HHS Public Access

Author manuscript

Curr Pediatr Rep. Author manuscript; available in PMC 2016 September 01.

Published in final edited form as:

Curr Pediatr Rep. 2015 September ; 3(3): 219–229. doi:10.1007/s40124-015-0087-7.

Paediatric HIV: Progress on Prevention, Treatment and Cure

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Abstract

Purpose of review—This review provides an update on current developments with prevention, treatment and cure strategies in the field of pediatric HIV.

Recent findings/Summary—There has been tremendous progress in the prevention and treatment of pediatric HIV infection. With new strategies for prevention of mother-to-child transmission, we are growing ever closer towards elimination of pediatric HIV, though challenges with retention of pregnant woman and their HIV-exposed infants remain. Ongoing vigilance regarding the potential hazards of *in utero* ART exposure to infants continues with no significant alarms yet identified. Though cure has not been achieved, evidence of the impact of early treatment on reducing HIV-1 reservoir size with subsequent prolonged remission has enlivened efforts to rapidly identify and treat HIV-infected newborns. There is an increasing array of treatment options for pediatric patients and reassuring evidence regarding long-term complications of ART. Unfortunately, despite evidence suggesting the benefit of early treatment, timely identification and treatment of children remains a challenge. Better strategies for effective case-finding and engagement in care are urgently needed in addition to an improved understanding of how to retain HIV-positive children and adolescents on treatment. However, further emboldened by recent international commitments and robust global support, the future is hopeful.

Keywords

Pediatric HIV; PMTCT; review

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COMPLIANCE WITH ETHICS GUIDELINES

Conflicts of Interest

Maria H. Kim, Saeed Ahmed, and Elaine J. Abrams declare they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

INTRODUCTION

There has been tremendous progress in the prevention and treatment of pediatric HIV infection. In well-resourced settings, comprehensive prevention of mother-to-child transmission of HIV (PMTCT) efforts have resulted in few new perinatal infections (Figure 1) [1**] and an aging cohort of children with established infection surviving into adolescence and adulthood [2*]. We are also finally seeing a shift in the same direction globally alongside an unprecedented international commitment to eliminate new pediatric HIV infections, as well as identify and treat those with established HIV infection.

In 2013, nearly 70% of the estimated 1.5 million HIV-positive pregnant women globally received antiretroviral drugs (ARVs) with a 58% decrease in new pediatric infections from 2002 [3]. The number of HIV-infected children receiving care and antiretroviral treatment (ART) also increased [4] and there is a widening array of antiretroviral medications for pediatric treatment. Finally, there is new interest in very early ART initiation, close to the time of birth, as a way to improve outcomes among HIV-infected infants, minimize viral reservoirs, and inform effort towards achieving a cure [5*,6*].

However, despite improving ART coverage, only 22% of HIV-infected children are currently receiving treatment [4], and a staggering number of childhood deaths, 190 000 [170 000 – 220 000] in 2013, continue to be attributed to HIV infection [7]. Furthermore, large numbers of adolescents are newly acquiring HIV, and HIV has become the second-leading cause of death among adolescents globally (Figure 2) [8]. This review outlines the progress towards prevention, treatment and cure in the field of pediatric HIV.

PREVENTION OF MOTHER-TO-CHILD HIV TRANSMISSION

The number of new pediatric infections globally continues to decrease with 240 000 [210 000–280 000] children less than 15 years of age newly acquiring HIV in 2013 (Figure 1) [4]. Improved access to HIV testing and ART along with better implementation of PMTCT services have likely contributed to this decline. Option B+ has provided a simplified PMTCT approach [9] with increasing evidence supporting its impact on improving maternal access to ART and retention across the PMTCT cascade. However, complex challenges to long-term retention of mothers and their infants throughout the period of MTCT risk are being described. There is also a growing body of research examining the potential adverse effects of *in utero* ART exposure and the cumulative evidence is increasingly reassuring.

