 9/PACTG 390), no difference was observed in term of virological failure between children initiated on PI-based regimen and those started on NVP after 4 years of follow-up[113]. However in this study, NFV was used in 48% of the patients treated with PI; NFV is less potent due to pharmacokinetic

issues and no more recommended for children. Nevertheless, data from an observational cohort of 437 European infants beginning either PI- or NNRTI- based ART and followed for a median of 5.9 years showed no significant difference in virological outcome between PI and NNRTI groups[114].

Three other issues make use of LPV/r more difficult in LMIC :

- The cost; for a child weighing 10 kg, a NNRTI-based regimen will cost 100 USD versus >300 USD for PI-based regimen[115].
- The taste; currently only a liquid formulation is available and palatability is poor.
- LPV/r syrup needs to be kept in fridge and cold chain could be an issue in some remote area. A new LPV/r formulation has been developed by Cipla (sprinkles 40/10 mg) and the first pharmacokinetic data from CHAPAS-2 presented at IAS 2012 and CROI 2013 in Atlanta are encouraging ; no subtherapeutic concentrations were observed and carers preferred this formulation to syrup for transport and storage issues. No difference in child acceptability was reported[116].

An alternative, suggested by NEVEREST trial, is to start PI-based regimen until VL is suppressed and then to switch to NVP-based cART. This strategy could preserve LPV/r for 2nd line and limit long term toxicity (metabolic side effects, see also chapter III 3.3) with reduced cost and limited adherence challenges for the caregivers[117]. In NEVEREST, in the short term, the switch strategy was associated with better CD4 and better growth in the children switched to NVP compared to the children kept on LPV/r-based regimen. Virological failures only occur within the first year after switch. Switching children once suppressed to a NVP-based regimen might be a potential option provided the fact that adequate virological monitoring can be performed[117]. A similar approach is under investigation in the NEVEREST-3 trial which is assessing a switch of LPV/r to an EFV-based regimen. The hypothesis is that switching to a regimen based on efavirenz will be as effective and safe as remaining on a regimen based on lopinavir/ritonavir.

Which NRTI backbone should we used ?

The Paediatric European Network for Treatment of AIDS (PENTA) 5 trial has shown that the association of ABC + 3TC was superior to ZDV + 3TC with largest and more durable decreased in VL, after controlling for baseline factors and use of NFV[118]. Safety profile of

ABC was comparable to adults. The mutations induced by ABC use (mostly M184V) and specific mutations (K65R, L74V, T215Y) do not impair susceptibility to ZDV which can be used in 2nd line therapy[118]. Tenofovir was recently approved by the US FDA and European Medicines Agency (EMA) for children aged ≥2 years. Its cost is inferior to ABC and if resistance to TDF develops, susceptibility to ZDV as 2nd line therapy is conserved. Paediatric TDF formulations have very recently been developed in doses of 150 mg, 200 mg and 250 mg for children aged 6 to 12 years, as well as an oral powder formulation to support dosing in paediatric patients aged 2 to 5 years. However, there are no paediatric fixed drug combinations (FDCs) containing TDF, and adult tablets are not scored. Issues regarding bone and renal safety of TDF in young children mandate long-term assessment. Another ongoing important 96 weeks trial, CHAPAS-3, will compare virological response, resistance and toxicity of ABC versus ZDV associated with NNRTI as first line therapy. This will provide complementary data on acceptability, toxicity and pharmacokinetics of different FDCs (ABC+3TC, ZDV+3TC and d4T+3TC all with NVP or EFV).

When to switch to second line treatment ?

The PENPACT 1 trial also compared children switching at ≥ 1000 copies/mL versus those switching at ≥ 30 000 copies/mL[113]. Robustness of PI-based regimen was confirmed by few PI mutations and protection of NRTIs in developing thymidine-associated mutations (TAMs). In fact, there was 10% extra NRTI resistance (predominantly TAMs and M184V) in the delayed switching NNRTI arm. NNRTI resistance was not avoided by switching at a lower VL threshold of 1000 copies/mL vs 30 000 copies/mL[113]. In the Children with HIV Early Antiretroviral (CHER) study, 5 years after randomization, only 2/32 children with VL >1000 copies, and having a resistance testing done, were harbouring a virus with 2 major PI mutations (V82A/L76V)[119].

In RLS, switching to 2nd line is often delayed or not done for several reasons, challenges in diagnosing treatment failure, lack of therapeutic options, lack of virological monitoring or absence of resistance testing. In 2010, it was estimated that only 3% of children in RLS were on 2nd line regimen[120]. Outside operational research, controlled trials such as CHER or ARROW are showing excellent response to first line therapy with respectively 84% and 83% of virological success (defined as VL < 400 copies/mL) after 5 years for CHER and 3.7 years for ARROW[119, 121].

What to switch to ?

Studies on children switching from NNRTI-based regimen to LPV/r-based regimen show reassuring results with 81%-88% of children obtaining VL<400 at 48 weeks after switch[122, 123]. When the treatment sequence is in this way, it is straightforward but a contrario if the child is failing a first line containing PI, NNRTI-based regimen will be the only available option in many settings where resources are limited and where alternatives with ritonavir (RTV)-boosted darunavir (DRV/r) is very expensive and FDCs do not exist to date. DRV/r is a robust option in children failing LPV/r even if they were treated for years with LPV/r[124].
Antiretroviral regimens should be chosen based on treatment history and current and previous resistance testing to optimize ARV drug effectiveness. New regimens should contain at least two, but preferably three, fully active drugs for durable, potent virologic suppression[39].
Current WHO and NIH guidelines for second line regimen are found in appendix 5.

2. COMBINATION ANTIRETROVIRAL THERAPY : EARLY DIAGNOSIS AND TREATMENT WITH cART IN HIV-INFECTED INFANTS

2.1 EARLY INFANT DIAGNOSIS

2.1.1 Early diagnosis : trend

As discussed in Chapter I, only 28% (25–31%) of children 0–14 years old eligible for treatment were effectively receiving cART in 2011, lagging significantly behind the 58% coverage for adults[6]. One explanation for this low number is that few of these children are being diagnosed and, as a consequence, not enrolled in paediatric HIV care. Globally, access to early infant diagnosis (EID) among HIV-exposed infants remains alarmingly low at 28 per cent in 2011, up from just 6 per cent in 2009[120]. On the basis of current estimates, more than 1 million infants born to HIV positive mothers went without a polymerase chain reaction (PCR) test at 6 weeks[120].

However, by increasing geographic access, integrating EID with vaccination programs, and investing in a robust mobile phone reporting system, Rwanda has increased coverage of EID from 28 to 72.4 per cent (more than 250% increase) among all HIV-exposed infants (approximatively 390 000 children are newly infected with HIV each year) between 2008 and 2010[125]. Between 2008 and 2011, the performance of routine PCR in south-african HIV-exposed infants younger than 2 months increased from 36.6% to 70.4%[126].

2.1.2 Early diagnosis : barriers and advantages

There are several barriers for EID. The costs of early diagnosis in infants is high[127, 128]. Diagnosis of HIV infection in young infants (less than 18 months) requires polymerase chain reaction (PCR) techniques, that are more costy than classical serological tests used in older children and in adults. Very limited data exist on CE of EID. One study showed rapid HIV test screening CE before a PCR was used[129]. Other issues include difficulties in reaching infants for testing, technical problems such as blood collection, transport of the specimen to the appropriate laboratory, work overload of laboratories performing PCR resulting in delayed results, returning results to the concerned patients and linking HIV-infected infants to care[38]. Table VI is summarizing barriers for EID and potential interventions to improve EID and early treatment in HIV-infected infants.

Table VI. Barriers to early infant diagnosis and treatment

Barriers to early EID and early cART in infants	**Interventions to improve early identification of young children with HIV**
Lack of integration of PMTCT with other mother-infant programs (immunization, nutrition etc..)*	One day training for lay HIV counsellors
Missed opportunities to post-natal diagnosis of HIV-infection	Documentation of HIV status for all children
Challenges in diagnosis (needs for PCR, low sensitivity and specificity of clinical algorithms)[133]	HIV testing during immunisation campaigns
Lack of laboratory capacity, transport problems	Clinical staging for all HIV positive children
Lack of trained staff to recognize and/or treat and/or refer HIV-infected children	Referral of all sick HIV exposed children for medical assessment
Lack of suitable and palatable paediatric formulations	Link with tuberculosis and malnutrition programmes
Lack of cold chain (eg : for use of LPV/r syrup)	HIV testing for children in hospital
Lack of prioritization in programs	Feedback of progress to clinic staff

*sometimes due to « vertical HIV program »

However, EID has clear advantages. An early negative virological test (PCR) for HIV-exposed infants provides reassurance to families and caregivers may more readily bond with a child known to be HIV-uninfected[130]. On the other hand, EID allows early treatment in those who are infected. An ongoing trial (NCT01433185) is evaluating if text messages sent through mobile phones to women enrolled in PMTCT programs could increase uptake of DNA PCR HIV testing at 6-8 weeks among infants exposed to HIV.

2.2 EARLY cART FOR TREATING HIV-INFECTED INFANTS

2.2.1 Rationale for early treatment

Since 1996, some countries, such as Belgium, elected to treat HIV-infected infants as soon as the diagnosis was established hoping by this way to avoid mortality and to reduce early morbidity such as HIV-encephalopathy[1]. A this time, this strategy was controversial. In an observational study, infants started on cART before 6 months of age did not suffer from severe form of HIV such as encephalopathy[131]. In Belgium, 17 infants started on cART before

66 days of life had a positive outcome with no progression to AIDS or death. In this study, viral suppression was obtained with the first regimen (PI-sparing regimen) in 71% of the subjects. The treatment was well tolerated with only one patient who experienced side effects. Among the 12 patients who achieved initial viral suppression, 6 of them became seronegative before the age of 19 months[1]. Other studies showed similar results[132-134].

More evidence came out in 2008 with CHER study[2]. This major randomized control trial provided evidence supporting early initiation of cART. In the CHER study, asymptomatic infants, aged 6–12 weeks, were initiated on cART as soon as feasible after the diagnosis of HIV infection (median age of 7 weeks)[2]. After 40 weeks of median follow-up, a 76% decrease in early mortality and a 75% decrease in HIV progression was observed in early starters compared to those starting cART at a median age of 6 months based on the 2006 World Health Organization (WHO) immunological or clinical criteria[2, 135]. Later on, a retrospective European study showed that infants started on cART before 12 weeks of age were five times less likely to develop AIDS or die in infancy[136]. Six years after randomization, CHER is still showing better outcome in early treated children with at least 2-fold higher number of deaths the cART deferred arm[137]. Therefore, until June 2013, WHO guidelines were recommending early cART in the 2 first years of life regardless of CD4 or clinical criteria[138]. This age extension was proposed not following strong data but due to the fact that risk of disease progression and mortality is still high between 1 and 2 years of age with poor prognosis markers for clinical progression[112]. New WHO guidelines released on June 30th 2013 aim to improve cART coverage and retention in care in children by considering universal treatment in all less than 5 years old children in settings where immunological testing facilities are limited and/or treatment coverage is low (Table VII)[61]. A recent Cochrane review concludes that immediate ART reduces morbidity and mortality among infants and may improve neurodevelopmental outcome[139]. Immunological response is also better in early treated infants with higher CD4 percentages until 1 year compared to infants who benefited from deferred treatment[140]. However, there are minimal data on the outcome of large early treatment cohorts from RLS, outside a well-controlled research environment.

Table VII. When to start – June 2013 WHO guidelines [61]

<Age	Criteria	Recommendation
All children	WHO clinical stage 3 or 4 regardless of age or CD4 count	Treat **(Strong recommendation, moderate quality of evidence)**
< 12 months old	Regardless of clinical or immunological criteria	Treat **(Strong recommendation, moderate quality of evidence)**
12-59 months old	Regardless of clinical or immunological criteria If limited access to CD4 testing If high endemic setting with low paediatric ART coverage	Treat **(Conditional recommendation, very low quality of evidence)** **Children < 2 years=priority**
12-59 months old	WHO clinical stage 3 or 4 or CD4 count ≤ 750 cells/mm^3 or CD4% ≤ 25%	Treat **(Strong recommendation, very low quality of evidence)**
> 5 y old	WHO clinical stage 3 or 4 or CD4 count ≤ 350 cells/mm^3	Treat **(Strong recommendation, high moderate quality of evidence)**
> 5 y old	WHO clinical stage 3 or 4 or CD4 count 350-500 cells/mm^3	Treat **(Conditional recommendation, very low quality of evidence)**

Table VIII. When to start – 2012 US guidelines [39]

Antiretroviral therapy (ART) should be initiated in all children with AIDS or significant symptoms (Clinical Category C or most Clinical Category B conditions) **(AI*)**

• ART should be initiated in HIV-infected infants <12 months of age regardless of clinical status, CD4 percentage or VL (**AI** for infants <12 weeks of age and **AII** for infants ≥12 weeks to 12 months).

• ART should be initiated in HIV-infected children ≥1 year who are asymptomatic or have mild symptoms with the following CD4 values:

- **Age 1 to <3 years**
  - with CD4 T lymphocyte (CD4 cell) count <1000 cells/mm3 or CD4 percentage <25% **(AII)**
- **Age 3 to <5 years**
  - with CD4 cell count <750 cells/mm3 or CD4 percentage <25% **(AII)**
- **Age ≥5 years**
  - with CD4 cell count <350 cells/mm3 **(AI*)**
  - with CD4 cell count 350–500 cells/mm3 **(BII*)**

• ART should be considered for HIV-infected children ≥1 year who are asymptomatic or have mild symptoms with the following CD4 values:

- **Age 1 to <3 years**
  - with CD4 cell count ≥1000 cells/mm3 or CD4 percentage ≥25% **(BIII)**
- **Age 3 to <5 years**
  - with CD4 cell count ≥750 cells/mm3 or CD4 percentage ≥25% **(BIII)**
- **Age ≥5 years**
  - with CD4 cell count >500 cells/mm3 **(BIII)**

• In children with lower-strength (B level) recommendations for treatment, plasma HIV RNA levels >100,000 copies/mL provide stronger evidence for initiation of treatment **(BII)**.

• Issues associated with adherence should be assessed and discussed with an HIV-infected child's caregivers before initiation of therapy **(AIII)**. Patients/caregivers may choose to postpone therapy, and on a case-by-case basis, providers may elect to defer therapy based on clinical and/or psychosocial factors.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, non-randomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, non-randomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar non-randomized trials or cohort studies with clinical outcome data; III = expert opinion

† Studies that include children or children and adolescents but not studies limited to postpubertal adolescents

2.2.2 Operational study in KwaZulu-Natal

The purpose of this study is therefore to demonstrate the feasibility of treating infants in a busy government clinic located in a poorly resourced South African township area. We describe the response to cART in a cohort of infants over an 18-month period, analyzing changes in growth, haematological, immunological and virological parameters.
A retrospective chart review was performed for all HIV-infected infants initiated on cART between 1 May 2005 and 31 May 2008 at the Edendale Family Clinic Pietermaritzburg, KwaZulu-Natal (KZN), South Africa, where >1000 children were on treatment during this period.

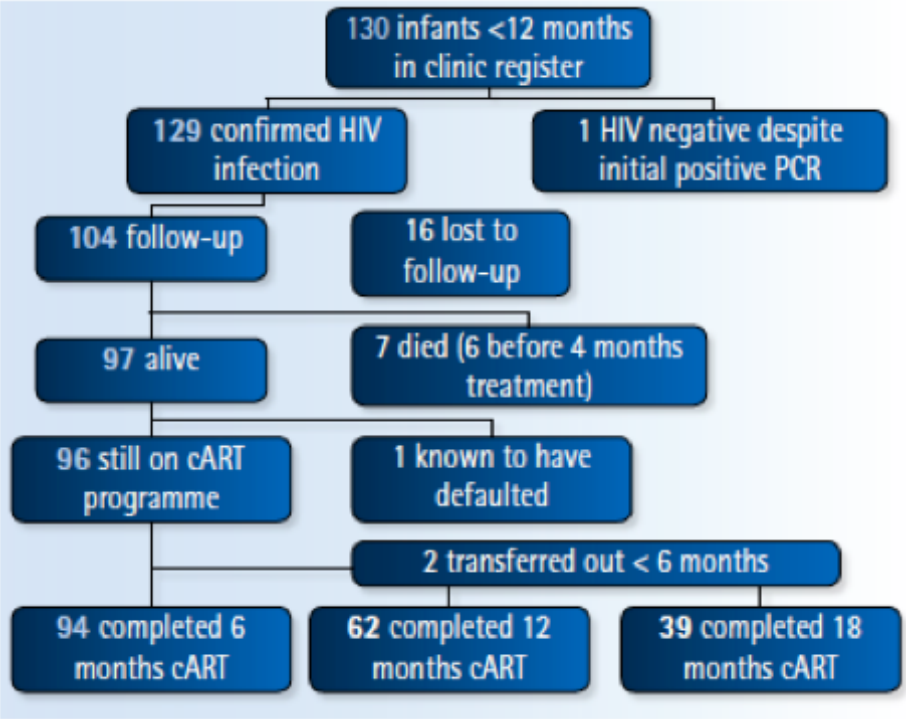
All HIV-infected infants who were <1 year of age at cART initiation and had completed at least 6 months of treatment were included in the study. Eligibility criteria for initiation of cART changed during the study period. Between May 2005 and May 2007, these included a positive HIV-1 DNA PCR, WHO stage 3–4 and/or CD4% <25%. From May 2007 to 31 May 2008, infants with WHO stage 2 and/or CD4 <30% were also included. Eligibility also required the presence of two reliable caregivers to facilitate treatment adherence. cART was administered according to 2005 National South African guidelines[141] in doses based on the infant's weight and adjusted in line with changing weight during monthly follow-up visits. After 6 months on treatment, follow-up was reduced to 3-monthly visits where appropriate. For <6 months old infants RTV-boosted lopinavir (LPV/r) dosages (300/75 mg/m2 twice daily)[142] were given with the parent's consent (at the time of this study, this dosage was under study investigation[142]). Adherence checks consisted of one-to-one counselling, recording of monthly visits and collection of leftover medication.

