The changing epidemiology of the global paediatric HIV epidemic: keeping track of perinatally HIV-infected adolescents

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Abstract

The global paediatric HIV epidemic is shifting into a new phase as children on antiretroviral therapy (ART) move into adolescence and adulthood, and face new challenges of living with HIV. UNAIDS reports that 3.4 million children aged below 15 years and 2 million adolescents aged between 10 and 19 years have HIV. Although the vast majority of children were perinatally infected, older children are combined with behaviourally infected adolescents and youth in global reporting, making it difficult to keep track of their outcomes. Perinatally HIV-infected adolescents (PHIVA) are a highly unique patient sub-population, having been infected before development of their immune systems, been subject to suboptimal ART options and formulations, and now face transition from complete dependence on adult caregivers to becoming their own caregivers. As we are unable to track long-term complications and survival of PHIVA through national and global reporting systems, local and regional cohorts are the main sources for surveillance and research among PHIVA. This global review will utilize those data to highlight the epidemiology of PHIVA infection, treatment challenges and chronic disease risks. Unless mechanisms are created to count and separate out PHIVA outcomes, we will have few opportunities to characterize the negative consequences of life-long HIV infection in order to find ways to prevent them.

Keywords: adolescent; HIV; outcomes; perinatal; surveillance.

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Introduction

The global paediatric HIV epidemic is shifting into a new phase as children on antiretroviral therapy (ART) age into adolescence and adulthood. The evolution of HIV into a chronic disease has no greater impact than on the life of a child. Children that families, clinicians and policymakers at one time expected to die are living into their 20s and having children of their own [1–6]. Unanticipated issues such as reproductive health, higher education and career training are now urgent needs [7].

Unfortunately, we do not know how many perinatally HIV-infected adolescents (PHIVA) are living in our communities today, a necessary, but only a first step towards addressing the needs of this population. UNAIDS reports that there are 3.4 million children under 15 years of age with HIV and 2 million adolescents between 10 and 19 years of age [8]. Although the vast majority of children were perinatally infected, older children are combined with behaviourally infected adolescents and youth in global reporting, without disaggregation by sex. Maintaining separate reporting for PHIVA and conducting appropriate surveillance and cohort studies are necessary to keep track of long-term complications and survival through national and UNAIDS reporting systems. Local and regional cohorts are currently the main source for surveillance and research among PHIVA. The objective of this review was to utilize available data to highlight the global epidemiology of PHIVA infection, and treatment challenges and outcomes, including metabolic and neurocognitive complications, and identify gaps for future research and policy change.

The challenge of reaching adulthood with active ART regimens

There are multiple reasons why PHIVA are at high risk of having treatment failure and multiclass antiretroviral (ARV) drug resistance, starting from ARV exposure to prevent their infection around birth [9,10], a history of sub-optimal mono- and dual-therapy regimens [11,12] and having a limited range of approved ARVs for children and paediatric formulations. In the Madrid paediatric HIV cohort, of 112 adolescents who have been transferred to adult care and followed for a median of 15.6 years, 60% had started with monotherapy, and had had an average of five different ART regimens [11]. An analysis of children within the Collaborative of Observational HIV Epidemiological Research Europe (COHERE) cohort demonstrated a 20% cumulative proportion of paediatric patients with triple-class failure by eight years of ART [13]. An urban cohort of PHIVA in the United States reported that patients had been exposed to a median of eight different ARVs across three classes due to resistance and toxicity [14].
In low- and middle-income countries (LMICs), there are added difficulties in identifying treatment failure early enough to prevent accumulation of drug resistance mutations [15]. Current World Health Organization (WHO) criteria to assess paediatric failure have been repeatedly shown to be inaccurate for predicting failure [16,17]. The sensitivity of the 2006 and 2010 WHO immunologic failure guidelines was as low as 6% in a multicentre South African study [16] and 5% in a Cambodian study [17]. Although targeted viral load testing can significantly improve failure classifications [18], the importance of routine access to viral load testing relative to other monitoring priorities continues to be debated in the paediatric literature [19].