Option B+: uptake and retention along the PMTCT cascade

One of the most notable recent developments in PMTCT globally has been the introduction of lifelong ART for all pregnant and breast-feeding women, the Option B+ approach [9]. Option B+ (B+) emerged at a time when there were significant losses along the PMTCT cascade due to the complexity of determining which pregnant women needed ART for their own health from those who required only ARV prophylaxis for PMTCT (Options A and B) [10]. Option B+ simplified the PMTCT implementation strategy by introducing a test and treat approach and reframing PMTCT as lifelong treatment for all pregnant and breastfeeding women, thereby improving access to ART and reducing opportunities for

dropout along the cascade. A recent report on B+ implementation in 11 Sub Saharan African countries, from January 2013–March 2014, demonstrated that at least 50% of HIV-positive women in antenatal care received ART in 8/9 countries, with >80% receiving ART in 4/9 countries [11*]. Another report [12*] from several health centers in urban central Malawi confirmed improved enrollment into PMTCT services after the introduction of Option B+ (68.3% vs. 92.6% post-Option B+; p<0.001) as well as a shorter time to ART initiation (median, IQR 48 days [19,130] vs. 0 days [0,15.5] post-Option B+; p<0.001) [12*]. The only published prospective study [13] comparing Option B+ and Option A, conducted in the Kingdom of Swaziland, reported that a higher proportion of women with CD4 <350 cells/mm^3 initiated ART in health zones implementing Option B+ versus those zones where Option A was the standard PMTCT approach (86% vs. 74%, p=0.032).

However, retention of women and infants within PMTCT services remains problematic. A recent study from Malawi (where Option B+ was first introduced) using aggregate data from 540 health facilities (n=21,939) and patient-level data from 19 facilities (n=11,534) found that loss-to-follow-up (LTFU) at 6 months was 17% amongst women starting ART under Option B+. Moreover, compared to women who initiated ART for their own health, women who started ART in PMTCT services were five times more likely not to return to clinic [OR 5.0, 95% confidence interval (CI) 4.2–6.1] [14**]. A study from northern Malawi also found that women starting ART for Option B+ experienced higher attrition than women of childbearing age starting treatment for other reasons [15]. Amongst women newly initiating ART post B+ at health facilities in central Malawi, a smaller proportion was alive-on-ART six-months after initiation (89.3% vs. 78.8% post-; p=0.0004) and a higher proportion stopped ART (2.2% vs. 8.2%, p=0.002) under Option B+ conditions [12*]. By comparison, in Uganda, retention at 6 months for women who initiated ART was 88%, similar to the 87% seen among other adults, in 149 health facilities supported by the Elizabeth Glazer Pediatric AIDS Foundation, an implementing partner for HIV service delivery in Sub Saharan Africa [11*].

Studies examining these losses reveal the complexity of retaining mothers and babies in HIV services and the myriad of inter-related factors that influence outcomes including health facility and patient-level factors, as well as patient-provider relations and quality of counseling.

A study from southeastern Malawi [16*] examined the relationship between models of service delivery at 141 health facilities and retention among pregnant women initiating ART. Factors independently associated with ART retention were district location, patient volume, and the model of care: facilities where women were referred from the antenatal clinic (ANC) to the ART clinic for initiation and follow-up were five times more likely to have higher retention rates than facilities where women initiated ART in the ANC and were subsequently referred to ART clinic for follow-up [adjusted odds ratios (aOR) 5.4(1.2–28)] [16*]. Another study from central Malawi [17*] described patient-level factors influencing retention. Of 577 HIV+ pregnant women classified as LTFU, 229 were successfully traced; common reasons for stopping ART included travel (38%), lack of transport money (16%), not understanding the initial ARV education session (10%), being too weak/sick (10%), and ARV side effects (10%) [17*]. Qualitative studies from South Africa [18*] and Tanzania

[19] have found that negative experienced and even anticipated [19] clinic staff treatment were important barriers to retention in PMTCT care. A cross-sectional study amongst 277 HIV+ pregnant women in Tigray, Ethiopia [20] found that after controlling for other factors, the odds of adhering to Option B+ PMTCT were 4.7 times higher among women who received medication counseling as compared to those who did not (aOR 4.7, 95% CI 1.98–11.35). Much research is currently underway exploring how best to optimize uptake and retention along the PMTCT cascade [21,22,23,24,25,26,27]. However, much work remains to be done to better understand the complexity of retention, measure long-term retention, and ultimately evaluate impact on MTCT and infant HIV-free survival.