There was no mechanism for tracing children lost to follow-up (LTFU). Study variables included: (i) gender; (ii) documentation of perinatal exposure to sdNVP, intervention for PMTCT during the study period; (iii) WHO clinical stage[138]; (iv) Weight-for-age Z scores, CD4%, HIV-1 VL and haemoglobin were collected at initiation of cART and at 6-month intervals; (v) hospital admissions from birth to initiation of cART and all admissions thereafter; (vi) Tuberculosis (TB) status recorded at initiation of cART and occurrence of Bacille Calmette-Guerin (BCG) Immune Reconstitution Inflammatory Syndrome (IRIS) was documented at 6-month intervals.

Weight-for-age Z scores including means were analyzed using Emergency Nutrition Assessment software (ENA 2010 version). Other data were analyzed using SPSS Statistics 18 package (SPSS inc., Chicago, IL). The Mann–Whitney U test was used for inter-group comparisons.

During the study period, 1441 children were initiated on cART of which 129 were infants. Ninety-four subjects (43 females and 51 males) had sufficient data for analysis. Sixty-two subjects completed 12 months and 39 completed 18 months of cART (Figure 3).

Figure 3. Flowchart of HIV-infected infants



Infants were started on cART at a median age of 8.6 months. Sixty-five percent had documented exposure to sd-NVP at birth. Seventy-seven percent of those with WHO staging had stage 3 or 4 disease. The infants were severely malnourished, with a mean weight-for-age Z-score of -2.7 (Table IX). Only three infants had a weight-for-age Z-score superior to 1.0 prior to cART. Median VL at baseline was 6.2 log10 copies/ml and median CD4% was 15.4%.

Thirty-eight subjects (40.4%) were on TB treatment at initiation of cART and four patients

(4.3%) were on isoniazid (INH) prophylaxis because of household TB exposure (Table IX). Baseline characteristics were not significantly different in those receiving 18 months of cART (39 subjects) compared to those who did not (55 subjects) except for the baseline CD4%, which was significantly lower in those who underwent 18 months of cART; [14% (range.0.8–28.8) versus 17.7% (range.0.1–43.4); *p*=0.005].

Table IX. Baseline characteristics of the 94 infants who completed at least 6 months of cART

Clinical		
Age (months); median (range)		8.6 (2.1-11.9)
Sex ratio (M/F)		51/43 (1.2)
sdNVP; n (%)		
yes		61 (64.9)
no		25 (26.6)
ND		8 (8.5)
WHO stage; n (%)		
1		12 (12.8)
2		9 (9.6)
3		25 (26.6)
4		46 (48.9)
ND		2 (2.1)
Mean ± SD of Weight for Age Z-score; **n=86**		-2.7±1.97
Tuberculosis; n (%)		
INH prophylaxis		4 (4.3)
TB treatment		38 (40.4)
	started<2 months	29/38 (76.3)
	started>2 months	9 /38 (23.7)
Immunological		
CD4%; median (range); **n=94**		15.4 (0.1-43.4)
Virological		
Plasma HIV-RNA (log10 copies/ml); **n=73**		
median		6,2
range		1.4-7.9
≥7		10
6-7		33
5-6		20
<5		10

Treatment

Seventy-four subjects (78.7%) were started on the standard South African regimen [141] of stavudine (d4T), 3TC and LPV/r. Children on TB treatment prior to starting cART received either a double dose of LPV/r, which is no longer recommended[143, 144], or extra RTV boosting to obtain a LPV/RTV ratio of 1:1[145]. Some of the youngest infants (n=16) were started on ZDV instead of d4T, due to concerns about accurate dosing with the dissolved 20 mg d4T capsules. Four infants (4.2%) with no previous exposure to sdNVP as part of the pMTCT program were started on NVP instead of LPV/r. Only four infants changed regimen during the study period, three due to initiation of TB treatment, and one switched from ZDV-3TC-NVP to ZDV-3TC-LPV/r due to virological failure.

Follow-up on cART

At the time of data collection, all 94 infants who had completed at least 6 months of cART were alive and in follow-up. By 6 months of cART, VL was undetectable in 46 out of 88 infants (52.3%) and was <400 copies/ml in 75% of subjects. After 1 year of cART, viral suppression (VL<50 copies/ml) was achieved in 33 out of 58 infants (56.9%) and was <400 copies/ml in 77.6% of them. Undetectable VL (VL<50 copies/ml) was found in 26 of the 33 (78.8%) children reaching 18 months; data was missing for six subjects. The CD4 percentage increased from a median of 15.4 to 33.1% in 35 of the 39 subjects completing 18 months of cART (Table X). The number of hospital admissions decreased steadily. Prior to baseline, 70 out of 94 subjects (74.5%) had been hospitalized at least once since birth. At 6, 12 and 18 months on cART in cohorts, 24.5, 12.9 and 2.6% of subjects, respectively, had been admitted to hospital at least once in the preceding 6-month period. Their nutritional status improved with the weight-for-age Z score increasing from a mean of –2.7 at initiation of treatment to 0.02 after 18 months of cART. Haemoglobin increased from a median of 9.7 to 11.6 g/dl at 6 months with no change thereafter (Table X). A presumptive diagnosis of BCG IRIS, presenting as
axillary lymphadenitis, occurred in 13 of 94 infants (13.8%), all within the first 6 months of cART.

Table X. Clinical, Immune and Virological Outcomes at 6 monthly intervals in cohorts

	cART initiation (n=94)	6 months cART (n=94)	12 months cART (n=62)	18 months cART (n=39)
Mean ± SD of W/A[a] Z-score	-2.7±1.97	-0.51±1.39	-0.05±1.25	0.02±1.10
missing data	8	7	2	0
CD4%				
median	15,4	22,7	30,6	33,1
range	0.1-43.4	4.7-66.9	7.5-48.7	9.7-46
missing data	0	2	3	4
Plasma HIV-RNA (log_{10} copies/ml)				
median	6,2	1,4	1,4	1,4
range	1.4-7.9	1.4-5.9	1.4-5.1	1.4-3.8
Plasma HIV-RNA (copies/ml)				
median	1700000	25	25	25
range	<25-89000000	<25-850000	<25-87000	<25-6500
<50 copies/ml	1/73 (1.4%)	46/88 (52.3%)	33/58 (56.9%)	26/33 (78.8%)
<400 copies/ml	1/73 (1.4%)	66/88 (75%)	45/58 (77.6%)	29/33 (87.9%)
missing data	21	6	4	6
Hemoglobin (g/dl)				
median	9,7	11,6	11,9	11,7
range	7.2-20.2	6.9-13.6	9.7-15.7	9.7-14.1
missing data	7	10	11	2
Number of hospital stays[b]				
0; n(%)	19 (20.2)	70 (74.5)	52 (83.9)	38 (97.4)
1; n(%)	48 (51)	22 (23.4)	8 (12.9)	1 (2.6)
≥ 2; n(%)	22 (23.4)	1 (1.1)	0	0
BCG IRIS[c]	NA	13/94 (13.8%)	0	0

[a] Weight-for-age Z-score; [b] Number of hospital stays : prior to start cART (cART initiation) – during the 6 previous months (6-12-18 months cART)
[c] Immune Reconstitution Inflammatory Syndrome

Studies in both well-resourced and resource-poor countries have documented good nutritional, immunological and virological responses to cART in older children[146-149]. In contrast there are very few studies documenting outcomes in young children and/or infants in RLS[2, 150-152]. A Doctors Without Borders (DWB) study on large-scale cART in children aged less than 5 years old showed encouraging outcomes, although infants still represented the minority (9%) of all treated children[153]. Similarly, in our clinic, 9% of all treated children during the study period were infants. This probably reflects delayed diagnosis and a national policy to initiate cART only after the age of 6 months. This chart review of 94 infants from a township in KZN shows a good early response to cART, despite very high baseline VL and clinically advanced disease. This advanced clinical presentation can be explained by comparatively old age at initiation of treatment (median age 8.6 months), as the chance of developing AIDS is dramatically lower if cART is started early in life[2]. These results are comparable with the DWB study, in which 70.7% of 307 infants starting cART at a median age of 8.4 months presented with stage 3 or 4 disease[153] but differ from the younger median age and less advanced stage shown in early treated infants from randomized trials[2, 151]. Advanced disease is also well reflected in our study by an early mortality rate of 7% (Figure 3) which is in line with previously reported data[2]. In our study, virological suppression rates were similar to those seen in the few available published studies [1, 133, 134, 152] but inferior to a clinical trial from KZN[151]. In that particular study, Prendergast et al. showed that 100% of 49

infants achieved viral suppression to <400 copies/ml and 94% to <50 copies/ml after 1 year of cART. However, these subjects were treated with four-drug cART and, as discussed by the authors, this favourable outcome may not be achievable outside a well-resourced study setting[151]. In our study, good restoration of immune function occurred early and continued over the following 12 months and the weight-for-age improved consistently over the first year but more slowly thereafter. In the present study, 38 patients out of 94 (40.4%) were on TB treatment at initiation of cART. This is similar to that recently reported in a study done in Durban, where 27% of children were co-treated for HIV-TB co-infection at initiation of cART[154]. This high prevalence may be explained by the fact that TB is very difficult to diagnose in infants, diagnosis is often based on clinical symptoms and, consequently, the threshold for starting TB treatment is low. Concomitant treatment for TB may have a negative impact on virological suppression[155] and Zanoni et al. reported lower rates of viral suppression among children receiving TB treatment together with protease inhibitor (PI) based cART but not among those receiving TB treatment with NNRTI-based cART[154]. In our study, all co-treated patients were started on PI based regimen which could have contributed to the slow initial response to cART.

BCG IRIS was common in our study, with an incidence comparable to that reported in other South African and international studies[156-159]. Diagnosis of IRIS can be challenging in children (see appendix 2). In our study, initiating cART decreased the number of hospital admissions over an 18-month period. This is significant for the well-being of the child and family and for resource utilization. Recently, a sub-study of CHER showed that the health care cost per child during the first year of life is lower with early therapy compared with deferred therapy or routine care[160]. The present study is retrospective, with some medical records unavailable for analysis. The clinic was extremely short-staffed, contributing to the large amount of missing data. In the DWB study the probability of remaining in care was significantly lower in infants <1 year of age than in older children[153]. Similar results were found in Malawi where age <18 months was significantly associated with LTFU and mortality[161]. It is likely that the high probability of being LTFU in this age group is linked to advanced disease and mortality. Another limitation in our study is that adherence was not properly assessed as pill-counting was not performed. Despite the obvious advantages of early cART, some concerns remain. Poor adherence may lead to the development of viral resistance; the risk of toxicity from long-term cART is unknown and acceptance by caretakers of treating asymptomatic infants in RLS has not been assessed. Planned treatment

interruptions (PTIs) are being investigated in a number of trials and may become especially valuable now that early cART is recommended for all less than 5 years old children[61, 137, 162]. The CHER study started cART at an average age of 7 weeks, compared with 8 months in our study, hence our high prevalence of advanced disease. RLS must aim for early diagnosis and intervention. Of even greater importance is the need for RLS to strengthen pMTCT programs in order to reduce the number of newly HIV-infected children. At the time of this study, pMTCT was limited to sdNVP, which can at best reduce MTCT to 10%[163]. Our findings show the limits of this intervention, as 65% of the infants in our study group had received sdNDV at birth. Treating HIV-infected infants is a challenge. There are difficulties with early diagnosis[164], dosing, adapted drug formulations[165] and reluctance to start them on life-long medication. Thus, in the face of competing priorities infants have been relatively neglected in the global cART roll-out so far[153]. The favourable outcomes from this study should encourage healthcare workers in all 'real world settings' to diagnose infants early and include them in their programs.

2.2.3 Early treatment : costs and cost-effectiveness

There is scarce data in the literature on CE of early treatment in HIV-infected infants. Treating children has a cost, *a fortiori* if this lifelong treatment is started early. Moreover there is some evidence suggesting that LPV/r based is more potent that NVP-based for first regimen although this is under debate (see Chapter III.1)[166] but LPV/r-based regimen is more expensive. For a child weighing 10 kg, a NNRTI-based regimen will cost 100 USD versus >300 USD for LPV/r-based regimen[115].

However, in South Africa, early cART reduces total yearly cost per child (1349 USD) compared to deferred therapy (2432 USD) or routine care (2908 USD)[160]. This was mostly due to cost savings from a drop in hospitalizations[160]. In the USA it has been calculated that 9 years of one child's survival cost $113,476, 15 years cost $151,849 and 25 years cost $228,155 and that cART-related costs are now outweighing hospitalization costs[167]. In another study from US, total costs were 25.2% inferior in the CART era (1997-2007) than in the previous era (1990 –1996) because higher drug costs were compensated by 57% lower ($p<0.001$) total inpatient plus outpatient costs[168]. In LRS, little is known about the cost of paediatric cART. A recently published south-african study, performed prior to early treatment guidelines, showed that costs/year were similar between 2 clinics and comparable to adult

costs[169]. Antiretroviral costs are expected to decrease overtime by further development of generic fixed-dose combination for children.

2.2.4 Issues on early cART

Six years after randomization, the last results from CHER study were presented at CROI in Seattle in 2012 and are expected to be published soon[137]. As explained before, CHER study was the first randomized trial to show absolute superiority in early treatment with a 4-fold reduction in mortality compared to delayed cART[2]. However, the risk of lifelong cART in children including potential toxicities and challenges of managing drug-related resistance requires to think about alternative strategies. Treatment interruption is a potential way to avoid long years of cART exposure and reduce costs. However, treatment interruption trials in adults were disappointing with higher rates of HIV-related events and deaths in patients interrupting cART[170, 171]. Therefore, current guidelines for adults do not recommend PTI[49, 172]. In the PENTA 11 trial, the first randomized multicenter trial on PTI, 109 children with HIV-RNA below 50 copies/ml and CD4% of at least 30% in younger children or at least 25% and CD4 cell count of at least 500 cells/ml in older children (from 7 y of age) were randomized to continuous therapy (53 children) or PTI (56 children). In the PTI group, cART was reinitiated if CD4% dropped to less than 20% or when cART has been stopped for 48 weeks. In this study, children experiencing PTI did not present any AIDS-related events or death and younger children had better immunological recovery after PTIs[162]. Nevertheless, there was a significant excess of minor clinical events in the PTI group after interrupting cART, such as lymphadenopathy and mild skin problems, compared to children on continuous therapy[162]. Impact of PTI on adherence has been assessed in one study as part of PENTA 11 trial. Adherence was not different between children with PTI compared to children with continuous treatment. The majority was happy to repeat PTI but experienced difficulties when restarting cART after PTI, also because of more frequent clinic visits.

In the CHER trial, 2 arms (immediate cART arms 2 and 3) were designed for PTI at 40 and 96 weeks respectively[137]. Reinitiation of cART was done if CD4 were dropping under 25% (or under 20% after infancy) or if presentation of CDC stage B or C clinical events. The primary endpoint was time to failure of cART (immunological or clinical) or death. 91% of enrolled children completed follow-up (341/377 infants) with a median follow-up of 4.8 years (maximal 5.9 years). The overall proportion of time spent on cART throughout the trial was

81%, 70% and 69% for arm 1 (deferred arm), arm 2 and 3 respectively. By week 240, 3/4 of arm 2 (interruption at 40 weeks) and 2/3 of arm 3 (interruption at 96 weeks) were on continuous cART. Time for restarting cART after interruption was longer in arm 3 (37 weeks longer than arm 2 after adjustment for the length of primary cART). Seven children, in treatment failure, were switched to second line cART (ddI, ABC and EFV/NVP), three in the deferred arm and four in the immediate arms (three in arm 2 and one in arm 3). Of note, death was at least 2-fold higher in the cART-deferred arm resulting in 31%, 25% and 20% primary endpoint achieved in arm 1, 2 and 3 respectively. When analyzing the Kaplan-Meier curve for time to death or failure of 1st line cART, relative to arm 1, there was a 27% reduction in arm 2, 42% in arm 3 and 35% for the arm 2 and 3 combined. When looking at the secondary endpoint (progression to CDC B or C diseases), the difference between arm 1 and arm 2 or 3 was highly significant. The reduction was 50% for arm 2 and 60% for arm 2. It is noteworthy to see that 9 children suffered from HIV-encephalopathy in the deferred arm compared to 5 the cART-40w interruption and 2 in the cART-96w interruption. When comparing the 2 immediate arms, 34 additional children were included (17 in each arm). No difference was observed for the time to primary endpoint. At the end of the trial there was a trend in fewer clinical events in arm 3 compared to arm 2[137]. Data are desperately needed on DR and immunological response after restarting cART in those 3 arms as well as data for patients with longer primary early cART (eg : 5 years).