Common to all settings is the challenge of maintaining life-long adherence and access to increasingly expensive ART regimens. Adolescent adherence is particularly complex because of the socio-economic pressures related to orphanhood, neurocognitive deficits associated with chronic and severe HIV infection, and stigma and discrimination [5,20–22]. In a US cohort of treatment-experienced adolescents, poor adherence and pre-existing resistance led to poor viral load responses despite regular access to the third- and fourth-line ARVs darunavir, raltegravir and etravirine [14]. The monthly cost of darunavir for an adult in Thailand is 400 USD, (source: Thai Red Cross AIDS Research Centre, Bangkok, Thailand), making compassionate use programmes a critical and frequently the only way that children in LMICs can access these types of drugs. Without an improved understanding of how to achieve adherence and continuous access to potent ARVs, LMICs are at risk of running out of options for PHIVA transitioning into adulthood.

Regional epidemiology and outcome data
The adolescents in LMICs today are in some ways part of survivor cohorts of those who were largely slower progressors and able to access ART before late childhood. They are beginning to experience long-term complications that mirror those of western cohorts, where more prolonged ARV access and research experience have led to a deeper literature on PHIVA outcomes. Within the wide spectrum of relevant clinical HIV research, two emerging focus areas are metabolic and neurocognitive deficits associated with chronic and severe HIV infection, and stigma and discrimination [5,20–22]. Since the WHO made recommendations in 2009 to begin phasing out of stavudine (d4T) in adults due to toxicities such as lipodystrophy and peripheral neuropathy, countries such as South Africa have begun dropping d4T from standard first-line ART regimens [29]. However, the WHO 2010 paediatric guidelines continued to recommend the use of d4T, noting the need for additional research in this area to document the extent of d4T-related toxicities [30]. The ongoing use of d4T in children and the broader implementation of first-line protease inhibitor-based (PI) regimens after perinatal non-nucleoside reverse transcriptase inhibitor (NNRTI) exposure are both reasons for greater pharmacovigilence of metabolic complications in developing children and PHIVA in sub-Saharan Africa.

Metabolic complications
Since the WHO made recommendations in 2009 to begin phasing out of stavudine (d4T) in adults due to toxicities such as lipodystrophy and peripheral neuropathy, countries such as South Africa may emerge into a larger and especially challenging sub-population than previously anticipated. A cross-sectional study of 364 children in Uganda using physical assessments of fat redistribution reported that 27% of children had lipodystrophy, primarily with lipoatrophy of the face, which was associated with d4T use (OR 3.43; CI 2.03, 5.80; p < 0.001), older age (≥5 years OR 3.87, CI 1.51, 9.88; p = 0.005) and Tanner stage >1 (OR 2.26, CI 1.33, 3.84; p = 0.003) [31]. A retrospective study of 2222 children in South Africa examined the frequency of d4T substitution as a marker for cases of severe d4T intolerance. After three years of d4T, 12.6% of children were switched; 91% of switches were due to lipodystrophy. In addition, toxicity-related switches were 1.5 times more common in girls (p = 0.07) [32]. Another cross-sectional study of 156 children completing the NEVEREST trial in South Africa added skin-fold and bioimpedence measurements to clinician assessments [33]. All children (mean age of five years) were on d4T and either lopinavir or nevirapine, and 8.3% had confirmed and 11.5% had possible lipodystrophy after four years of ART. The effects of d4T may be less easily recognizable, although...
still potentially present, in younger children due to the natural pattern of fat distribution in this age group.

Recent data have also raised concerns over d4T-associated peripheral neuropathy. A cross-sectional study of 174 children in a rural setting in South Africa discovered that 24% met criteria for peripheral neuropathy [34]. Children were a median of nine years of age, and had been on ART for a median of two years; 86% were on d4T. Passively reported adverse event data and other cross-sectional studies have not previously demonstrated such high rates of neuropathy [35,36].

With regards to hyperlipidemia, available data to date have emphasized improvements in lipid profiles after initiation of ART in younger children [37,38]. The known association with PIs in adults has been observed in the children in NEVEREST; those on lopinavir had higher rates of elevated cholesterol (19% vs. 8.5%, \( p = 0.03 \)) and triglycerides (13% vs. 3%, \( p = 0.04 \)) compared to nevirapine [33]. Available resources for laboratory monitoring limit data on older children and PHIVA from larger cohorts. In a survey of 53 paediatric HIV sites across Africa in the International Epidemiologic Databases to Evaluate AIDS (IeDEA) global consortium, only 26% of sites regularly monitored lipid levels [39].

**Behavioural and neurocognitive outcomes**

It is clear that immediately starting HIV-infected infants on ART drastically improves both mortality as well as neurodevelopmental outcomes [40,41]. However, most African PHIVA today would not have been able to access ART until they were older and after meeting previously more restrictive treatment criteria. Studies of school-age South African children who started ART after clinical and immunologic disease progression have demonstrated that up to 90% of them have significant developmental delays, with a seven-fold higher likelihood of severe delay (OR. 7.88, CI 1.96–31.68) than HIV-uninfected controls [42].