Efficacy and complications of antiretroviral regimens for PMTCT

The use of a once daily regimen, tenofovir (TDF) + emtricitibine (FTC) + efavirenz (EFV), for all pregnant and breast feeding women, the same regimen recommended for non-pregnant adults initiating ART in low and middle income countries is an essential component of the Option B+ approach [9]. The first evidence of the efficacy of EFV-based ART during pregnancy and breastfeeding was provided by the PROMOTE trial (ClinicalTrials.gov, NCT00993031) conducted in rural Uganda [28**]. Among 389 study participants randomized to one of two ART regimens, the proportion of women with virologic suppression (HIV-1 RNA </=400 copies/ml) at delivery was higher with an EFV- vs. lopinavir/ritonavir(LPV/r)-based regimen (97.6% in the EFV arm and 86.0% in the LPV/r arm, p< 0.001) and similar at 48 weeks postpartum (91% and 88.4% for EFV- and LPV/r-based regimens respectively, p=0.49). HIV-free infant survival was also similar between study arms: 97.2% (EFV) versus 92.9% (LPV/r), p=0.10. Effectiveness under non-trial conditions has not yet been evaluated.

There is also an increasingly large body of research examining the impact to infants of HIV and ARV exposure *in utero* and through breastfeeding [28**,29**,30,31*,32*,33,34*,35*,36*,37*,38*,39**,40*,41,42,43*]. Thus far there have been no significant safety alarms or ARVs identified as especially hazardous to the fetus. However, while the substantial benefits of combination ARVs for prevention of pediatric infection and maternal treatment have been repeatedly demonstrated, these drug exposures are not without some cost, albeit modest, to the fetus and infant. Historically efavirenz was contraindicated during pregnancy due to concerns around first trimester exposure and possible central nervous system (CNS) congenital anomalies. A recent meta-analysis confirmed the safety of this drug during pregnancy and found no evidence of increased risk of CNS anomalies with early EFV exposure [29**]. The association between ART during pregnancy and adverse birth outcomes (prematurity, stillbirth, low birth weight and small for gestational age) remains open to debate though emerging evidence suggests that ART during pregnancy, particularly PI-based treatment, may increase the risk of some of these outcomes [29**,30,31*,32*,33]. Protease inhibitor use has been associated with decreased progesterone levels during pregnancy possibly contributing to these outcomes. In an elegant set of experiments, investigators examined the association between lower birth weight and PI-based ART [32*, 34*]. PI exposure was associated with reduced trophoblast progesterone production in vitro; lower progesterone levels and fetal weight in pregnant mice and; lower progesterone levels and smaller infants in 27-HIV-infected vs. 17 HIV-uninfected pregnant women.

Several studies provide reassurance regarding the potential adverse impact of ARV exposure on congenital anomalies [35*], cardiac toxicities [36*], cognitive and language developmental outcomes [37*,38*], hematologic [41,42], mitochondrial and metabolic outcomes [31*]. However, ongoing vigilance will be important, especially as new drugs are introduced into adult treatment regimens, as there will likely be new fetal exposures as women become pregnant. For example, while the Pediatric HIV/AIDS Cohort Study's Surveillance Monitoring of ART Toxicities (SMARTT) Study, a prospective observational cohort study of HIV and ARV exposed uninfected children, found no association of first-trimester exposures with congenital anomalies for any ARV, combination ARV regimens or any drug class. However, among protease inhibitors, first trimester atazanavir (ATZ) was associated with increased risk for skin and musculoskeletal anomalies [35*].

In addition to potential ARV-associated toxicities, there are emerging concerns that HIV-exposed uninfected infants may have other vulnerabilities [40*]. A recent study demonstrated significantly increased risk of invasive pneumococcal disease and mortality among HIV-exposed compared to unexposed young infants in South Africa [43*]. However, many well described, often preventable and easily treated health conditions such as pneumonia, diarrhea, malnutrition, and malaria continue to pose the greatest threats to survival among populations of HIV-exposed, uninfected infants.