Decrease HIV reservoirs and possible HIV-cure of HIV in early treated HIV-infected infants

Long term data on early initiated patients without treatment interruption are crucial. In CROI 2013, Luzuriaga and colleagues presented a study in which they compared 5 teenagers who were early treated when they were infants (treatment started at a median age of 2 months) with 4 teenagers also diagnosed with HIV when they were infants who started antiretroviral therapy later in childhood[173]. They made virological studies at a median age of 16 years and showed no replication-competent virus in the early antiretroviral therapy group but yes in all 4 subjects in the delayed treatment group. Early treated patients had lower proviral DNA levels and lower residual plasma viremia. HIV-specific antibody and CD8+ T-cell responses were identified in 1 of 5 subjects in the early treatment group and all 4 patients in the delayed treatment group. These results suggest that early cART of HIV-1 perinatally-infected infants leads to a marked decrease in HIV viral reservoir[173]. The same team presented the case of a

child with possible cure of HIV. The infant was born to an HIV-infected mother who had not received PMTCT care and was diagnosed during delivery and no prophylaxis was administered to the mother. The child was started on cART (ZDV+3TC+NVP) at 30 hours of life because of the high risk exposure and the lack of PMTCT[174]. The infant had an initial plasma HIV-1 RNA level of 19812 copies/mL and detectable HIV-1 DNA in her peripheral blood cells, suggesting in utero infection. On cART, the infant's VL progressively decline and was undectable by 1 month of age and it remained undetectable though 15 months of age. The infant was not seen at the clinic until he was 23 month of age and treatment was not given during this time. The VL was still undetectable even in the absence of antiretroviral therapy. The child was HIV-1 antibody negative. Ultra-sensitive virological assays only detected 1 HIV-1 RNA copy and 37 HIV-1 DNA copies/million PBMC. No viral replication was detected[174]. To confirm those findings on possible functional cure of HIV, very early treatment will be repeated in other perinatally HIV-infected infants.

Long term data on early initiated patients without treatment interruption

Very scarce data exist on longer term follow-up of early treated children. Since 1996, Belgian guidelines recommend early treatment of HIV-infected infants and effectiveness was demonstrated at the time[1]. In CHU Saint-Pierre, Brussels, 16 patients were started on early cART from 1996 and 2007. Two patients are lost to follow-up. The median follow-up of the 14 patients is 12.6 years (range: 5.7-16.3). Eight never stopped their treatment and at last follow-up had undectable VL and CD4% above 25%. One never restarted after interruption and 5 had to restart cART after a mean time of 4.9 years, all had a drop in CD4 count and 8 significant clinical events were recorded. Among the 14 patients, 5 became seronegative for HIV-1 and 3 remain so at last follow-up (Marc Hainaut, personal communication).

2.2.5 PMTCT and paediatric treatment : are there enough resources ?

RLS face a double challenge: first, to reach full coverage of PMTCT and, second, to provide continuous cART for infected infants. However, the question remains as to whether RLS can ensure that these two interventions are implemented, both in terms of coverage and the necessary financial resources. If budgets and human resources are limited, which strategy should be prioritised in order to save the maximum of lives? Is it preferable to invest in both strategies or to choose the most CE ? As cART is lifelong treatment it seems at first analysis

that prevention takes priority over treatment in term of CE. PMTCT offer benefits for both mother and child's health. However, in many parts of the world, the used PMTCT regimens PMTCT coverage are not perfect. On the other hand, neglecting treatment for infants who failed PMTCT would not be acceptable. However one of the problems is that the barriers for PMTCT and for early diagnosis and treatment in infants are often coexisting in the same and in settings with limited resources. Failure in one stage of the cascade will often be associated with failure in other parts. In some settings with other major health problems such as malnutrition or tuberculosis and/or in difficult context such as war, natural disaster, management of HIV/AIDS might not be a priority and all interventions should be replaced in the specific context.

We only found one study forecasting costs and human resources requirements for both PMTCT and paediatric treatment for the period 2007-2015 with available AIDS budgets and health personnel in 7 countries[175]. It was estimated that PMTCT would absorb 86% of the budget and paediatric treatment 14%. According to their resources and future planned funding, the authors further predicted that 2 countries (Côte d'Ivoire and Malawi) would not receive sufficient funding to achieve both PMTCT and paediatric treatment[175]. Lack of human resources was the most important bottleneck for scaling-up both PMTCT and paediatric treatment in 6 countries. If the coverage of interventions increases to 80% then UNGASS goal of a 50% reduction in the number of children infected with HIV can be reached. However, their model predicts that only one out of the 7 assessed countries would have both human resources and enough funding to achieve this goal[175].

We did not find studies on CE of early initiation of cART although one study shows decreased costs in term of hospitalizations and associated-costs[160]. However long term costs including life-long antiretroviral treatment and related complications are unknown and could counterbalance the current benefits in term of health economy. But, as stated above, with PMTCT scaling-up, the number of HIV-infected infants should dramatically decrease resulting in reduced global paediatric treatment cost. However, mathematical models predict that even with optimal coverage the goal of elimination of paediatric HIV infection in 2015 will not be reached[176]. Mahy et al. estimated that transmission would drop to 8% and new paediatric HIV infections would represent 72000 in 2015, a 79% reduction from 2009 estimates[176]. With the best scenario, early diagnosis and treatment of HIV-infected infants

will still be a reality for many years although the total number of children requiring treatment is expected to decrease.

In light of the current drive to eliminate new HIV infections in children, is early cART still a priority? In my opinion, the answer to this question is affirmative. Although PMTCT remains the top priority and is CE (see chapter II), it is still seriously hampered by bottlenecks (Figure 2). The remaining children who will escape from PMTCT and being infected will imperatively require early diagnosis and treatment, a lifesaving strategy, with decreased costs overtime as number of perinatally HIV-infected children and prices of antiretrovirals are expected to continue to drop.

When the opportunity is missed to detect HIV-infection in children, the consequences can be dramatic with high burden of chronic complications of HIV/AIDS in children surviving into adolescence. In Zimbabwe, HIV is the commonest cause of hospitalisation in adolescents mainly due to adult-spectrum opportunistic infections and HIV-related chronic diseases[177]. Related costs for the management of those chronic conditions and the negative consequences on the future adult population and workforce need also to be taken into account in the global picture[177].

2.3 TOXICITIES OF ANTIRETROVIRAL THERAPY IN CHILDREN

Toxicities

Exhaustive review of antiretroviral toxicities in children is out of the scope of this thesis but last updates can be found on the aidsinfo website (Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection)[113].
http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf
Antiretrovirals are generally safe and well tolerated in both HIV-infected and HIV-exposed uninfected children (as discussed in chapter II.2). The aims of cART are to insure good health for life, growth and development for HIV-infected children, whilst reducing the risks of short and long-term adverse events. As we discussed above, emergence of long-term toxicity must be recognized as treatment is now started at an early age. Toxicity can affect kidneys, skin, central and peripheral nervous system, bone density, liver and gastro-intestinal system, blood

and the metabolism (lipids, glucose, lactic acidosis). However, availability of new molecules and formulations has led to more potent regimen with lower toxicity, less pills and once-daily (OD) administration allowing better adherence and hopefully better outcomes[39].
One of the difficulties in attributing side effect to a particular molecule is that children are treated with at least three drugs. One way to approach this issue is to perform nested case–control studies where investigators compare groups taking and not taking the specific antiretroviral molecule[178].

Pharmacovigilance

In Europe, the EMA is requiring from pharmaceutical companies to address long-term toxicities for each paediatric drug in their paediatric investigation plan[179]. To support this, a pharmacovigilance system has been developed within the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC), a collaboration including 13 pregnancy and paediatric HIV cohorts out of 15 European countries. To date, data are available for 5000 HIV-infected children ever in follow-up and 2500 in current follow-up from eight paediatric cohorts. Data are merged on an annual basis using a standardized database (http://www.hicdep.org/). Adverse events are categorized according to grading tables[180].

In LMIC, where often cheaper generic drugs are used, pharmacovigilance appears to be suboptimal. However, due to the concern of mitochondrial toxicity and lipodystrophy, many countries are now moving from d4T-based to ZDV or ABC-based paediatric FDCs. Zidovudine was shown to be well tolerated in young children living in non-malarious areas. Abacavir hypersensitivity seems to be not an issue in African children[181]. New initiatives to improve pharmacovigilance activities in LMICs include guidance from WHO and the Global Fund on establishment of pharmacovigilance toolkit[182]. A recent review is summarizing major ART side effects in children focusing on LMICs[181].

- **Early diagnosis of HIV is crucial in order to start prompt therapy**
- **Many barriers exist for early diagnosis and treatment in infants**
- **Early treatment of HIV-infected infants is associated with dramatic decrease of early mortality and morbidity compared to infants with deferred treatment**
- **Early treatment of HIV-infected infants is also effective outside a well-controlled research environment**
- **WHO is now recommending to start treatment in all less than 5 years old children**
- **Wether use NNRTI or PI-based regimen as first line regimen is still under debate**
- **Combination antiretroviral therapy is generally safe for children but close monitoring of potential toxicities is mandatory**
- **Some countries may lack resources (including human resources) in the future to support both PMTCT and paediatric antiretroviral treatment**
- **High burden of chronic diseases in surviving perinatally-infected adolescents is due to diagnosis delay of HIV infection in children**

Children are now surviving and more and more are transitioning to adult care. In the next chapter we will now focus on HIV in adolescence and challenges of transition.

CHAPTER IV

1. TRANSITION OF HIV-INFECTED ADOLESCENTS INTO ADULT CARE

Increasing numbers of HIV-infected adolescents are now transitioning to adult care. Transition is defined as the purposeful, planned movement of adolescents and young adults with chronic medical conditions from a child-centered to an adult-oriented health care system[183]. The need to transition from paediatric care to adult-oriented care is shared by adolescents with chronic conditions such as diabetes or cystic fibrosis and studies showed that many of these adolescents are lost to follow-up, and have had worsening of their health status in the first few years after leaving paediatric care[184-187]. In contrast, little is known about outcome of HIV infected teenagers at the time of transfer and after they have left paediatric settings. Paediatricians are increasingly concerned that these young adults will have few treatment options available to them in adulthood if all available options are used early on in their care.

A few studies reporting on HIV infected adolescents just prior to transfer highlighted some challenging features: all of 74 teenagers from a cohort in Buenos Aires had detectable VL (VL)[188], and nearly a third of the adolescents in the Collaborative HIV Paediatric Study (CHIPS) cohort were severely immunosuppressed[4]. Most of these patients were exposed to diverse antiretroviral drug regimens during their lifetime, including mono or bi-therapy before cART became available. This is of particular concern with respect to the development of DR[189, 190].

2. HIV-INFECTED ADOLESCENTS AT THE TIME OF TRANSFER IN MONTREAL

To further understand the clinical, immunological and virological status of HIV infected adolescents, a cross-sectional study based on a group of HIV-infected adolescents (n = 45) at

the time of transfer to adult care. To our knowledge, this is the first such study to report on HIV-infected adolescents at the time of transfer within the Canadian health system.

All study subjects were participants to the Centre Maternel et Infantile sur le SIDA (CMIS) (CHU Sainte-Justine, Montreal, Canada), in which 169 HIV-infected children were enrolled between 1988 and 2010. This research protocol was approved by and carried out according to the guidelines of the Ethics Review Board of CHU Sainte-Justine, Montreal, Canada. Informed consent to participate to the study was obtained from all study participants, their parents or legal guardians. All CMIS subjects who were transferred to adult services were selected for the cross-sectional study. Data collection was performed at the last time point prior to transfer. The first patient was transferred in June 1999 and the last one before June 1st 2011. A retrospective review of clinical and socio-demographic data was performed. Study variables included: gender; ethnic origin; country of birth; Centers for Disease Control and Prevention (CDC) clinical stage and conditions during follow-up and up to transition to adult care[191]; $CD4^+$ and $CD8^+$ T cell counts (absolute and %, nadir and prior to transition) measured by flow cytometry, with severe immunosuppression defined as a $CD4^+$ T cell count < 200 cells/mm^3 (CDC immunologic category 3)[192]; and HIV-1 plasma RNA levels, measured using the Versant HIV-1 RNA assay (Bayer, Pittsburgh, PA), with a detection threshold of 2.70 $\log_{10}$ (500) HIV RNA copies/ml plasma (version 2.0) or 1.70 $\log_{10}$ (50) HIV RNA copies/ml plasma (version 3.0).

When HIV-1 VL was >1000 RNA copies/ml plasma, HIV-1 genotyping was performed based on sequencing of a 1497 base pair fragment of the HIV-1 *pol* gene (Virco BVBA, Mechelen, Belgium). When VL was <1000 copies/ml, HIV-1 viral RNA was extracted from frozen plasma samples and a 524 base pair *pol* segment was amplified, subcloned and sequenced as previously described[193-196]. Cumulated HIV-1 mutations observed in each subject during follow-up were examined using HIV resistance interpretation algorithm (2009 ANRS consensus technique[197]). Cumulated DR profiles were reported based on the classes of antiretroviral agents used: NRTIs/NtRTIs, NNRTIs, PIs, fusion inhibitors (FIs) and integrase inhibitors (INSTIs), in accordance with the latest contemporaneous updates[198]. FI, INSTI and newer PIs (DRV, tipranivir) were classified as recent generation antiretroviral agents.
Descriptive statistics were used to characterize the study population, and normality of data assessed by tests of skewness and kurtosis. For continuous variables, medians and interquartile ranges (IQR) were reported. For discrete variables, percentages were reported.

Given the nonparametric distribution of data, group-wise comparisons for continuous outcomes were done using the Mann-Whitney U test. All data were analyzed using SPSS 18 (SPSS Inc., Chicago, IL).

Forty-five adolescents (27 females and 18 males) who were transferred to adult services at a median age of 18.1 years were studied. Table XI depicts the socio-demographic profile of the study subjects. Median age at admission in the CMIS was 4.3 years (IQR: 1.3-10.6). The mode of HIV infection was MTCT in 32 (71%) cases, blood transfusion in 2 (4.4%), sexual 2 (4.4%) and unknown for 9 (20%). HIV subtyping was successfully performed in all 45 subjects and 36 of 45 (80%) were infected with clade B. One subject was co-infected with hepatitis B virus and one with hepatitis C virus. At the time of transfer, 33 subjects (73.3%) were asymptomatic, 2 had CDC clinical category C conditions and 4 had CDC category B conditions. Six subjects had other significant clinical issues (Table XI). Figure 4 summarizes the virological, immunological and DR status of this group of patients.