Children diagnosed after two to three years of age with CD4 levels above ART thresholds frequently have ART deferred, but there may be serious negative consequences to their neurodevelopment. A study of Ugandan children with CD4 levels ≥ 350 cells/mcl and >15% used three different neuropsychological batteries to compare them to HIV-uninfected children (i.e., Test of Variables of Attention; modified Kaufman Assessment Battery for Children; Bruininks-Oseretsky Test of Motor Proficiency, second edition) [43]. Children with HIV (median age of 8.7 years) lived in similar home environments with regards to stimulation and learning opportunities, but had lower socio-economic status. Although some of the testing outcomes were similar, children with HIV did significantly worse with regards to visual reaction times, sequential and simultaneous processing, planning/reasoning, and motor proficiency. Higher viral loads were associated with worse testing outcomes, indicating that deferring ART based on CD4 criteria alone may put children at risk of poorer long-term cognitive outcomes due to ongoing direct viral damage to the developing brain.

Using a brief assessment of psychiatric disorders, investigators in Kenya found high rates of features consistent with anxiety disorders (32%) and major depression (17%) in a cohort of 162 children between 6 and 18 years of age (mean age of 9.7 years) [44]. Of note was that 49% of the study participants were also at least two grades below their age-appropriate levels, reported by the families to be due to poor health (41%) and/or poor performance (31%). The link between these delays and deficits and behaviour and functional outcomes remains to be studied.

**Asia**

**Epidemiology**

An estimated 180,000 children under 15 years of age were living with HIV in the Asia-Pacific in 2010, with 39% ART coverage [8]. The largest national treatment programme for children <15 years of age in Asia is in India, where 18,000 of the 70,000 of those infected were on ART in 2009 [23]. In the same period, there was an estimated 16,000 children with HIV in Thailand, with 8000 receiving ART [23]. A study of those in the national ART programme before 2007 reported an 88% survival rate at five years of ART [45]. China’s national programme had enrolled around 5100 children by 2009 [46], with 1600 on ART [23]. Although general surveillance data for children are inconsistent, Cambodia was treating 3600 and Vietnam 2000 children by 2009 [23].

The largest regional adolescent cohort in Asia is the TREAT Asia Pediatric HIV Observational Database (TApHOD), which is part of the IeDEA network [47]. Of the 4045 children in the database from six countries enrolled through March 2011, 31% were adolescents 12 years of age or above, of whom 53% were female [6]. Of those reaching adolescence, 4.2% were lost to follow-up and 8.6% had been transferred out, but 85% were still under care at cohort sites. Most of those still under care (73%) were single- or double-orphans, 62% knew about their own HIV status [45] of 12–14 year-olds; 82% of ≥15 year-olds), and 93% were attending school of some kind. Of those on ART, 96% had been on highly active ART for a median of six years, with 71% on NNRTI-based regimens. The median CD4 count was 567 cells/mm³, and 718 of 830 (86%) with viral load testing were below 400 copies/mL. Overall, those who had reached adolescence at these primarily urban referral centres were on stable ART, with good immunologic and virologic disease control.

Much of the data on long-term HIV and ART complications in Asia have come from Thailand, which has the oldest cohort of PHIVA due to earlier implementation of their national paediatric ART programme [45].

**Metabolic complications**

Lipodystrophy was the first major toxicity of ART described in Thai children. Investigators prospectively monitoring children with serial photography and standardized assessments reported that 65% had lipoatrophy, lipohypertrophy, or both after 144 weeks of d4T-based ART. Girls had a higher prevalence of lipodystrophy than boys (61% vs. 39%, \( p = 0.04 \)) [48]. Subsequent studies after switching d4T for zidovudine (AZT) showed that these children and adolescents had no clinically significant AZT-associated anaemia [49], and that 73% of lipoatrophy and 47% of lipohypertrophy resolved by 96 weeks [50]. Other studies confirmed the association with d4T use, and the Thai national paediatric HIV
treatment guidelines were revised in 2010 to recommend short-term (i.e., <6 months) d4T only in cases of pre-ART anaemia [51]. However, hyperlipidaemia continues to be a challenge, as more children are switched to second-line PI-based regimens. Although lipid screening is seldom part of routine paediatric treatment monitoring in LMICs, there is growing evidence that this will be a larger problem than previously anticipated. Within a cohort of ART-naive younger children from Cambodia and Thailand, 28% already had hypertriglyceridemia and 45% had low HDL [52]. In the TAPHOD cohort, among children switched to PI-based second-line ART at a median of 10 years of age, 32% had hypercholesterolemia, 73% had hypertriglyceridemia, 18% had HDL, and 49% had elevated triglyceride to HDL ratios at 48 weeks of follow-up [53]. It remains unclear what this abnormal lipid metabolism will mean for PHIVA and their risk of cardiovascular disease.