TREATMENT OF HIV INFECTION IN CHILDREN

Due to the tremendous success of PMTCT efforts, the perinatal pediatric epidemic in high and many middle income countries is predominantly adolescent with many already transitioned into adulthood. While there is also a growing population of aging adolescents with perinatal HIV in high burden, low resource settings, adolescent issues are still often overshadowed by the need to address the still too many [4] new pediatric infections and substantial unmet treatment need. A new global movement aims to close the treatment gap, but evidence to guide approaches to pediatric HIV case finding is very limited. Substantial delays in both diagnosis and treatment of HIV infection amongst infants and children continue alongside new studies demonstrating the benefit of ART earlier initiation. Amongst adolescents, large numbers are newly acquiring HIV, and are being recognized as a particularly vulnerable group (Figure 2) [8]. At the same time studies determining drug dosing and efficacy of new agents as well as long and short term toxicities and complications continue to shape treatment options for children.

The pediatric treatment cascade

Early infant diagnosis, case finding, ART initiation and retention—Despite improved coverage and uptake of PMTCT, early infant HIV diagnosis (EID) programs continue to underperform. An MMWR report [44*] documented results from the EID program in Francistown, Botswana from 2005–2012. Despite being among the most successful PMTCT programs in sub-Saharan Africa, the report identified substantial challenges in the EID program. Almost one third of the 10,923 HIV-exposed infants did not receive a virologic test to determine infection status and of the 202 infants identified as HIV-infected, only 123 (60%) initiated ART. Similarly, a study from Malawi reported that in the context of Option B+, only 52% of 513 HIV-exposed infants were tested at 6–12 weeks

[45]. Results from a national assessment of missed EID opportunities in South Africa [46*] found that 68% of immunization clinics provided EID testing for infants with reported or documented HIV exposure but only 9% offered testing to infants with undocumented/ unknown HIV exposure. Finally, a cohort study described HIV-exposed infant outcomes in Kinshasa, Democratic Republic of Congo, between 2007 and 2013 [47*]. Despite improvements over time, in 2011–2012 only 63% of infants had EID testing by 2 months of age (95% CI: 59–68%).

Beyond infancy, evidence on the most effective strategies to identify and link HIV-infected children to care is scarce [48,49] and delays in diagnosis and ART initiation persist. One study from Malawi [50*] introduced dedicated community health workers to improve identification and enrollment into care of HIV-infected infants and children by expanding both facility and community based HIV testing. Following the intervention there was a six-fold increase in rate of enrollment of children into HIV care from 3.2 to 19.8 per month. Provider initiated testing and counseling on inpatient wards has been shown to be an effective approach to identify HIV-infected children in high HIV prevalence settings but is rarely implemented routinely. Additional efforts to identify HIV-exposed and infected children and research on the most effective approaches to case finding are warranted.

Timely ART can dramatically reduce morbidity and mortality in HIV-infected children [51]. However, timely ART initiation remains a challenge particularly in countries with the highest burden of pediatric infections [7]. A multi-study collaboration [52*] described trends and determinants of CD4 cell count at ART initiation amongst 34,706 children less than 16 years of age spanning sub-Saharan Africa, Asia, Latin America, and the United States. The study found that although the estimated percentage of children starting treatment with severe immunodeficiency declined over time, in 2010, 70% of children less than 2 years still started ART with severe immunodeficiency despite guidelines recommending universal treatment for all children in this age group.

Unfortunately, not only are children initiating ART late, but they are not optimally retained in care. A study from Mozambique [53*] examined 2-year mortality and LTFU for children <15 years of age initiating ART between June 2006–July 2011. Of 753 children, 29.0% (95% CI: 24.5, 33.2) were confirmed dead by 2 years and 39.0% (95% CI: 34.8, 42.9) were LTFU with unknown clinical outcomes. Treatment was initiated late (WHO stage III/IV) among 48% of those with WHO stage recorded, emphasizing the need for earlier diagnosis and treatment. Similarly, a systematic review including 55,904 pediatric patients receiving first-line ART in routine settings in 23 countries found that retention at 12, 24, and 36 months was estimated at 88, 72, and 67% [54**].