Table XI. Characteristics of 45 adolescents at the time of transfer to adult care

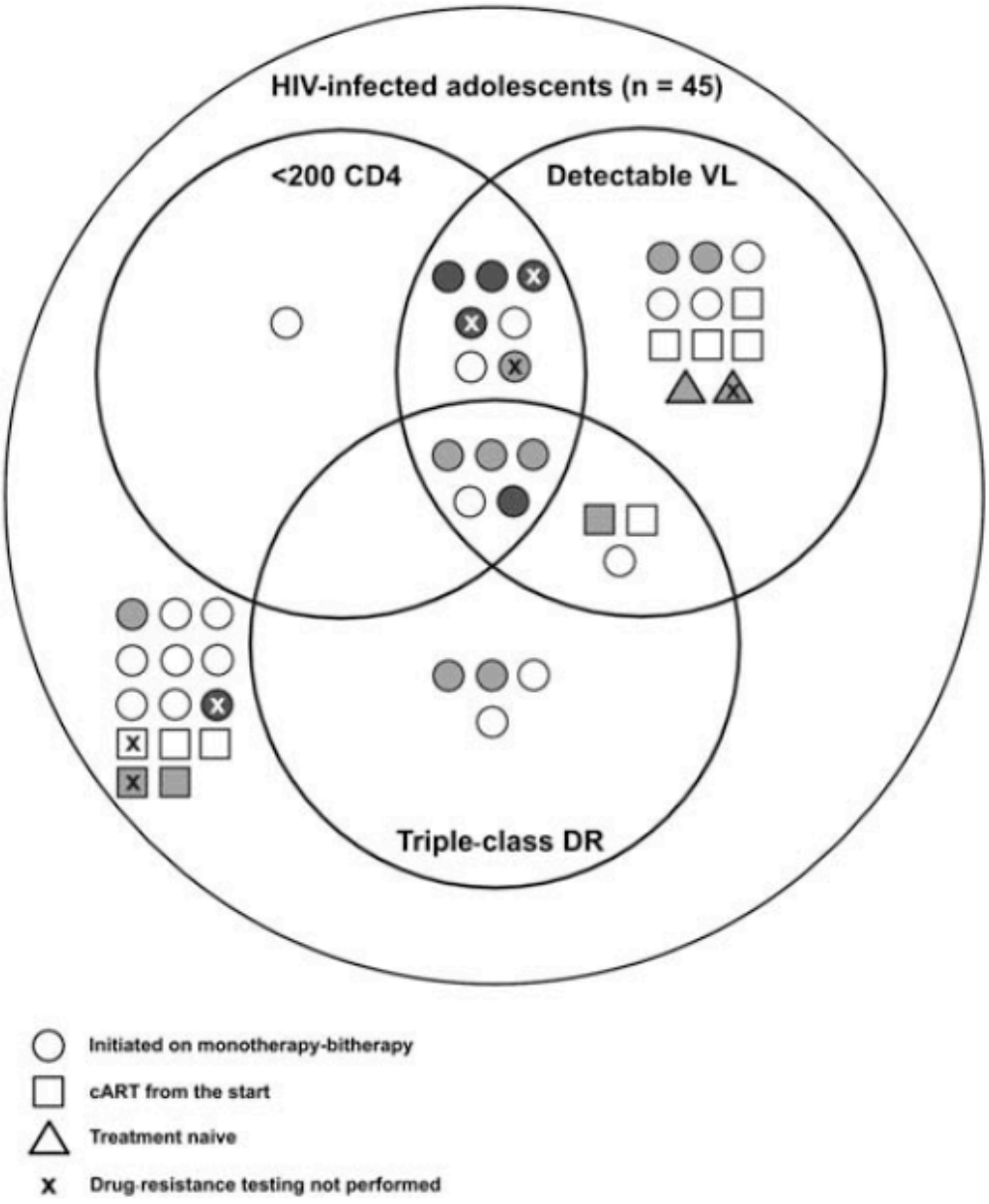
Age in years, median (IQR)	18.1 (17.7-18.5)
Gender, male / female, n	18/27
Haitian origin, n (%)	22 (48.9)
Caucasian origin, n (%)	12 (26.7)
African origin, n (%)	8 (17.8)
Other origin, n (%)	3 (6.7)
Born in Canada, n (%)	28 (62.2)
CDC clinical category C[a], n (%)	2 (4.4)
CDC clinical category B[b], n (%)	4 (8.9)
Other clinical conditions[c], n (%)	6 (13.3)
CD4+ T cells/mm^3, median (IQR)	420 (150-644)
CD8+ T cells/mm^3, median (IQR)	780 (609-920)
< 200 CD4+ T cells/mm^3, n (%)	13 (28.9)
VL undetectable / detectable, n (%)	19 (42.2%) / 26 (57.8%)
VL detectable, (log_{10}) copies/ml of plasma, median (IQR)	4.13 (3.6-4.7)

[a]CMV retinitis (n=1), wasting syndrome and esophageal candidiasis (n=1)

[b]Lymphoid interstitial pneumonia and bacterial pneumonia (n=1), herpes zoster (n=1), chronic thrombocytopenia (n=2)

[c]HIV encephalopathy sequelae plus Moya-Moya for one of them (n=3), chronic arthritis (n=1), severe neuropsychological symptoms (n=1) and *Streptococcus agalactiae* mediastinal abscess (n=1)

Figure 4. Distribution of 45 adolescents infected with HIV-1 according to markers of treatment failure at the time of transfer to adult healthcare services



Dark shading illustrates the year of transfer during 1999–2003; light shading illustrates the year of transfer during 2004–2007; no shading indicates the year of transfer during 2008–2011.

At some point during their follow-up, 43 out of 45 subjects were treated with ART. Earlier in the epidemic, 32 subjects (71.1%) were first exposed to mono- or bi-therapy before being switched to cART. Eleven subjects were treated with cART from the start. Subjects were exposed to a median number of 9 antiretroviral agents (IQR: 7-12). All 43 treated patients were exposed to NRTIs, 32 (74.4%) to NNRTIs, and 40 (93%) to PIs. A total of 9 patients had received recent generation ARVs at some point during their treatment, and 6 remained on these at the time of transfer. Three patients, not on recent generation ARV at transfer, had received boosted-tipranavir (TPR/r) at some point. Treatment regimens at time of transfer are described in Table XII.

Table XII. Antiretroviral regimen in 45 adolescents at the time of transfer

Regimen	**n**
Nil[a]	6
3TC[b]	3
AZT-3TC-EFV	1
AZT-3TC-LPV/r	1
D4T-ddI-EFV	1
D4T-ddI-APV	2
D4T-3TC-IDV	2
D4T-3TC-LPV/r	1
D4T-3TC-RTV	1
D4T-3TC-TDF-ATV/r	1
ABC-3TC-LPV/r	3
ddI-3TC-NFV-SQV	1
TDF-3TC-ATV/r	2
TDF-FTC-EFV	6
TDF-FTC-LPV/r	7
TDF-FTC-ATV	1
TDF-FTC-ETR-DRV/r-RAL	**3**
TDF-FTC-RAL	**1**
ABC-3TC-DRV/r	**1**
3TC-ddI-ETR-RAL	**1**
Total	45

In **bold** : patients receiving recent generation antiretroviral agents at transfer (ETR, DRV/r or RAL)

[a] 2 subjects treatment-naïve, 3 off treatment for non-adherence; 1 off treatment because of side effects.

[b] 3TC monotherapy for lack of adherence.

At the time of transfer, 19 subjects (42.2 %) had undetectable VL. Among the 26 subjects with detectable viremia, median VL was 4.13 log_{10} HIV-1 RNA copies/ml plasma (IQR: 3.6 – 4.7 log_{10} HIV-1 RNA copies/ml plasma). Median $CD4^+$ T cell count was 420 cells/mm^3 (IQR: 150 - 644). In terms of median $CD4^+$ T cell count, there was no significant difference between females and males (399 cells/mm^3 vs 423 cells/mm^3, $p = 0.788$) nor between patients infected with clade B *versus* non-B HIV-1 (459 cells/mm^3 vs 216 cells/mm^3, $p = 0.253$). Severe immunosuppression, corresponding to CDC Clinical Stage 3 ($CD4^+$ T cell counts < 200 cells/mm^3)[192], was observed in 13 of 45 subjects (28.9 %) (Figure 4, Table XIII). All of these subjects were first treated with mono- or bi-therapy (Table XIII). Only one had undetectable HIV-1 VL at the time of transfer.

Table XIII. Characteristics of subjects with $CD4^+$ T cell counts < 200 cells/mm^3 at transfer

	Age (years)	**HIV-1 clade**	**CD4 counts** (cells/mm^3)	**Plasma VL** (log_{10} RNA copies/ml)	**Treatment at transfer**	**ARV ever used** (#)	**DR**[a]
1	17.6	C	119	2.19	ABC-3TC-DRV	12	No
2	17.8	B	156	<1.69	TDF-FTC-RAL	9	No
3	18.1	B	115	4.50	TDF-FTC-DRV-ETR-RAL	20	Yes
4	18.3	B	144	4.38	APV-D4T-ddI	8	No
5	18.0	B	84	4.36	D4T-3TC-IDV	8	ND
6	20.0	B	132	4.65	D4T-3TC-IDV	7	No
7	17.8	B	77	5.25	TDF-3TC-ATZ/r	13	Yes
8	18.2	C	60	4.01	TDF-FTC-LPV/r	10	No
9	17.7	D	160	2.37	D4T-ddI-EFV	7	ND
10	17.8	B	15	5.50	ddI-3TC-NFV-SQV	10	ND
11	18.0	B	20	5.68	D4T-ddI-APV-RTV	9	Yes
12	17.5	F1	39	5.52	D4T-3TC-TDF-ATZ/r	13	Yes
13	18.1	B	14	4.11	TDF-3TC-ATZ/r	15	Yes

ARV: antiretroviral agents

[a]Drug Resistance to at least one agent of the 3 main classes of ARV (Triple-class DR)

ND: drug resistance testing never performed

Genotypic DR testing was performed at least once in 38 of 45 (84.4%) study subjects. The median number of cumulated total (major and minor) mutations over time in individual subjects was 13 (IQR: 7-20), with a maximum of 38 in a single patient. The median number of cumulated major mutations was 4 (IQR: 1 - 8). Analysis of the mutations using the French ANRS HIV resistance interpretation algorithm revealed DR to at least one antiretroviral agent in 28 of 38 tested subjects (73.7%). Twenty-one of 38 (55.3%) subjects tested harboured HIV-1 isolates considered resistant to first generation NNRTIs (*i.e.* NVP, EFV). In the PI category, 19 of 38 subjects (50 %) harboured isolates resistant to this class with 13 showing resistance to LPV/r. Overall, 12 subjects of 38 (31.6%) were resistant to at least one agent of the 3 major classes (including NRTIs, NNRTIs and PIs), ie, triple-class DR.

Among the 13 patients with severe immunosuppression, 5 out of 10 who had resistance testing (50%) were harbouring virus with triple-class DR (Table XIII). In terms of number of major resistance mutations detected, there was no significant difference between females and males (median 4.0 vs. 6.0, $p = 0.526$) or between patients infected with clade B *versus* non-B HIV-1 isolates (median: 5.5 vs. 0.5, $p = 0.58$).

3. DISCUSSION ON THE CHALLENGES OF TRANSITION IN HIV-INFECTED ADOLESCENTS

This cross-sectional study provides a unique picture of a group of Canadian HIV-infected adolescents who were followed at the same center for most of their lives. It highlights some of the many challenges currently facing paediatric and adult care providers as adolescents infected with HIV reach the age of transfer to adult services. They were all transferred to another hospital as CHU Sainte-Justine is a children's hospital. We did not look at the post-transfer status of those young patients, for example if they were transferred to the same center than their parents and how they linked with the adult services.

Despite universal access to healthcare, ART as it became available, and a multidisciplinary approach to patient management, 68.9% of transferring adolescents were failing treatment, which was manifested by detectable viremia, CD4 counts <200, and/or triple-class DR. One fifth of these patients had already been exposed to recent generation antiretroviral agents

(DRV, raltegravir, etravirine), which is of particular concern for their future therapeutic options. However we could be analyze this situation with more optimism. In fact, 4 subjects have an undectable viral load and more than 200 CD4 but triple DR. This could be due to the fact that they were initially treated with suboptimal treatment. Those 4 patients are in fact doing well and one can hope they will continue in this way after transfer. Two other patients have detectable viral load but they were still treatment-naïve at the time of transfer and one last patient had CD4 less than 200 but an undetectable viral load and absence of triple DR. If we consider those positive figures, the number of patients who seem to at risk of failure after transfer to adult service can drop to 24 on 45 (53%).

Our results are consistent with the findings from the CHIPS cohort study[4] and previous data suggesting lower rates of virological suppression in HIV-infected adolescents compared to adults and younger children[199-202]. In our study, 28.9% of study subjects had CD4 counts of < 200 cells/mm^3, which is close to the 27.2% reported in the CHIPS cohort[4]. This result differs from the 16.6% of subjects with CD4 counts of < 200 cells/mm^3 reported in the French Perinatal Cohort[203], however, this may be explained by a younger median age at last follow-up in the French cohort, *i.e.* 15 years *versus* 17 years in the CHIPS Cohort and 18.1 years in our study group. In a more recent study, severe immunosuppression were observed in more than two thirds of transferred patients with less than 15% CD4+ cell counts and half (57.1%) with less than 200 cells/mm^3 [204].

But are young HIV-1 vertically infected young adults more at risk of severe immunodepression and virological failure than behaviourally-infected adults treated for the same duration? At CROI 2013, Nelly Briand and colleagues presented the first study comparing virological outcome of perinatally infected adults with older patients infected during adulthood after stratification on time since infection. The proportion of patients with undectable VL was significantly lower in children, adolescents, and young adults infected since birth, than in adults infected in adulthood, for each strata of HIV infection duration (Table XIV). This difference was also observed in patients on stable cART, and independent of the duration of infection. When looking at immunological data, the children or young adults infected for more than 13 years had significantly lower CD4% than adults infected for the same time. Those findings confirm that treating and maintaining children on cART can be difficult.

Table XIV. Immunological and virological differences between perinatally HIV-infected young aduls and adults treated for the same duration of time
(Nelly Briand et al. CROI 2013)

	<13 years since HIV acquisition			13-17 years since HIV acquisition			≥ 18 years since HIV acquisition		
Time of acquisition:	Perinatal	Adulthood	p	Perinatal	Adulthood	p	Perinatal	Adulthood	p
Median age	7.1	41.0	<0.01	17.0	49.7	<0.01	20.0	53.9	<0.01
% unchanged ARV since ≥ 6m	80.6	69.1	0.02	75.3	83.9	0.12	64.3	84.8	<0.01
% PI-based last regimen	63.9	53.3	0.06	74.6	35.8	<0.01	73.9	51.5	<0.01
Median CD4 cells/µl	931	618	<0.01	614	695	0.12	565	520	0.23
Median CD4%	34	34	0.60	30	37	<0.01	29	30	0.09
% CD4 ≥ 25%									
Overall	88.9	87.3	0.67	74.2	89.5	<0.01	67.1	81.0	0.07
If unchanged ARV ≥ 6m	92.8	93.1	0.94	78.9	90.3	0.05	70.5	79.6	0.29
% viral load < 50 copies/ml									
Overall	68.2	76.1	0.10	51.9	89.4	<0.01	63.4	89.2	<0.01
If unchanged ARV ≥ 6m	74.6	93.1	<0.01	60.2	95.8	<0.01	70.5	87.5	0.03

The prevalence of triple-class DR was much higher in our study than in CHIPS (31.6% vs. 16%). This may be due to an underestimation of DR in the CHIPS cohort, since only 39.8% of their subjects underwent genotypic testing, as opposed to 84.4% in the present study[4]. In the recent study from Madrid triple-DR in the cohort of transferred teenagers was similar to the control group of non-transferred paediatric patients although prevalence of DR mutations was higher in the transferred group[204]. One of the major bias in this study from Madrid is the year of diagnosis in both groups. 81.3% of transferred patients were diagnosed before 1994 when antiretroviral treatment was suboptimal while 70.2% of the patients in the control group were diagnosed after 1994. This is logical that, patients treated in the first days of the pandemics are harbouring a more resistant virus than children benifiting from cART from the beginning. It is why, in our study, we finally decided not to compare the group of patients who were first exposed to mono- or bi-therapy with those who were treated with cART from the start. Delaugerre *et al.* reported a 26.9% prevalence of triple-class DR among a group of 119 HIV-infected children of any age in France, which is comparable to our prevalence of 28.9% [205].

The major limitations of our study are (1) the differential effect of the treatment regimens that were available over time and (2) the expected differences in comparing patients initiating treatment with cART versus those who received sequential therapy as drugs became available. Hence, our results may overestimate the prevalence of DR among current and future cohorts of adolescents who would have begun treatment during the cART era.

Furthermore, the chart review did not allow for reliable collection of data on adherence, a key factor in the emergence of DR.

These results indicate that many adolescents infected with HIV face serious interconnected issues with respect to DR and immunodeficiency. This places them at a high risk of morbidity upon transfer to adult care, where they, paradoxically, are often the youngest but also the most treatment-experienced patients. With millions of perinatally infected children soon to reach adolescence, an innovative integrated multidisciplinary approach is needed among adult and paediatric care providers to facilitate this transition and to optimize the management and outcome of future generations of young adults living with HIV.

Outcome AFTER transfer to adult services

However, there is a current lack of information regarding the progression of their disease ***after*** they have left paediatric care. There is a concern that a large percentage of these teenagers may be lost to follow-up after transfer and/or experienced worsening of their disease. The causes for such poor outcomes are multiple and may be related to a lack of preparation of the transfer. The reasons for a "failed transition" may be found in a lack of support of the young patients' emerging autonomy regarding self-management while they are still in paediatric care, as well as to barriers that are met once they are reaching the adult clinic. These young adolescents may feel uncomfortable into this new environment by being in contact with a very different population of patients (eg : behaviourally HIV-infected patients, drug users, etc..), far from the « cocooning » environment of the paediatric HIV clinic and sometimes being separated from their peers followed-up in different clinics[206].

Best practices for the transition of HIV infected adolescents have not yet been established, although protocols and transition programs exist at different centres in the United States and the United Kingdom[183, 207]. The goals of the paediatric team is to prepare at best their young patients to succeed their transition. More than just focusing on survival and avoidance of OIs, it is crucial to offer appropriate counselling to these young patients to help them to gain autonomy in other life aspects such as choosing adapted schools, making career choices as well as to prepare them for future social condition when they will leave the paediatric clinic. Comprehensive reproductive health management and family planning are also of extreme

importance as sexually-transmitted diseases and unexpected pregnany are not rare in perinatally HIV-infected young adolescents[208, 209].

4. RESEARCH AGENDA FOR PERINATALLY HIV-INFECTED ADOLESCENTS

A special issue of the Journal of International AIDS Society on "Perinatally HIV-infected adolescents" has just been released, reviewing all the important issues related to this specific population of HIV-infected adolescents who are infected since birth[210]. It includes review of adherence challenges in adolescents and management of multi-drug resistant viruses in highly-treatment experienced patients, review of potential long term toxicities (eg : cardiac, metabolic, bone), mental and reproductive health issues as well as challenging management of co-infection (eg : tuberculosis) and chronic lung diseases.
An important gap in knowledge is the paucity of global and local epidemiologic data regarding the population of young adults with perinatal HIV infection. One explanation for this is that database are often not making the difference between behaviourally-infected adolescents and perinatally-infected youths. Another issue is that perinatal infection can not always be proved outside prospective follow-up from birth.