Alongside reports of late treatment initiation is a burgeoning body of evidence suggesting the need for earlier treatment across all ages. The CHER study [51] demonstrated that early antiretroviral therapy, started at 6–12 weeks of age, reduced mortality and HIV progression by 75% [5*]. However, a recent study from South Africa suggests that ART initiation by three months of age may not adequately prevent disease progression [55**]. The investigators extracted records of all infants started on ART by three months of age between June 2007 and September 2010 at 20 public clinics and one large ART hospital service. On

logistic regression, each month increase in age at ART initiation lowered the odds of initiating ART in an optimal state (OR: 0.56, CI: 0.36–0.94) and increased the odds of advanced HIV disease at ART initiation (OR: 1.69, CI: 1.05–2.71).

Results from several studies are building a case for universal treatment for all HIV-infected children independent of age, CD4 cell count or viral load. A secondary analysis [56] of data from the ARROW trial, a strategy trial comparing clinical and laboratory monitoring among children on ART, examined patterns of long-term CD4 reconstitution in HIV-infected children starting ART in sub-Saharan Africa. Using nonlinear mixed-effects models the study found that higher long-term CD4 counts were predicted for children starting ART at younger ages, and with higher CD4 counts ($p<0.001$) suggesting that children who remain ART näive beyond 10 years of age are unlikely to achieve a normalized CD4 count. Another ARROW analysis demonstrated that delaying ART initiation until older childhood substantially delayed pubertal development and menarche, independent of immunosuppression [57*]. These findings suggest that earlier ART initiation may lead to better long-term outcomes among HIV-infected children.

At the same time as evidence emerges to support early treatment initiation, studies are delineating the particular challenges of engaging and retaining adolescents with HIV in treatment. In a retrospective cohort study of 16,421 patients aged ≥15 years starting ART in seven African countries, 2004–2012, higher rates of LTFU were recorded among adolescents and young adults, aged 15–24 years, compared with adults, >/=50 years [58*]. Another cohort study utilizing routinely collected patient-level data from pre and post ART patients at least 10 years of age from 160 HIV clinics in Kenya, Mozambique, Tanzania, and Rwanda found that youth (15–24 years) experienced substantially higher attrition before and after ART initiation compared with younger adolescents and older adults [59*]. Optimizing adherence outcomes among youth are equally challenging. A recent meta-analysis including over 10,725 patients globally demonstrated that only 62.3% [95% CI 57.1–67.6; I:97.2%] of the adolescent population were adherent to therapy [60**]. In a study from the Adolescent Treatment Network, adherence and viral suppression were measured among youth with behaviorally and perinatally acquired HIV infection receiving care at 20 adolescent specialty centers in the US. Of 488 perinatally HIV-infected youth and 517 behaviorally infected youth who reported taking an ART regimen consecutively for at least the past 6 months, virologic suppression rates were 45.9% and 63.6% respectively [61**].

Antiretroviral treatment options: efficacy and safety—Antiretroviral drug options for children continue to lag behind adults for whom a number of new drug classes and formulations have become available in recent years. However, there is a slowly expanding array of treatment options for pediatric HIV. Once-daily atazanavir (ATV), a protease inhibitor (PI), has been studied down to infancy amongst both treatment experienced and naïve children and was shown to be safe and well tolerated with acceptable levels of viral suppression. The Pediatric AIDS Clinical Trials Group 1020A study of ATV [62*] enrolled participants from 91 days to 21 years of age, and at week 96 found respective rates of VL suppression of 57.0% in treatment naïve and 39.3% in treatment experienced patients. Raltegravir, an integrase inhibitor (INI), available as a film-coated tablet 400 mg twice daily (6 to <19 years, and >/= 25 kg) and chewable tablet 6 mg/kg (maximum dose 300 mg) twice

daily (2 to <12 years), was shown to be well tolerated with favorable virologic and immunologic responses in a multicenter trial [63*] of drug experienced children and is now approved for children 4 weeks of age and older [64]. Once-daily darunavir/ritonavir 800/100 mg, a PI, has been shown to be to be effective and well-tolerated for treatment of HIV-1-infected, antiretroviral-naive adolescents (>/=12 to <18 years) [65*]. Dolutegravir, another INI, was the first ARV to receive simultaneous approval in young adolescents and adults [66]. Unfortunately none of these new drugs are yet widely available in the global marketplace for children.

There is increasing evidence confirming the benefit of starting LPV/r-based ART as first-line therapy in infants regardless of PMTCT history [67**,68]. Unfortunately in low resource settings programs have been slow to incorporate LPV/r into their first line regimens and nevirapine-based ART is more often prescribed for infants and young children [69]. This is particularly worrisome in light of new evidence on resistance among ART naïve HIV-infected children. A study of 230 newly diagnosed children under 2 years of age in South Africa [69] in 2011 found high rates of drug resistance: among the 67.4% of children with reported PMTCT exposure, 56.8% had NNRTI and 14.8% NRTI mutations; of those with no reported or recorded PMTCT exposures, resistance to NNRTI was detected in 24.0%, NRTI in 10.7%. It is anticipated that new formulations of LPV/r as sprinkles [70*] may improve uptake of PI-based treatment among infants by addressing issues of palatability, storage, transport and cost.

More information is also becoming available on the long term safety of ARVs commonly used to treat pediatric HIV infection. The ARROW study found that long-term zidovudine (ZDV)-based ART was associated with similar body circumference and skinfold thickness as abacavir-based ART, with low rates of lipid abnormalities and clinical lipodystrophy [71]. A prospective, open-label study evaluated the efficacy, safety and pharmacokinetics of TDF (given as TDF/3TC/EFV once daily) in treatment-experienced children 3–18 years of age in Thailand found no evidence of increased renal glomerular or renal tubular toxicity. However, the investigators reported a statistically significant decrease in spine bone mineral density Z-score in the TDF vs. non-TDF group [72*,73*]. A Gilead sponsored trial [74*] in the United States, United Kingdom and Panama randomized HIV-infected children (2 to <16 years) on a stavudine (d4T) or ZDV containing regimen with HIV-1 RNA <400 copies/mL to continue d4T or ZDV or switch to TDF. In this study TDF did not demonstrate non-inferiority in maintaining HIV-1 RNA <400 copies/mL at week 48 as compared to d4T or ZDV and 4/79 patients discontinued TDF due to late occurrence (study weeks 84–156) of renal tubular dysfunction. Additional surveillance for the long term, especially bone effects, of TDF in children are needed [73*].

Very early treatment and prospects for CURE

The report of a functional cure in the ‘Mississippi baby,’ brought great optimism to the HIV community. The possibility that very early treatment could result in sustained virologic control off ART (remission) for an infection that necessitates a lifelong commitment to treatment was very compelling. In the case of the ‘Mississippi baby,’ triple ARV therapy was initiated very close to the time of birth (at 30 hours) and discontinued after 18 months of

treatment, with no evidence of viral rebound including undetectable proviral DNA, plasma HIV-1 RNA and HIV-1 antibodies [75]. Unfortunately, more than two years after treatment cessation, the period of remission ended and HIV RNA was detectable at 16,750 copies/mL, dashing hopes that the child may have attained permanent virologic control off ART [76**]. Thus far, additional cases of early treatment have also failed to demonstrate evidence of sustained viral remission off ART. A British child was initiated on triple ARV therapy within hours of life and virally suppressed on treatment for four years, but had a rapid viral rebound when ART was temporarily discontinued [77*].