To address Belgian epidemiology and to better understand the factors associated with successful transition and outcomes of perinatally infected young adults we are currently initiating a multi-centered Belgian study with two distinct objectives : the first is to identify patients who failed transition defined as:- failure to attend any follow-up appointment with the adult healthcare team after initial contact has been made or - attendance to less than 2 appointments attended/year of follow-up in the first two years after transfer (or less than 1 appointment attended/year in those living overseas who were seen once a year in the paediatric clinic or in agreement with the treating physician), among those alive at two years post-transfer; and the second objective is to determine the clinical, immunological and virological outcome of HIV-infected adolescents after transfer from paediatric to adult care in Belgium (appendix 3).

- **Increasing numbers of HIV-infected adolescents are transitioning into adult care**
- **Globally, in HIC, the picture is positive with the majority of the patients being in good health condition at the time of transfer**
- **First generation of perinatally HIV-infected adolescents were initially treated with sub-optimal therapy**
- **At transfer, some perinatally HIV-infected young adults may be at risk of poor outcome by harbouring virus with triple drug resistance, being severely immunosuppressed and having a detectable viral load**
- **Lack of adherence is a critical issue in adolescence with the risk of developing drug resistance**
- **Comprehensive reproductive health management and family planning is needed**
- **Protocols to improve adherence and facilitate transition are being developed and piloted**
- **Long-term follow-up of perinatally HIV-infected young adults is crucial**
- **HIV care in adolescents is increasingly an issue in low- and middle-income countries**

GENERAL CONCLUSIONS

Thirty years after the discovery of the virus causing AIDS, paediatric HIV has evolved into a chronic disease (Picture 3). Topics discussed in HIV conferences have shifted from treatment of opportunistic infections to long term management of HIV in order to live longer and better without complications of HIV and its treatment[211].

Despite the recent prospect of functional cure for HIV in a child who was treated very early after birth and the hope to reproduce this observation at larger scale[174], children are likely to continue being infected and affected with HIV for many more years. As seen in the second chapter, there is a considerable hope of eliminating paediatric HIV through PMTCT. This strategy has proven to be cost-effective compared to no intervention, although the optimal strategy of achieving this is still under debate[74]. Antiretrovirals are generally safe for both mother and baby[82] but constant monitoring of side-effects is mandatory. Despite maximal efforts to reduce or eliminate MTCT, failures still continue to occur.
Early diagnosis and treatment, ideally within the first months of life, is a priority to reduce early mortality and morbidity. Except for rare cases of late diagnosis, this strategy has been in place since 1996 in some high-income countries such as Belgium. However, in low- and middle-income countries, diagnosis is often delayed and many children present with HIV-related symptoms and/or AIDS manifestations[153, 212]. Only a minority of children who need treatment are currently on cART. In this thesis, we showed that early initiation of cART was also highly effective in a busy paediatric HIV state clinic in KwaZulu-Natal although treatment was still delayed compared to randomized control trials. Undetectable viral load was found in nearly 80% of children who reached 18 months of treatment, their clinical, immunological conditions dramatically improved during the follow-up and the number of hospital admissions decreased. Newly released 2013 WHO recommendations will encourage all settings with limited resources to initiate cART in all children younger than 5 years of age, irrespectively of clinical or immunological signs, in order to reduce the number of HIV-infected children progressing to AIDS or death[61].

Growing-up with HIV and have a “normal life” is possible but some obstacles can occur along the road. Young infants need a favourable environment in order to adequately receive antiretrovirals and to attend the planned follow-up visits. Many factors can contribute to treatment failure at an early age (eg: social factors such as being an orphan or having parents denying the disease). Some parents may refuse to give the treatment to an asymptomatic infant by fear of poisoning them. Appropriate medical follow-up is also crucial and in some

parts of the world, health care workers are not trained for treating children. This lack of training could result in uncorrected dosage resulting in suboptimal drug level (that could lead to early emergence of drug resistance) and absence of early detection of cART complications such as immune reconstitution inflammatory syndrome (Appendix 2) or immediate side-effects.

Palatability of antiretroviral drugs is also an important issue with some infants refusing to take the medication because of bad taste. Paediatric HIV is still often neglected in the world of drug development with lack of pharmacokinetic data forcing the physicians to use some antiretrovirals off-label. Health care workers dealing with paediatric HIV must do constant monitoring for long term toxicity associated with lifelong antiretroviral use but in some parts of the world this monitoring is very limited. Optimal management include the choice for optimal treatment strategies to limit the emergence of resistance mutations[213]. Early development of drug resistance is a concern for early treated children. Although recent data from CHER trial are reassuring about this issue[119], operational research is crucial in order to get data from "real life" settings. In this perspective, we set-up an operational research project to describe the current drug resistance profile found in the cohort of early treated children (described in this thesis) compared to a control group of HIV-infected children who started combination antiretroviral therapy above 2 years of age. Our hypothesis is that early initiation of antiretroviral therapy is associated with more drug resistance in this setting (Appendix 4).

Progressively, through different specific tools used at the clinic, the child will learn more about his condition and diagnosis should ideally be fully disclosed by 12 years of age. Disclosure of HIV infection status is a critical step and has obvious implications for adherence. Beginning the disclosure process as early as 8-9 years of age and combining it with specific support may result in improved adherence in children[214]. When the young patient will gain in autonomy, adherence will not only be the parent's responsibility. Many barriers exist for adherence. The most common reported cause of non-adherence is that the child forgot to take his medication. Other barriers for adherence include bad taste, number of pills, change in habitude (eg: holidays, sleeping outside), drug schedule interfering with sleep or activities[215]. The role of the multidisciplinary team is to give them appropriate counselling and tools to improve adherence. In certain case, when adherence is poor with the risk to jeopardize future therapeutic options, we decide, in agreement with the teenager, to interrupt the treatment with close clinical and immunological follow-up. This "holiday" time is often beneficial and allow to restart the treatment in good conditions. The mission of the paediatric

clinic, including paediatricians, nurses, social workers and psychologists, is to prepare them at best to succeed their transition. In order to do this, each team should think about its own strategy or protocol to involve the young patient as soon as they enter into adolescence. Paediatricians must work in close partnership with adult physicians to plan the transfer and to facilitate the initial contact with the adult team, directly or through transition clinic. In this thesis, we showed that a number of these vertically-infected young adults are heavily treatment-experienced at transfer, very challenging to treat and harbouring multidrug resistant viruses. But we have to put this in perspective; some of the less favourable outcome can be explained by treatment history with initial sub-optimal therapy in the old days, when combination antiretroviral therapy was not available. We have to see the positive part of the reality, those who survived have now access to potent regimen. We can hope that new generations of perinatally-infected adolescents who were treated with combination antiretroviral therapy from the start will have a better virological condition at the time of transfer. Another positive point is that hospital admission is a rare event in this population, at least in high-income countries. In general, those young adults attending our clinics are healthy and can have normal activities. Some are experiencing difficult social situations needing help from our social services. Peer-groups and psychological follow-up can help them to express deep feeling about their condition, stigma, secret and the way they have to live with this disease. Issues concerning transition are not unique to HIV. In other chronic diseases, this phenomenon is also observed and failure of transition is well known. For example, it was shown that one third of renal transplant patients are losing their graft after transfer into adult clinic[185]. Studies on transition to adult care for adolescents with HIV infection are less numerous than are those for adolescents with other chronic illnesses. This may be explained by the fact that chance of survival into adulthood for children infected with HIV-perinatally has increased because of improvement of antiretroviral regimens[183]. Some centers have developed special adolescent clinics (SAC) or transition clinic in order to facilitate this process. In one US center, the team is currently piloting a specific transitioning protocol. The patients start the transition process as soon as they turn 23 years old. Previous attempts to start the process earlier (at 21 years of age) was associated with a high number of failures. The process is very progressive. After a first visit explaining all the process, the adult infectious diseases (ID) physician comes first to meet the patient at the SAC and the consult is still done with the paediatrician. If it goes well, the next appointment is still at the SAC but the consult is done by the adult ID physician. Then the young patient is seen at the adult clinic and close follow-up of the process is still done by the SAC during 1 year. If the patient experiments

some problems or difficulties, he can still return to the previous stage of the protocol[183]. However, longer-term outcomes in perinatally-infected children are still unclear and very scarce data exist about health status of those patients after transfer into adult services. Some surviving patients are now in their thirties, having started treatment at birth. It is difficult to predict their health status and quality of life in their sixties or seventies, after 60 years of cART. Long term follow-up of vertically-HIV infected young adults will be critical to answer those questions. We are concerned that a large percentage of these teenagers may be lost to follow-up, have worsening of their disease, and increased mortality as a result of problems with the transition process. As future perspective and in order to provide some answers to this crucial question; we are setting-up a Belgian multi-centered study to study transition, clinical, immunological, social and virological outcome of HIV infected adolescents in Belgium after they left paediatric care (Appendix 3).

Since recently, HIV care in adolescents is also an important issue in low- and middle-income countries. In Zimbabwe, 42% of HIV-infected children are aged 10-19 years[216]. The primary focus of paediatric HIV programmes has been on infants and young children for whom management is very different from the one of HIV-infected adolescents. One can hope that the experience gained in high income countries in treating HIV-infected adolescents and transitioning them into adult care could be used in the future to support highly endemic countries to deal with this challenging issue.

Picture 3. HIV is a chronic disease (http://www.acon.org.au/hiv/HIV-and-Ageing)

APPENDICES

1. ARTICLES

For copyright issues, all published articles cannot be accessed in this document.

Is early treatment of HIV-infected infants still a priority in the era of highly effective prevention of mother-to-child-transmission ?

Article submitted for publication (Tropical Medicine and International Hygiene)

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Abstract

Introduction: Is early combination antiretroviral therapy in HIV-infected infants still a priority in settings where prevention of mother-to-child transmission (PMTCT) is now highly promoted and implemented in a time where resources and fundings are lacking ?
Methods: a PubMed search was conducted using terms [prevention of mother-to-child transmission cost-effectiveness], [PMTCT cost-effectiveness], [early infant HIV-1 diagnosis cost-effectiveness], [early infant diagnosis of HIV cost-effectiveness], [antiretroviral therapy infants cost-effectiveness], [early (combination) antiretroviral therapy infants (children) cost-effectiveness], [early HIV treatment infants (children) cost-effectiveness], [PMTCT early initiation of combination antiretroviral therapy]. Papers published between 2008 and 2013 were assessed for inclusion.
Results: Eight studies show that the use of lifelong antiretroviral therapy only for pregnant and breastfeeding women eligible for treatment « option B » (and lifelong for all pregnant and breasfeeding women « option B+ » in 2 studies) is cost-effective compared to no or simpler intervention. One study forecasting costs and human resources requirement for 2007-2015 conclude that 2 countries will lack funding to support both PMTCT and pediatric treatment in the future. We reviewed the evidence of early diagnosis and treatment of HIV-infected infants which is essential to avoid unacceptable high mortality in HIV-infected infants. There is scarce data on cost-effectiveness of early diagnosis and treatment in HIV-infected infants.
Conclusion: Early treatment of HIV-infected infants is still a priority as delay will result in high mortality and morbidity. However, as more cost-effective PMTCT strategies are being implemented it will hopefully lead to potential elimination of pediatric HIV. Due to bottlenecks hampering full PMTCT effectiveness, new pediatric HIV infections will still occur and it is crucial for those infants escaping PMTCT to be early diagnosed and treated. Cost-effectiveness analysis of early infant diagnosis and treatment are lacking.

Keywords : HIV, prevention of mother-to-child transmission, cost-effectiveness, early cART, infants

Introduction

The Joint United Nations Programme on HIV/AIDS (UNAIDS) has declared that the elimination of mother-to-child-transmission (MTCT) of HIV is possible (UNAIDS 2011). Simultaneously, the World Health Organization (WHO) published a strategic vision for 2010-2015 on the prevention of MTCT (PMTCT) (WHO 2010). The bold new vision of the 'Three Zeros' articulated by UNAIDS, WHO and other international institutions such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) includes the elimination of MTCT of HIV, the reduction of child mortality and improvement of maternal health (Millenium Development Goals 4 and 5) by 2015.

Significant progress has already been achieved globally. Incident child HIV-infections peaked in 2002 at 560 000 infections per year. By 2010, the number of infections had fallen to an estimated 390,000 per year, with most (86%) of this decrease occurring in sub-Saharan Africa (UNAIDS 2011). Between 2009 and 2011, 409 000 infections were prevented by PMTCT in low- and middle-income countries (LMIC) (WHO 2012a).

Despite these successes, many pregnant women still have no access to combination antiretroviral therapy (cART), the most effective intervention in preventing vertical infection to their children. In the last UNAIDS report, only 30% of eligible pregnant women were treated with cART for their own health compared to 54% of all eligible adults (WHO 2012a). In 2013, the first systematic review on uptake of integrated PMTCT programs (implemented between 1997 and 2006) in low- and middle-income countries was published. It showed overall low uptake of PMTCT with a median proportion of 55% HIV-infected women provided with cART in antenatal care and attending labor word. Overall, 79% of infants were tested for HIV and 11% (range 3-18%) were infected (Tudor Car *et al.* 2013).

Resource-limited settings (RLS) face a double challenge: first, to reach full coverage of PMTCT and, second, to provide continuous cART for infected infants. However, the question remains as to whether RLS can ensure that these two interventions are implemented, both in terms of coverage and the necessary financial resources. If budgets and human resources are limited, which strategy should be prioritised in order to save the maximum of lives? Is it preferable to invest in both strategies or to choose the most cost-effective ? As cART is lifelong treatment it seems at first analysis that prevention takes priority over treatment in

term of cost-effectiveness (CE). PMTCT offer benefits for both mother and child's health. However, in many parts of the world the PMTCT regimens used, and coverage are not perfect. On the other hand, neglecting treatment for infants who failed PMTCT would be unethical as rapid progression occur in at least 20% of untreated infants during the first year of life in RRS (Blanche *et al.* 1997; Gray *et al.* 2001) and half will die within the 2 first years of life in RLS (Newell *et al.* 2004).

In this paper, we describe the evidence and success of PMTCT. We analyse the current evidence for early infant diagnosis (EID) and systematic treatment of all HIV-infected infants under the age of 2 years. We perform a review of CE studies on both strategies. Finally, we discuss issues regarding future policies for the fight against pediatric HIV in RLS.

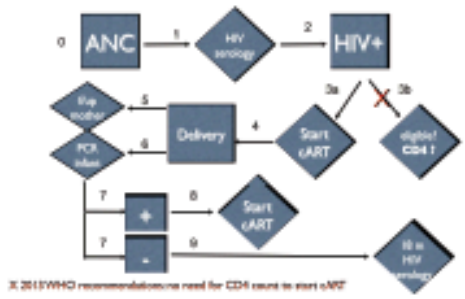
Material and methods

We performed a review on data from peer-reviewed publications, guidelines or abstracts at international meetings concerning PMTCT, (early) cART in HIV-infected infants, CE and public health strategies for elimination of pediatric HIV. Papers were selected on PubMed using terms [prevention of mother-to-child transmission cost-effectiveness], [PMTCT cost-effectiveness], [early infant HIV-1 diagnosis cost-effectiveness], [early infant diagnosis of HIV cost-effectiveness], [antiretroviral therapy infants cost-effectiveness], [early (combination) antiretroviral therapy infants (children) cost-effectiveness], [early HIV treatment infants (children) cost-effectiveness], [PMTCT early initiation of combination antiretroviral therapy]. Papers published between 2008 and 2013 were assessed for inclusion.

PMTCT cascade also known as Piot's model (Fig. 1) is used as a thread to assist in understanding the importance of each step. PMTCT cascade is a tool used to assess program coverage, defined as the final product of a crucial pathway of events that must be put in place to assure prophylaxis and access to treatment in HIV infected/exposed mother/infant pairs. Incremental CE ratio (ICER) is a ratio between net costs and health benefits and means that both cost and health benefits are incremental compared to less expensive and less effective intervention. ICER is often expressed as the net cost per DALY (Disability Adjusted Life Year) averted (Kahn *et al.* 2011). According to WHO, the value of ICER can be fixed by comparison with the country's annual gross domestic product (GDP) per capita. An intervention with an ICER below the annual GDP per capita is considered "very

cost-effective". An ICER below three times the annual GDP per capita is defined "cost-effective" (Kahn *et al.* 2011; WHO 2012c).

Figure 1. PMTCT cascade



Results

Prevention of mother-to-child transmission

In the absence of prophylaxis, the rate of MTCT reaches up to 40% (25-40%). Most infections occur in the peripartum (50-70%) while in-utero transmission accounts for 15-20% (IPHG 1999). In RLS, breastfeeding is responsible for 15-40% of all infections (Kourtis *et al.* 2006). High HIV-1 viral load and low CD4 count are recognized as the most important risk factors determining transmission from the mother to the child (Khouri *et al.* 1995; John *et al.* 2001). Soon after the epidemic emerged, different strategies were deployed to decrease MTCT (Table I. is summarizing the major PMTCT randomized trials).