Although there has been great disappointment around the failure of early treatment initiators to sustain viral remission off treatment, very early treatment appears to reduce replication competent HIV-1 reservoir size. Reduction of latent replication-competent HIV reservoirs is believed to be critical to attain a sustained remission [6*,78*,79*]. A report on outcomes of early treated children from three centers in Canada described four vertically-infected children with sustained viral suppression on ART [78*]. At 2–5 years on treatment, levels of proviral HIV-1 DNA and replication-competent virus in the peripheral blood were dramatically reduced: HIV serology, HIV specific cell-mediated immune response, and ultrasensitive viral load were negative, cell-associated HIV-1 DNA in plasma and virion-associated HIV-1 RNA in stimulated CD4 +T cells were undetectable. Only one of two children tested had a low level of replication-competent HIV-1 in CD4+ T cells. These findings provide evidence to the hypothesis that early treatment can lead to reduced replication competent reservoirs. However, treatment interruption is required to determine if any of these children can sustain viral suppression off treatment and achieve a period of remission. Several studies are currently in progress to examine the impact of very early treatment of the HIV-infected newborns to prevent HIV disease progression, limit and possibly prevent establishment of latent reservoirs, and test approaches to viral eradication [5*,6*,79*].

CONCLUSION

There is enormous optimism that the future holds opportunities for more effective prevention, treatment, and possible cure of pediatric HIV infection. With new PMTCT implementation strategies bolstered by robust global support, we are growing ever closer towards elimination of pediatric HIV. PMTCT uptake is being further optimized and there is increasing interest in understanding and addressing challenges with retention. Ongoing vigilance regarding the potential hazards of *in utero* ART exposure to infants continues with no significant alarms yet identified. Though cure has not been achieved, evidence of the impact of early treatment on reducing HIV-1 reservoir size has enlivened efforts to rapidly identify and treat HIV-infected newborns. There is an increasing array of treatment options and reassuring evidence regarding long term complications of ART. Unfortunately, alongside burgeoning evidence suggesting the benefit of even earlier treatment, timely identification and treatment of children remains a challenge. Evidence regarding most effective case-finding and linkage strategies are urgently needed in addition to an improved understanding of how to engage and retain HIV-positive children and adolescents on treatment. However, further emboldened by recent international commitments, the future is hopeful.

ACKNOWLEDGEMENTS

MHK was supported by the Fogarty International Center of the National Institutes of Health under award number K01 TW009644

The authors would like to thank Rachael Sabelli for her assistance with the references and Robbie Flick for his assistance in developing Figures 1 and 2.

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* “of importance”

** “of major importance”

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with undetectable HIV-1 RNA and DNA but experienced rapid viral rebound within days of treatment discontinuation at 48 months of life.

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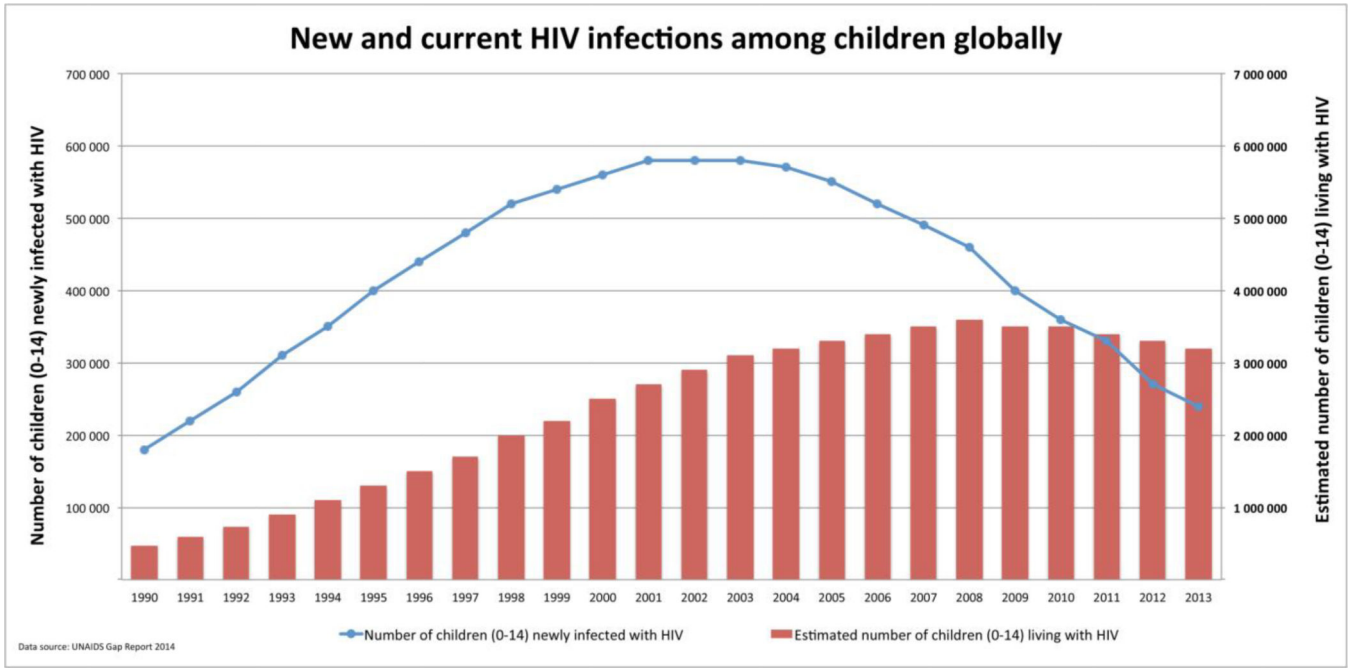

Figure 1.
New and current HIV infections among children globally

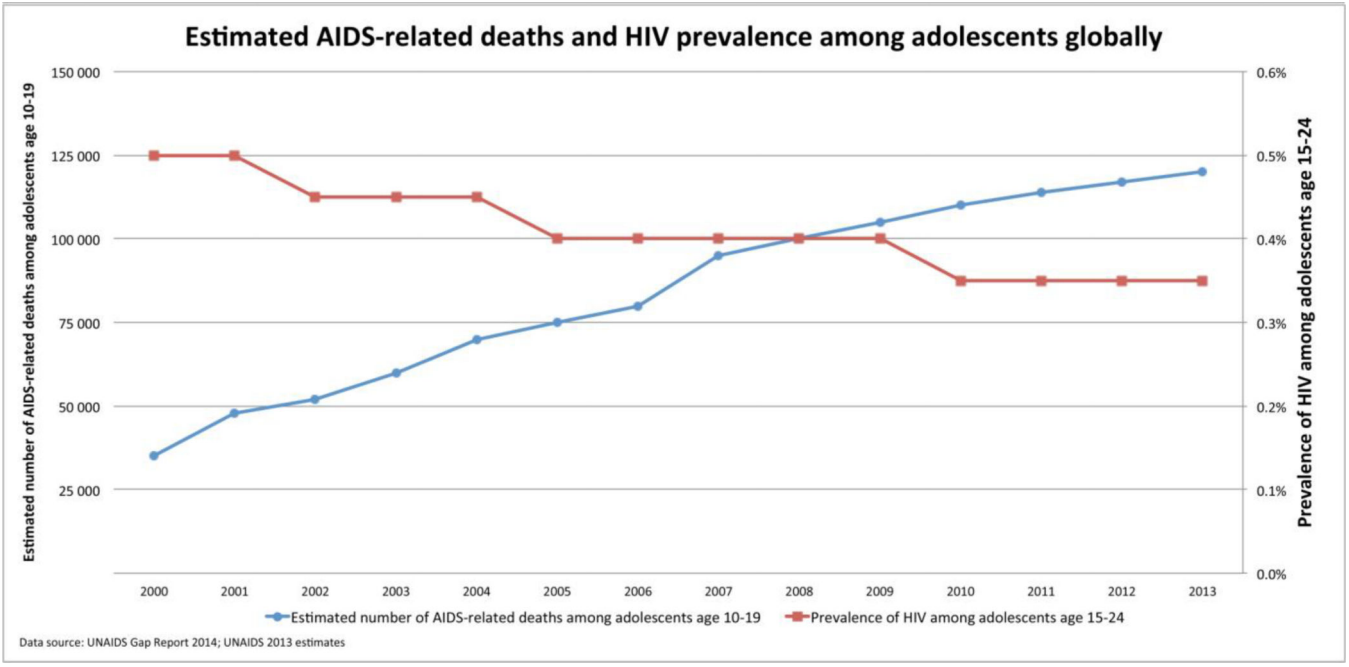

Figure 2.
Estimated AIDS-related deaths and HIV prevalence among adolescents globally