First, systematic formula feeding was introduced in countries where it was believed to be safe and feasible. In 1994, in PACTG 076, administration of zidovudine (ZDV) during pregnancy, at delivery and to the newborn reduced the risk of MTCT by approximately two thirds (Connor *et al.* 1994). In 1998, obstetrical practices contributed to decrease MTCT with the introduction of elective cesarean section (EMDC 1999; IPHG 1999; Landers *et al.* 1999). Currently, there is a strong body of evidence showing that treating pregnant women with cART is the most effective strategy to prevent transmission of HIV from mother to child (Siegfried *et al.* 2011). Most of the studies assessing different PMTCT regimens and length of treatment were carried out in RLS in order to choose the most cost-effective strategy (Jackson *et al.* 2003; Plipat *et al.* 2007; Leroy *et al.* 2008; Robberstad *et al.* 2010). In RLS, the efficacy of short-course antiretroviral therapy has been demonstrated with the reduction of MTCT to <1%-10% compared with HIV transmission rates of 12%-40% without any intervention (Palombi *et al.* 2007; Plipat *et al.* 2007; Tonwe-Gold *et al.* 2007; Chigwedere *et al.* 2008; Leroy *et al.* 2008; Peltier *et al.* 2009).

Despite this evidence from clinical studies, there are many challenges in RLS to achieve efficient PMTCT. Interventions to

Table I. Overview of major PMTCT interventions (randomized control trials)

Intervention	Author	Year	Setting	Breastfeeding	Intervention	Results (MTCT%)	n	*p*
Caesarean section	European Mode of Delivery Collaboration	1999	Europe	no	201 C/S delivery vs 235 vaginal delivery	3.4% at 18 m vs 10.2% at 18 m	*436*	*P*<0.001
Zidovudine	Connor, E. et al PACTG 076	1994	USA/France	Only 1 mother in the placebo group (baby was not infected)	ZDV pregnancy & IV ZDV labour, oral ZDV baby 6 w vs Placebo	8.3% at 18 m vs 25.5% at 18 m	*402*	*P*=0.00006
	DITRAME	2000	Ivory Coast	yes	ZDV mothers 36 to 38 w gestation, labour & 7 days post delivery vs Placebo	19.8% at 18m vs 29.75% at 18m	*431*	*P*=0.03
	RETRO-CI	1999	Ivory Coast	yes	ZDV mothers from 36 w + labour vs Placebo	12.2% at 4w vs 21.7% at 4w	*280*	*P*=0.05
	Thai-CDC Shaffer, N. et al	1999	Thailand	no	ZDV mothers from 36w + labour vs Placebo	9.4% at 6 m vs 18.9% at 6 m	*1140*	*P*=0.006
ZDV+3TC	PETRA	2002	Tanzania-Uganda-South-Africa	yes	arm1 ZDV-3TC mothers from 36w+labour+7days PP AZT-3TC newborns 7 days arm2 as arm 1 without prepartum component arm3 only intrapartum AZT-3TC	arm1 5.7% & 15% at 6w & 18 m arm2 8.9% & 18% at 6w & 18 m arm3 14.2% & 20% at 6w & 18 m	*1797*	*P*=0.001* 6w NS 18m (vs placebo) *P*=0.025 6w NS 18m (vs placebo) *P*=0.74 6w NS 18m (vs placebo)
Long ZDV vs Short ZDV	PHPT Lallemand, M. et al	2000	Thailand	no	ZDV mothers from 28w ZDV newborns 6w vs ZDV mother from 35w ZDV newborns 3d	4.1% at 6m vs 10.5% at 6m	*1437*	*P*=0.004
sdNVP vs IP and PP ZDV	HIVNET 012	2003	Uganda	yes	sdNVP mothers labour sdNVP newborns vs ZDV mothers labour ZDV newborns 7d	15.7% at 18 m vs 25.8% at 18 m	*616*	*P*=0.0023

*Efficacy of arm 1 and 2 disappeared at 18 months due to MTCT through breastfeeding

Table I (next). Overview of major PMTCT interventions (randomized control trials)

Intervention	Author	Year	Setting	Breastfeeding	Intervention	Results	n	*p*
sdNVP vs Short ZDV	Chung, M.H. et al	2005	Kenya	Yes	sdNVP mothers labour sdNVP newborns vs ZDV mothers from 34w +labour	6.8% at 6w** vs 30.3% at 6w	*76*	*P*=0.02
NVP vs NVP+ZDV	Taha, T.E. et al	2003	Malawi	Yes	sdNVP newborns after birth vs sdNVP newborns after birth + ZDV 7d	15.3% at 6-8w vs 20.9% at 6-8w	*1119*	*P*=0.03
Triple cART vs others	Kesho Bora	2011	Kenya, Burkina-Faso, South Africa	Yes (mixed feeding)	ZDV-3TC-LPV/r mothers from 28-36w until cessation breastfeeding (max 6.5m) sdNVP newborns + 7d ZDV vs ZDV mothers from 28-36w sdNVP mothers labor ZDV-3TC mothers 7d PP sdNVP newborns + 7d ZDV	5.6% at 12m (in breastfed infants) vs Shapiro et al[27] 10.7% at 12m (in breastfed infants)	*882*	*P*=0.02
Triple cART vs Triple Cart	Mme Bana Shapiro R.L. et al	2010	Botswana	Yes	ABC+3TC+ZDV mothers from 26-34w until 6 m PP sdNVP newborns after birth + 4w ZDV vs ZDV+3TC+LPV/r mothers from 26-34w until 6 m PP sdNVP newborns after birth + 4w ZDV	2.1% vs 0.4%	*560*	NP

NP : not powered to compare difference in HIV-transmission

** sustained viral suppression in breastmilk in single dose nevirapine (sdNVP) group

assure PMTCT have been exposed in the PMCT cascade (Fig.1). One of the main challenges is to reach sufficient coverage and uptake of HIV testing for pregnant women after getting them into antenatal care (Fig. 1 step 0 -1). In 2010, an estimated 35% of pregnant women in LMIC were tested for HIV compared to 8% in 2005 (WHO 2011a). This is an improvement but it is far from optimal. To increase HIV testing uptake rates, WHO is promoting the integration of HIV prevention, care and treatment services within maternal health programmes. In 2010, only 63% of pregnant women were tested in Uganda (Larsson *et al.* 2012). In this study, barriers for testing include lack of onsite testing facilities, poverty, lack of male partner support and distance to health facilities (Larsson *et al.* 2012). Retesting during pregnancy is another important issue and potential barrier to efficient PMTCT (Figure 1 step 4-5). At first HIV testing some women will be tested negative because they are in the serological window period. Other seronegative women will get infected during late pregnancy or during breastfeeding (Johnson *et al.* 2012). Retesting strategy during late pregnancy or at labor has been shown to be cost-effective in endemic countries (Soorapanth *et al.* 2006; Kim *et al.* 2013). In the first study, retesting women at 34 weeks of gestation (after initial test at 20 weeks) would prevent 76 new pediatric infections and was CE if ART is available to treat children (Soorapanth *et al.* 2006). In the second study, different strategies were compared using one or 2 tests during pregnancy and/or using confirmatory HIV-RNA testing by PCR. The strategy of repeating HIV serology at delivery was considered CE with 415 765 life years saved and an ICER of 379 USD (Kim *et al.* 2013).

Once diagnosed, pregnant women need to access to appropriate care including cART (Fig 1 step 2). In the last WHO update, in june 2013, two options for PMTCT programmes are promoted (WHO 2013). The first option involves the administration of lifelong cART to all HIV-infected pregnant and breastfeeding women, regardless of CD4 count or clinical stage (ex-option B+, WHO 2012b). The second option is to provide cART for pregnant and breastfeeding women with HIV during the MTCT risk period and to continue lifelong cART only for the women who are eligible for their own health (ex-option B, WHO 2012b) (Table II).

Table II. WHO PMTCT options (2013 update)

<table>
<tr><th>National PMTCT programme option</th><th colspan="2">Pregnant and breastfeeding women with HIV</th><th colspan="2">HIV-exposed infant</th></tr>
<tr><td rowspan="2">Use lifelong ART for all pregnant and breastfeeding women ("Option B+")</td><td colspan="2">Regardless of WHO clinical stage or CD4 cell count</td><td>Breastfeeding</td><td>Replacement feeding</td></tr>
<tr><td colspan="2">Initiate ART and maintain after delivery and cessation of breastfeeding</td><td rowspan="3">6 weeks of infant prophylaxis with once-daily NVP</td><td rowspan="3">4–6 weeks of infant prophylaxis with once-daily NVP (or twice-daily AZT)</td></tr>
<tr><td rowspan="2">Use lifelong ART only for pregnant and breastfeeding women eligible for treatment ("Option B")</td><td>Eligible for treatment[a]</td><td>Not eligible for treatment[a]</td></tr>
<tr><td>Initiate ART and maintain after delivery and cessation of breastfeeding [b]</td><td>Initiate ART and stop after delivery and cessation of breastfeeding [b,c]</td></tr>
</table>

Current PMTCT WHO strategies : review of cost-effectiveness studies

1. Setting and methods

Eight studies on PMTCT CE were published in the last 5 years with a large spectrum of results. Heterogeneity derives from the area of intervention, the level of the country's health expenditure and the urban/rural environment (Table IIIa and 3b). All except one study was conducted in sub-Saharan Africa (Table IIIa). All studies used sensitivity analysis except Schmidt et al. who made a cost-comparison but not using common variables such as ICER or DALY. Number of HIV-infected babies at birth was only reported in 2 studies for the year 2009 with 67000 to 125 000 and 110 000 new infections per year for Nigeria and Uganda respectively. All except one study (Schmidt *et al.* 2012) were comparing WHO «option B» to other PMTCT strategies. In this last study, the objective was to see if costs of cART given during second and third trimester of pregnancy might be offset by the hypothetical lower costs of treating a decreased number of perinatally HIV-infected infants (Schmidt *et al.* 2012). Two studies included « option B+ » in their CEA (Table IIIa).

Table IIIa. Settings and methods of studies on PMTCT cost-effectiveness (2008-2013)

Authors (years)	Setting	ANC HIV preval (%)	ANC PMTCT (%)	Interventions/objectives
Shah, M. (2011)	Nigeria	4	10%	Compare MSOC vs option B at 3 different levels of PMTCT coverage : 10-58-100%
Schmidt,NC. (2012)	Dom.Republic (Capital + La Romana)	2.5	ND	Could extra-cost of cART (vs sdNVP) be offset by reduced infant HIV infection?
Orlando S. (2010)	Malawi DREAM study	25.07	ND	Compare option B with no intervention[*]
Ciaranello, AL. (2013)	Zimbabwe	16	56	Compare 5 options : no intervention, sdNVP, option A, B and B+[#]
Kuznik, A. (2012)	Uganda (single rural hospital)	ND	51.6	Compare 4 options : no intervention, sdNVP, dual therapy or option B. Assessment for 18 months cART & lifelong cART[**]
Binagwaho A. (2013)	Rwanda	4.3	68 (year 2009)	Compare dual therapy with option B[##]
Robberstad, B. (2010)	Tanzania	2	ND	Compare PMTCT+ (option B) with sdNVP[***]
Fasawe, O. (2013)	Malawi	ND	23-31 (year 2010)	Compare option B+ with current practice[###], option A and B

CEA : cost-effectiveness analysis, ND : no data ; SA : sensitivity analysis, CC : cost-comparison, MSOC : minimum standard of care (zidovudine + lamivudine from 34 weeks of pregnancy until 7 days post- partum and sd-NVP at delivery for mother and baby)
[*]Option B in this study: cART : stavudine/zidovudine + lamivudine + nevirapine (from 25th week of gestation until weaning breastfeeding at 6 months = 10 months cART) ; [#] Clinical outcomes :HIV-infection risk at weaning, Maternal LE from delivery, Infant LE from birth ; economic outcomes: ANC costs, maternal HIV-related costs, infant healthcare costs. [**] Clinical outcome : MTCT ; 1st study to evaluate CE for lifelong cART ; [##]Children HIV infections averted and 18 months HIV free survival. [***] Child infection averted = primary outcome ; [###] Depending on availability and setting, sdNVP or dual-drug regimen or cART prophylaxis until cessation of breastfeeding.

Table IIIb. Results of cost-effectiveness of PMTCT studies (2008-2013)

Authors (years)	Infant HIV infection averted	ICER/DALY averted	ICER/HIV infection averted	DALY averted	Discount rate (%)	Cost-year currency	GDP per capita	Cost-effectiveness
Shah, M. (2011)	7680[*]	113[*]	3203[*]	230400[*]	3	2010 USD	1191[**] (year 2010)	Option B CE compared to MSOC
Schmidt,NC. (2012)	698	ND	ND	ND	ND	ND	ND	cART CE compared to sdNVP
Orlando S. (2010)	370	35	998	10449	3	2007 USD	667	Option B CE compared to no intervention
Ciaranello, AL. (2013)	ND[#]	ND[##]	ND	ND[###]	3	ND	400[####] (year 2008)	Option B+ CE compared to no interevention, sdNVP, option A and B.
Kuznik, A. (2012)	ND[¶]	46, 99, 34[¶¶]	ND	5.21, 3.22 and 8.58	3	2011 USD	490 (year 2009)	Option B CE compared to simpler interventions
Binagwaho A. (2013)	3863[§]	ND	11882[§§]	ND	3	570 RF= 1USD	ND	Option B CE compared to dual therapy
Robberstad, B. (2010)	0,0027/ pregnancy[π]	162	4062	0,0067/ pregnancy[π]	3	2007 USD	ND[ππ]	Option B CE compared to sdNVP
Fasawe, O. (2013)	15606-15997[ß]	38-68-64[ß ß]	844-1331-1265[ß ß]	ND	ND	ND	310[ß ß ß] (year 2010)	Option B+ CE compared to simpler interventions

CE : cost-effective ; RF : Rwandan Franc ; ND : no data ; WTP : willingness to pay
[*]Compared with MSOC if implemented at 58% (current ANC coverage) ; [**] per DALY averted ; [#] 18-month infant HIV infection risk 5.7% for option B+ compared to 7.5%, 14.2%, 24.8% for option A, sdNVP and no intervention respectively ; [##] ICER/YLS : 1370 USD option B+ compared with option B; [###] Option B+ increases combined mother-infant LE to 39.04 y (from 36.03 without intervention); [####] per year life saved (YLS); [¶] MTCT 3.8% with option B compared to 17.4%, 25.8% and 40% for dual therapy, sdNVP and no intervention respectively ; [¶¶] 18 months ART compared with sdNVP, dual therapy and no intervention for a cost per DALY averted of US$ 46, US$99 and US$34 ; [§] Number of infection averted with Sc HAART + replacement feeding compared to no intervention ; [§§] Sc-HAART with 12 months breastfeeding (BF) : more children alive HIV-uninfected by 18 months than Sc-HAART with 6 months BF for ICER/child alive and uninfected of 11,882 USD ; [π] 5.2 times more effective than sdNVP (0.00051 infection and 0.013 DALYs averted per pregnancy) ; [ππ] if WTP is superior to 162 USD/DALY, the option B is CE ; [ß] Option A, B and B+ averted the same amount of new infant HIV infections ; [ß ß] ICER/DALY averted and ICER/ HIV-infection averted for option A, B and B+ respectively (ICER/DALY averted compared to current practice) ; [ß ß ß] Option A, B or B+ have ICER/DALY averted less than 3x GDP per capita and are CE compared to current practice.

Cost-effectiveness analysis results

In all studies including «option B » in their model, this strategy was more CE than simpler or no PMTCT intervention (Table IIIb). For example in Nigeria, if «option B » is implemented at 58% ANC coverage instead of minimal standard of care, this will prevent 3203 new vertical infections per year with an ICER/DALY averted of 113 USD (Table IIIb). In 2 out of the 8 studies, "option B+" was also simulated and was superior to all other options. In one of those studies, the 3 options (A, B and B+) were in fact similarly CE in preventing new pediatric infections compared to the practice they were using at the time but "option B+" had the advantage to increase maternal ten-year survival by more than four-fold. "option B+" will save more than 250,000 maternal life years compared to mothers receiving only Option A or B (Table IIIb).

2. Limitations

There are several limitations in the cited studies. One study was limited to a single rural hospital limiting generalizablitity to other contexts (Table IIIa). The model developed in Malawi may not be applicable to low prevalence setting, using replacement feeding or with low fertility (Fasawe *et al.* 2013). Two important factors were considered to influence CE in some studies; HIV prevalence and PMTCT coverage. If coverage is low, some more complex PMTCT interventions become less CE (MSOC more CE than "option B" in Nigeria) (Shah *et al.* 2011). Similarly, in Malawi, in mothers with high CD4 counts, poor adherence or lost to follow-up after delivery, projected maternal life-expectancy is superior with option A compared to "option B". In areas with lower HIV prevalence, CE was improved when simulating higher prevalence such in Tanzania comparing sdNVP with "option B". If HIV prevalence increases from 2% to 6.6%, ICER improves from 162 to 60 USD/DALY.

Adherence was not taken into account in most of the studies (Kuznik *et al.* 2012; Binagwaho *et al.* 2013; Fasawe *et al.* 2013). Estimating life-expectancy of HIV-infected children and the lifetime costs for ART was also challenging (Shah *et al.* 2011; Ciaranello *et al.* 2012). Another limitation is that studies do not account drug resistance and needs for 2nd or 3rd line treatment, important factors that could influence CE (Ciaranello *et al.* 2012; Fasawe *et al.* 2013).

Early infant diagnosis (EID) and systematic early treatment of HIV-1 in infants

1. Early diagnosis : trends

In 2011, only 28% (25–31%) of children 0–14 years old eligible for treatment were effectively receiving cART lagging significantly behind the 58% coverage for adults (WHO 2012a). It is explained by the fact that few of these children are being diagnosed or not enrolled in pediatric HIV care (figure 1 step 8). Globally, access to EID among HIV-exposed infants remains alarmingly low at 28 per cent in 2011, up from just 6 per cent in 2009 (WHO 2011a). On the basis of current estimates, more than 1 million infants born to HIV positive mothers went without a polymerase chain reaction (PCR) test at 6 weeks (WHO 2011a), (Figure 1 step 6).

However, significant progress was recently documented in Rwanda showing an increase of more than 250 per cent in overall EID coverage among all estimated HIV-exposed infants in Rwanda between 2008 and 2010 (Binagwaho *et al.* 2012). Between 2008 and 2011, the performance of routine PCR in south-african HIV-exposed infants younger than 2 months increased from 36.6% to 70.4% (Barron *et al.* 2013).

2. Early diagnosis : barriers and advantages

There are several barriers for EID. The costs of early diagnosis in infants is high (Sherman *et al.* 2005; Creek *et al.* 2008). Diagnosis of HIV infection in young infants (less than 18 months) requires polymerase chain reaction (PCR) techniques, that are more costy than classical serological tests used in older children and in adults. Very limited data exist on CE of early infant diagnosis. One study showed rapid HIV test screening CE before a PCR was used (Menzies *et al.* 2009). Other issues include difficulties in reaching infants for testing, technical problems such as blood collection, transport of the specimen to the appropriate laboratory, work overload of laboratories performing PCR resulting in delayed results, returning results to the concerned patients and linking HIV-infected infants to care (Ciaranello *et al.* 2011).

However, EID has clear advantages. An early negative virological test (PCR) for HIV-exposed infants provides reassurance to families (Creek *et al.* 2007) and caregivers may more readily bond with a child known to be HIV-uninfected (Varga *et al.* 2005). On the other hand, EID allows early treatment in those who are infected. An ongoing trial (NCT01433185) is evaluating if text messages sent through

mobile phones to women enrolled in PMTCT programs could increase uptake of DNA PCR HIV testing at 6-8 weeks among infants exposed to HIV. This could potentially decrease the attrition in the cascade (Fig. 1 step 6).

3. Rationale for early treatment

One major study provides evidence supporting early initiation of cART. In the Children with HIV Early Antiretroviral (CHER) study, asymptomatic infants, aged 6–12 weeks, were initiated on cART as soon as feasible after the diagnosis of HIV infection (median age of 7 weeks). A 76% decrease in mortality was observed in early starters compared to those starting cART at a median age of 6 months based on the 2006 World Health Organization (WHO) immunological or clinical criteria (WHO 2006; Violari *et al.* 2008). Later on, a retrospective European study showed that infants started on cART before 12 weeks of age were five times less likely to develop AIDS or die in infancy (Goetghebuer *et al.* 2009). Six years after randomization, CHER is still showing better outcome in early treated children with at least 2-fold higher number of deaths in the cART deferred arm (Cotton *et al.* 2012). Therefore, WHO guidelines now recommend early cART (as soon as the diagnosis is established) and to initiate cART in the 5 first years of life regardless of CD4 or clinical criteria (WHO 2013). A recent Cochrane review concludes that immediate ART reduces morbidity and mortality among infants and may improve neurodevelopmental outcome (Penazzato *et al.* 2012).

4. Early treatment : costs and cost-effectiveness

There is scarce data in the literature on CE of early treatment in HIV-infected infants. Treating children has a cost, *a fortiori* if this lifelong treatment is started early. Moreover there is some evidence suggesting that ritonavir-boosted lopinavir (LPV/r) based is more potent that NVP-based for first regimen (Violari *et al.* 2012) but LPV/r-based regimen is more expensive. For a child weighing 10 kg, a NNRTI-based regimen will cost 100 USD versus >300 USD for LPV/r-based regimen (CHAI 2012).

However, early cART reduces total yearly cost per child (1349 USD) compared to deferred therapy (2432 USD) or routine care (2908 USD) (Meyer-Rath *et al.* 2010). This was mostly due to cost savings from a drop in hospitalizations (Meyer-Rath *et al.* 2010). In the USA it has been calculated that 9 years of one child's survival cost $113,476, 15 years cost $151,849 and 25 years cost $228,155 and that cART-related costs are now outweighing hospitalization costs (Sansom *et al.* 2006). In another

study from US, total costs were 25.2% inferior in the higly active antiretroviral era (HAART) era (1997-2007) than in the previous era (1990 –1996) because higher drug costs were compensated by 57% lower ($p<0.001$) total inpatient plus outpatient costs (Wilson *et al.* 2010). In LRS, little is known about the cost of pediatric cART. A recently published south-african study, performed prior to early treatment guidelines, showed that costs/year were similar between 2 clinics and comparable to adult costs (Meyer-Rath *et al.* 2013). Antiretroviral costs are expected to decrease overtime by further development of generic fixed-dose combination for children.

PMTCT and pediatric treatment : are there enough resources ?

We only found one study forecasting costs and human resources requirements for both PMTCT and pediatric treatment for the period 2007-2015 with available AIDS budgets and health personnel in 7 countries. It was estimated that PMTCT would absorb 86% of the budget and pediatric treatment 14%. The average cost of preventing a case of MTCT over the duration of the model is US$1285 but after scale-up is complete in 2010, it drops to under 1150 US$/case prevented. They further predicted that Burkina-Faso, Rwanda and Zambia (if AIDS funding continues as previously) would have enough resources to attain the United Nations General Assembly Special Session (UNGASS) targets and to scale-up pediatric treatment with universal access. However, Côte d'Ivoire and Malawi would not receive sufficient funding to achieve both PMTCT and pediatric treatment (Nakakeeto *et al.* 2009). Human resources were a major problem to ensure both interventions with only Zambia having enough healthcare workers. If the coverage of interventions increases to 80%, UNGASS goal of a 50% reduction in the number of children infected with HIV can be reached but human capacities is predicted to be the major bottleneck in most settings (Nakakeeto *et al.* 2009).

Discussion

In light of the current drive to eliminate new HIV infections in children, is early cART still a priority ? In our opinion, the answer to this question is affirmative. Although PMTCT remains the top priority and is cost-effective, it is still seriously hampered by bottlenecks (Fig.1). The remaining children who will escape from PMTCT and being infected will imperatively require early diagnosis and treatment, a lifesaving strategy, with decreased costs overtime as number of

perinatally HIV-infected children and prices of antiretrovirals are expected to continue to drop.

The first part of our review focused on CE of PMTCT strategies which include for the first time studies comparing "option B+" with other PMTCT interventions.
In light of those studies, it clearly appears that "option B" is CE compared to simpler strategies such as sdNVP or dual-therapy. In 2 studies including "option B+" in their CEA, this last option pretends to be superior. The authors claim that B+ should be strongly considered for its numerous advantages.

Arguments pro "option B+"
Positive impact on retention in care with decreased risk for opportunistic infections and prevention of maternal deaths with positive effect on child survival, reduction of AIDS orphans and reduction of HIV transmission within discordant couples (Anglemyer *et al.* 2011; Jia *et al.* 2012). Other advantages of this strategy is simplicity as there is no need for CD4 testing to judge woman's eligibility to start cART (Fig 1 step 2b). This could improve PMTCT uptake in some countries such as Malawi where access to CD4 count is limited (MOH Malawi 2013). The message is clear for the community: once cART is started, it is for life. In Malawi, "option B+" was recently launched by the Ministry of Health in order to provide the best public-health approach adapted to their setting (Schouten *et al.* 2011). The chosen ARV regimen is the fixed-dose combination of tenofovir (TDV), lamivudine (3TC) and efavirenz (EFV). The efficacy of this regimen for hepatitis B-HIV coinfection is an added value as 10-15% of HIV-infected patients in Malawi are coinfected with hepatitis B.

Arguments against "option B+"
Serious objections have been raised against "option B+" (Coutsoudis *et al.* 2013). For them, current evidence for superiority of "option B+" is lacking and this option could potentially disorganize HIV program by interfering with existing activities (eg : treatment of medically eligible HIV-infected patients). Current or future resources, including scarce health personnel, may be insufficient. Retention rates and adherence are unknown in pregnant women with no need of cART for their own health and long-term consequences on HIV drug resistance could be negative (Fig 1 step 5). (Coutsoudis *et al.* 2013). A meta-analysis shows that only 73.5% of pregnant women achieved optimal adherence to cART (>80%) and that adherence was significantly lower during postpartum (Nachega *et al.* 2012). More recently a

south african study showed that 57.5% (95% CI 51.6–63.3%) were lost between HIV testing and 6 months post-delivery (Clouse *et al.* 2013). However a recent report from Malawi shows a 12 months retention rate (77%) similar to the rate for all adults in the national program. This represents a huge improvement as in a previous study, although 9 on 10 women were tested for HIV in rural Malawi, more than three-quarters of this cohort was lost to follow-up by the 6-month postnatal visit (Manzi *et al.* 2005).

«Option B » or « Option B+ » ?

To answer the question of whether or not "option B+" is superior, a randomised trial (PROMISE study) comparing « option B » and B+ is ongoing and first results are expected for early 2016 (NIH 2010). For the time being, each country will have to choose its own strategy according to existing resources and feeding practices. "Option B+" is probably the best option for countries like Malawi and Mozambique with high fertility and long breastfeeding period but not for South Africa where fertility is lower and breastfeeding is a less common practice.

During the last 10 years, we found 2 systematic reviews on PMTCT CE (Scotland *et al.* 2003; Johri *et al.* 2011). In the first study, 9 studies were included. The quality of reporting was found to be lacking regarding amounts of resources required for interventions, and the methods for estimating health outcomes and unit costs. In this systematic review, more recent studies were showing more CE ratios than older studies due to lower drug costs and in some studies the use of shorter drug regimens (Scotland *et al.* 2003). In the second systematic review, the authors found 19 articles published from 1996 to 2010. Sixteen articles concluded that an MTCT intervention was cost-effective. Divergent results were found by 1 study, which analyzed long course AZT and reflected older (higher) drug costs, and 2 other studies, which considered very low HIV prevalence settings (Johri *et al* 2011). The authors conclude that in low HIV prevalence settings, PMTCT may offer a low relative value as compared to competing interventions to improve population health. In those 2 reviews, such as in ours, comparison of those studies was hampered by heterogeneity. The contexts are very different and the costs were contemporaneous to each study period and now outdated. A way to overcome this difficulty is to apply the model developed by Nakakeeto by comparing existing health workforce and available budgets with forecasted costs and human resources needs (Nakakeeto *et al* 2009).

The second part of our review focused on early diagnosis and treatment of HIV-infected infants. We reviewed latest progress of early infant diagnosis scaling-up and its advantages as well as the bottlenecks impeding with full coverage and effectiveness. Early cART in infants below 1 year of age is now an evidence (Violari *et al.* 2008). In WHO 2010 guidelines, this recommendation was further extended to include all children under 2 years of age (WHO 2010b). This age extension was proposed because the risk of disease progression and mortality remains high between 1 and 2 years of age if left untreated (WHO 2010b). New WHO guidelines released in June 2013 are now recommending universal treatment in all less than 5 years old children. This new strategy should improve cART coverage and retention in care in children (WHO 2013).

We did not find studies on CE of early initiation of cART although one study shows decreased costs in term of hospitalizations and associated-costs (Meyer-Rath *et al.* 2010). However long term costs including life-long antiretroviral treatment and related complications are unknown and could counterbalance the current benefits in term of health economy. But, as stated above, with PMTCT scaling-up, the number of HIV-infected infants should dramatically decrease resulting in reduced global pediatric treatment cost. However, mathematical models predict that even with optimal coverage the goal of elimination of pediatric HIV infection in 2015 will not be reached (Mahy *et al.* 2010). Mahy et al. estimated that transmission would drop to 8% and new pediatric HIV infections would represent 72000 in 2015, a 79% reduction from 2009 estimates (Mahy *et al.* 2010). With the best scenario, early diagnosis and treatment of HIV-infected infants will still be a reality for many years although the total number of children requiring treatment is expected to decrease.

Conclusion

HIV is now a chronic disease and lifetime costs are likely to increase further in the vertically-infected population, highlighting the CE of preventing mother to child transmission. "Option B+" appears to be the ideal option by its numerous advantages for the patients, their partners and their children, in settings with high fertility rate and long breastfeeding practice. However generalization of this strategy requires further evidence. Maximal effort should be focused on full coverage of PMTCT and strengthening of the cascade of care especially when resources are scarce in HIV highly endemic countries. If success is achieved,

it will lead to progressive elimination of new diagnosis of HIV infection in infants, saving years of life-long cART, drug-related adverse events and long-term complications of HIV. However in case of treated very early after his birth (Persaud, Gay et al. 2013) efforts should still remain PMTCT failure, it is still a priority to establish early diagnosis and treatment in HIV-infected infants. In conclusion, despite the recent hope of possible functional cure of HIV in a child who was focused on elimination of mother to child transmission.

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2. IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME IN CHILDREN

Within days to months after initiation of cART, the recovery of immune response may manifest as paradoxical clinical deterioration due to the restoration of responses to infectious and non-infectious antigens[217]. This may result in the deterioration of previously diagnosed infection (paradoxal IRIS) or the manifestation of previously undiagnosed subclinical infection (unmasking IRIS)[218]. Currently the consensus is to call this phenomenon immune reconstitution inflammatory syndrome (IRIS)[219]. Although IRIS was first described in HIV-infected patients, a similar phenomenon can occur in HIV-negative patients such as neutropenic hosts, solid-organ or stem cell transplant recipients, and patients receiving immunosuppressive drugs[220, 221].

In November 2006 I have participated to the first international workshop on IRIS in Kampala. At this meeting, consensus case definitions for paradoxical tuberculosis-associated IRIS, ART-associated tuberculosis, and unmasking tuberculosis-associated IRIS were designed. It was planned that these definitions could be used by clinicians and researchers in different settings to promote standardisation and to compare their data. At this time, no real consensus was existing for paediatric IRIS case-definition and few data were available on IRIS in the paediatric population in general. At this meeting I have presented a retrospective study on IRIS performed in Pietermaritzburg, South Africa.

During my work at the HIV clinic in Pietermartizurg, where at the time 1500 children were on cART, IRIS manifestations were daily observed in children. One of the commonest was BCG IRIS (picture 4). We were also intrigued by the fact that many children starting cART were developing skin problems shortly after initiation of treatment. The clinical spectrum was wide, from plane warts (picture 5) or mollusca contagiosa (picture 6) to aggressive zoster (picture 7).

For this purpose, we performed a retrospective study of the first 100 children started on cART at Edendale Hospital, Pietermaritzburg, between 2004 and 2005. We collected clinical and laboratory data in order to both identify IRIS events and to correlate them with immunological and biochemical markers. Two independent observers (Dr Sanjay Patel and myself) reviewed all the data collected and classified each case as either likely, possible or unlikely IRIS.

Case definitions :

Likely IRIS

•Severe inflammatory event (requiring admission)

OR/AND

•Number of significant inflammatory events occurring around the same period

At least 2 weeks after commencement of cART

Possible IRIS

•Inflammatory event occurring at least 2 weeks after commencement of cART

–Ex: Cough for more than 2 weeks, skin rash

Unlikely IRIS

No significant inflammatory event

OR

Minor events (impetigo, self limited cough…)

at least 2 weeks after commencement of cART

Results

Twelve children were defined as having likely IRIS and 39 defined as not having IRIS, as shown in Table XV. The children with likely IRIS experienced a total of 19 inflammatory events (9 chest and 10 skin) with a median time of onset of 8 weeks (IQR 4-16). The median time for chest signs was 12 weeks (IQR 2-12) and median time for skin signs 8 weeks (IQR 4-48). Baseline characteristics were similar between the 2 groups apart from baseline CD4% - likely IRIS 5.7% (IQR 4.6-5.9) and unlikely 10.5% (IQR 6.6-14.2%). Skin manifestations were predominant with 58 out of 100 children presenting with a new onset skin rash after starting cART. In these 58 patients, there were 73 skin pathologies, as seen in Figure 5. Examples of new onset skin rashes are shown in pictures 4-7.

In conclusion of this study, we acknowledge considerable difficulty in diagnosing IRIS, especially based on clinical findings alone. This was evidenced by the high discordance between the 2 observers in the classification of cases. This study suggests that low CD4% at baseline may be a risk factor for IRIS, as suggested by previous studies[217, 222, 223]. In our study, IRIS presented as early as 2 weeks after commencement of cART. On the other hand, new onset skin rashes presented up to a year after starting cART. A significant observation in our cohort of patients was the high incidence of new onset skin rashes in children following cART (58%). It remains unclear if this represents a skin manifestation of IRIS. If so, the coexistence of a new onset skin rash may act as a surrogate marker in assisting with the

diagnosis of IRIS in cases of worsening chest pathology such as TB IRIS after starting cART. A study performed on a cohort of adult patients has also suggested a high incidence of skin IRIS.

Thereafter, skin manifestations of IRIS have been documented in several studies in adults and in children[224-226] and more recently in a study where new onset of papular pruritic eruption was documented in 47 out of 110 children initiated on CART[227].

Boulware et al. proposed case definitions for IRIS in children to which I have participated (Table XVII)[228]. Management of IRIS in children is summarized on table XVII, issued from this review.

Table XV. Baseline characteristics of recruited patients
(IRIS study 2004-2005,Pietermaritzburg)

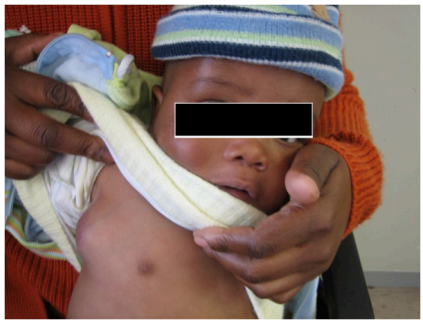
	LIKELY IRIS	UNLIKELY IRIS	ALL RECRUITED
TOTAL NUMBER	12	39	100
AGE (Years)	6,5	5	5,9
WEIGHT (Kg)	16,6	16,9	16,9
STAGE	3	3	3
CD4% at baseline	5,7 (IQR 4.6-5.9)	10,5 (IQR 6.6-14.2)	8,85 (IQR 4.6-12.7)
VIRAL LOAD (copies/ml) at baseline	47000	140000	135000
Hb(g/dl)	10,8	11,8	10,3
Albumin(g/L)	29	31	36
ALT(IU/L)	29	21	19

Table XVI. IRIS events in 12 children (IRIS study 2004-2005, Pietermaritzburg)

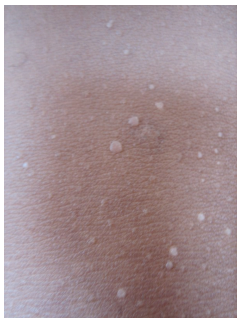
Pts	Skin	Chest	Other
1	Mollusca at 52w	Severe pneumonia at 8w*	
2	Anal warts at 8w	Pneumonia at 16w	
3	Herpes at 5w	LIP 12w#	
4	Fungal rash at 12w	Persistent cough + crackles from 12-40w	
5	Warts at 24w		
6	Herpes at 4w Tinea corporis at 16w	Persistent cough + crackles from 4-28w	
7	Warts at 4w Tinea capitis at 16w	PTB** at 32w	
8	Mollusca at 24w-40w	Persistent cough + crackles from 2-8w	
9		Persistent cough + crackles from 12-28w	
10		Persistent cough + crackles from 12-20w	
11	Fungal rash at 2w Mollusca at 8w		Severe abdo pain at 8w
12	Extensive mollusca at 52w		

** PTB: pulmonary tuberculosis

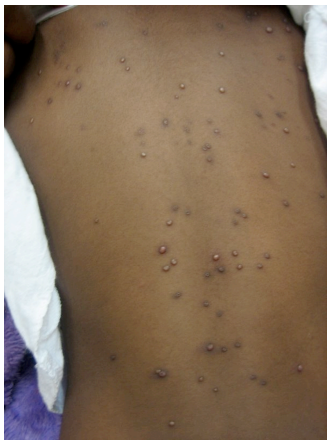
Picture 4. BCG IRIS



Picture 5. Plane warts IRIS



Picture 6. Mollusca contagiosa IRIS



Picture 7. Zoster *IRIS*

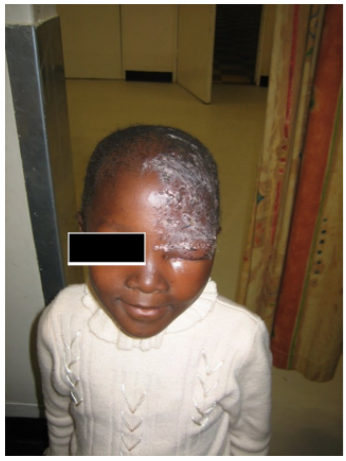


Figure 5. Distribution of skin rashes after starting CART
(73 new rashes in 58 patients)

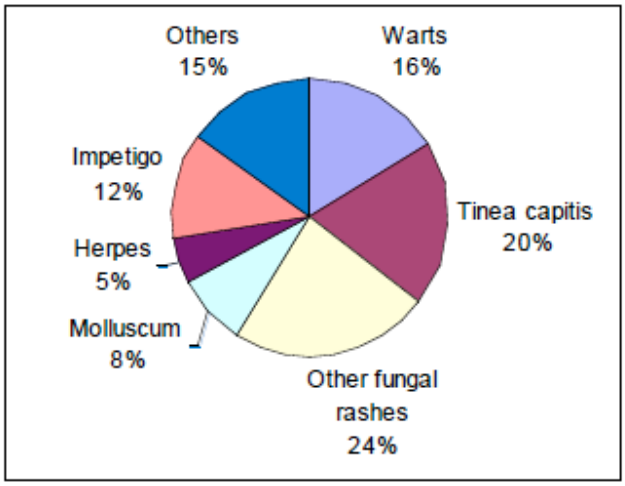


Table XVII. IRIS case definition and treatment strategies

Case Definition: Consensus Criteria for Diagnosis of Pediatric IRIS

1 Evidence of clinical response to ART with:
   a. Virologic response with >1 $\log_{10}$ copies/mL decrease in HIV RNA (if possible).[1]
2 Clinical deterioration from an infectious or inflammatory condition temporally related to the initiation of ART
   a. Unmasking IRIS requires a new active diagnosis[2]
   b. For Paradoxical TB-IRIS, refer to Table 3 for clinical criteria
3 Symptoms cannot be explained by:
   a. An alternate infection or neoplasm
   b. Treatment failure of the opportunistic infection.[3]
   c. Adverse drug reaction
   d. Complete non-compliance to ART or TB treatment[4]

[1] IRIS can occur in the absence of a meaningful rise in CD4 count. In ART naïve persons, an initial virologic response generally always occurs. In non-naïve persons or with known ART resistance, proof of virologic response becomes more important.

[2] Unmasking caveats:

- Active infections, such as TB, should be excluded at time of ART initiation.
- Diagnosis of incident TB infections should conform to national or WHO guidelines. In children, bacteriologic confirmation may not always be achieved.
- "Unmasked" incident infections may have accelerated presentations with exaggerated symptoms.
- Refeeding syndrome of malnourished children may contribute to unmasking opportunistic infections [45*].
- Generally occurs within 6 months after ART initiation.

[3] Paradoxical IRIS can occur with MDR and XDR TB; however, the primary concern is the efficacy of the TB therapy. For TB-IRIS, non compliance and TB treatment failure are critical to exclude.

[4] Even with imperfect ART compliance and lack of HIV virologic suppression, immunologic reconstitution and CD4 rise can occur temporarily.

Treatment Strategies for IRIS

Clinical Severity	Treatment Options
Mild	**Observation**
Moderate	**NSAIDS**
Severe	**Corticosteroids**
	Temporary Cessation of ART
	Surgical debulking
Potential Alternative Strategies	**Chloroquine (anti-TNFα)**
	Thalidomide (anti-TNFα)
	Leflunomide (anti-NFκβ)

No treatment has been prospectively studied in IRIS patients

IRIS can be even more challenging to manage when multiple manifestations occur such as in this case of a child with presumed TB and hepatitis B IRIS that we have previously described[229]. (see article section for full text describing this case report)

3. TRANSITUM – BEYOND TRANSFER: OUTCOME OF HIV-INFECTED ADOLESCENTS

Due to the success of CART, paediatric HIV cohorts are aging and increasing number of adolescents are transitioning to adult care. However little is known about their outcome after transfer to adult services. In Belgium, HIV infected teenagers are looked after by paediatric HIV specialists until they are ready to be transferred to adult HIV specialists. The process of moving adolescents from child health providers to adult care is referred to as the "transition process". It is commonly practiced for children who have other chronic medical conditions such as diabetes or cystic fibrosis and studies showed that many of these adolescents are lost to follow-up, and have had worsening of their health status in the first few years after leaving paediatric care. In contrast, little is known about outcome of HIV infected teenagers after they have left paediatric setting. HIV can be exceptionally challenging to treat, given the virus' unique ability to mutate and develop resistance to antiretroviral medications. Children born with HIV have often been exposed to multiple antiretroviral medications through their lives, and by the time they are teenagers, many have developed resistance to these medications. There is concern that these young adults will have few treatment options available to them in adulthood if we continue to use all available options early on in their care. However, we do not have any information on the progression of their disease after they have left paediatric care in order to change our current practice. We are concerned that a large percentage of these teenagers may be lost to follow-up, have worsening of their disease, and increased mortality as a result of problems with the transition process.

Therefore, the main goal of this study is to study transition and outcome of HIV infected adolescents in Belgium after they left paediatric care.

4. HIV DRUG RESISTANCE IN EARLY TREATED CHILDREN : OPERATIONAL RESEARCH PROJECT

Efficacy of early cART on infant mortality in resource limited settings (RLS) has been demonstrated in the CHER study. Long term virological and DR data are scarce in infants receiving cART in RLS especially in « real-life settings ». Objectives: To describe the current spectrum of resistances found in a previously described cohort of children living in RLS who initiated treatment before 1 year of age, compared to a control paediatric population who

started cART above 2 years of age. Populations: 94 study subjects who were part of a previously described cohort detailled in chapter III.3.B.2.[222] Children were initiated on cART between 2005 and 2008 in South Africa. All HIV infected infants were below 1 year of age at treatment initiation and had completed at least 6 month of treatment. The control group is composed by 100 children initiated on cART > 2 years of age matched for sex and age in a first analysis and for sex and treatment duration in a second analysis.

Methods: We will perform a case control study including children of this previously described cohort. Patients will be seen at their planned appointment or this appointment will be organized if the child is no more followed-up at the clinic. Complete clinical history, anthropometric data and blood samples will be recorded during the visit. Complete blood count, CD4 percentage and routine VL will be analyzed in South Africa and genotypic resistance testing will be performed in Belgium. Collected data will be analyzed in order to determine if introducing cART early in life is associated with increased risk of cumulated mutations.

5. SECOND LINE REGIMEN

Second line antiretroviral treatment in case of treatment failure

WHO second-line treatment (June 2013 update)

After failure of a first-line NNRTI-based regimen, a boosted PI plus 2 NRTIs are recommended for second-line ART; LPV/r is the preferred boosted PI **(Strong recommendation, moderate quality of evidence)**
After failure of a first-line PI-based regimen, a NNRTI plus 2 NRTIs are recommended for second-line ART **(Strong recommendation, very low quality of evidence)**
After failure of a first-line regimen of AZT or d4T + 3TC, ABC or TDF + 3TC or FTC is the preferred NRTI backbone option for second-line ART; ABC + ddI is an alternative regimen **(Strong recommendation, low quality of evidence)**
After failure of a first-line regimen of ABC or TDF+ 3TC or FTC, AZT + 3TC is the preferred NRTI backbone option for second-line ART; AZT + ddI is an alternative regimen **(Strong recommendation, low quality of evidence)**
After failure of a first-line NNRTI-based regimen, a boosted PI plus 2 NRTIs are recommended for second-line ART; LPV/r is the preferred boosted PI **(Strong recommendation, moderate quality of evidence)**

After failure of a first-line PI-based regimen, a NNRTI plus 2 NRTIs are recommended for second-line ART **(Strong recommendation, very low quality of evidence)**
After failure of a first-line regimen of AZT or d4T + 3TC, ABC or TDF + 3TC or FTC is the preferred NRTI backbone option for second-line ART; ABC + ddI is an alternative regimen **(Strong recommendation, low quality of evidence)**
After failure of a first-line regimen of ABC or TDF+ 3TC or FTC, AZT + 3TC is the preferred NRTI backbone option for second-line ART; AZT + ddI is an alternative regimen **(Strong recommendation, low quality of evidence)**

US second-line treatment (last update november 2012)[113]

Antiretroviral (ARV) regimens should be chosen based on treatment history and drug-resistance testing, including both past and current resistance test results • The new regimen should include at least two, but preferably three, fully active ARV medications with assessment of anticipated ARV activity based on past treatment history and resistance test results • Interpretation of resistance test results showing complex combinations of mutations and assessment of future treatment options should be made in collaboration with a paediatric HIV specialist • Use of novel agents with limited available pharmacokinetic and/or safety data in paediatric populations should be undertaken only in collaboration with a paediatric HIV specialist	
Prior regimen	Recommended change in order of relative preference
2 NRTIs + NNRTI	• 2 NRTIs + PI or • 2 NRTI + integrase inhibitor*
2 NRTIs + PI	• 2 NRTIs + NNRTI • 2 NRTIs + alternative RTV-boosted PI • 2 NRTIs + integrase inhibitor* • NRTI(s) + integrase inhibitor* + (NNRTI or alternative RTV-boosted PI)
3 NRTIs	• 2 NRTIs + (NNRTI or PI) • 2 NRTIs + integrase inhibitor* • Integrase inhibitor* + 2 other active agents (chosen from NNRTI, PI, NRTI[s])
Failed regimen(s) including NRTI(s), NNRTI(s), and PI(s)	• 1 NRTI + RTV-boosted PI • NRTI(s) + RTV-boosted PI + integrase inhibitor* (consider adding T-20 and/or MVC**, if additional active drug[s] needed) • NRTI(s) + RTV-boosted DRV, LPV or SQV + ETR (consider adding one or more of MVC**, T-20 or integrase inhibitor*, if additional active drug[s] needed) • 1 NRTI + 2 RTV-boosted PIs (LPV/r + SQV, LPV/r + ATV) (consider adding T-20 or an integrase inhibitor* if additional active drug[s] needed)

* limited pharmacokinetic data in < 6 y old children ** Not FDA-approval for use in children

CURRICULUM VITAE

Dimitri Van der Linden was born on February 15th, 1973. He received undergraduate education (Latin-Greek) at the Petit-Séminaire of Floreffe from 1986 until 1991. He studied the 3 first years of medicine at the University of Namur (former Facultés Notre-Dame de la Paix) and pursued his master at the University of Louvain (UCL) where he obtained his medical degree (magna cum laude) in 1998. Subsequently he specialised into paediatrics at UCL and was trained in different hospitals by outstanding paediatricians (Tournai, Jolimont, Luxembourg, Rocourt, UCL St Luc and the children's hospital Westmead in Sydney, Australia). After his return from Australia, in 2004, he obtained a grant from the European Clinical AIDS Society to work in the Paediatric Department of CHU Saint-Pierre headed by Prof. Jack Levy where he had the great opportunity to learn about paediatric HIV and to perform clinical research. In 2005, he got a diploma in Tropical Medicine at the Tropical School of Antwerp. He then obtained a position of Principal Medical Officer at Pietermaritzburg Metropolitan Hospitals Complex (South Africa) where he was deeply involved in HIV care in children, running a clinic with more than 1500 children treated with antiretroviral therapy. After his return in Belgium in August 2007, he worked for Doctors Without Borders at the head-quarter in Brussels to revise paediatric guidelines for use in the field. In January 2009, he was appointed at the Cliniques universitaires Saint-Luc in the General Paediatrics Department headed at the time by Prof. Didier Moulin with the goal to develop paediatric infectious diseases consultancy inside the Paediatric Department. From 2009 to 2011, he got an additional training and a diploma in paediatric infectious diseases at the CHU Sainte-Justine, Montreal, in the Paediatric Infectious Diseases Department headed by Prof. Bruce Tapiero. Currently, he is adjunct-clinic head of the General Paediatrics Department working as paediatric infectous diseases specialist in the Paediatric Department of the Cliniques universitaires Saint-Luc in Brussels and is active in different local and national committees involved in Infectious Diseases.

Since 2012 he is teaching paediatric infectious diseases for Master 1 students at UCL Medical School and is part of the lecturers committee for the inter-university (ULB, UCL, Ulg) course on infectious diseases and clinical microbiology. From September 2013, he will start teaching Clinical Microbiology at University of Namur's Medical School.

During the past few years, he is active in different local and national committees involved in Infectious Diseases and he is involved in several national and international collaborative research projects.

Dimitri is married to Caroline Ginion, they have three children (Alexandre born in 2005 in Belgium, Julien born in 2007 in South Africa and Camille born in 2009 in Canada).

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Van der Linden D, Lapointe N, Soudeyns H, et al. Portrait de résistance aux antirétroviraux chez des adolescents infectés par le VIH au moment du transfert vers la clinique adulte. Presented at the Journée des Etudiants, Stagiaires, Résidents du réseau SIDA et maladie Infectieuses FRSQ. 19-11-2010, Montreal, Canada. *Won first price (500 $) in the clinical research section.*

Van der Linden D and Patel S. Retrospective study on Immune Reconstitution Inflammatory Syndrome (IRIS) in HIV infected children, Family Clinic, Edendale Hospital, Pietermaritzburg, South Africa. Data presented at the 1st International Workshop on TB-IRIS in Kampala, Uganda (28/11/06-30/11/06)

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