Bone mineral density (BMD) assessments using dual-energy x-ray absorptiometry (DXA) in Thai children has similarly raised questions about future fracture risk. Lumbar spine DXA scans were done in 101 PHIVA in Bangkok after a mean of seven years on successful ART (median CD4 646 cells/mm3; 90% with HIV viral load <50 copies/ml) [54]. Compared to healthy Thai controls, 24% of PHIVA had BMD Z-scores <2, and 25% had 25-hydroxy vitamin D levels <20 ng/ml; only 15% overall and 8% of those with low BMD were on tenofovir-containing regimens. There were no differences by sex. The percentage of low lumbar DXA scores in Thai PHIVA was much higher than the 4% seen in a national US cohort [55]. Although no fractures have yet been reported, these data reflect the negative impact of long-term ART and HIV on the metabolism of developing children and maturing adolescents.

Behaviour and neurocognitive outcomes

In the most comprehensive neurodevelopmental and neurocognitive testing done in children with HIV in Asia, investigators used a combination of multiple forms of IQ testing (i.e., Beery Visual Motor Integration, Purdue Pegboard, Colour Trails, Child Behavioural Checklist, Wechsler Intelligence Scale, Stanford Binet Memory test) to study outcomes of children in Thailand and Cambodia [56]. There were significant reductions in scores and performance across almost all domains tested in intelligence, memory, and psychomotor and behavioural outcomes for children with HIV (median age, nine years) in comparison to uninfected controls (median age, seven years).

The impact of these clear differences in developmental and cognitive outcomes has been seen in school performance. Thai investigators compared children with HIV to HIV-exposed and HIV-unexposed children (overall and group-specific median age of nine years) [57]. Only 21% of those with HIV scored at or above average intelligence levels, compared to 76% of unexposed children. On multivariate analysis, HIV was the sole factor significantly associated with higher risk of poor cognitive outcomes (OR 6.20, p < 0.01). Of particular concern was that 20% of HIV-infected children were below their age-appropriate grades in school compared to only 2% of HIV-exposed and 0% of HIV-unexposed children (p < 0.01). Beyond these neurodevelopmental issues, families with HIV had lower income and caregiver education levels, while primary caregivers were older due to orphanhood and parental illness. Only 28% of those with HIV were cared for by one or both of their biological parents compared to 98% of HIV-unexposed children (p < 0.001).

In a pilot study using an audio computer-assisted self-interview (ACASI) within TAPHOD, investigators began assessing behavioural risk among PHIVA in Malaysia and Thailand. Of 46 PHIVA (median age, 14.5 years), 24% reported trying alcohol, 11% cigarettes, and 11% had engaged in sexual intercourse between 14 and 16 years of age [58]. How cognitive and performance deficits impact mental health, and risk-taking behaviour in Asian PHIVA remains largely unknown, and represents an essential area for future research.

United States

Epidemiology

According to UNAIDS, approximately 4500 HIV-infected children under 15 years of age lived in North America in 2013, the vast majority in the United States [8]. However, given the ageing population of PHIVA, this number under the age of 15 years likely represents less than half of the total number who are perinatally infected. By 2007, according to the CDC, 49% of PHIVA in the United States were over 15 years of age [59]. UNAIDS reports less than 100 deaths among HIV-infected children less than 15 years of age, but again, given the age distribution of the perinatally infected population, this likely represents less than half the number of deaths among the perinatally infected in the United States, especially since older individuals are at increased risk of death [1]. Nevertheless, given the low mortality and very low number of newly infected babies (<100 per year), the perinatally infected population in the United States is at a relatively stable number of over 10,000 individuals, most of whom are now young adults and with the oldest members now entering the fourth decade of life.

Approximately two-thirds of PHIVA in the United States are African-American/non-Hispanic, and approximately 20% are Hispanic; 53% are female [59]. There are a number of epidemiological studies focused on this population, including the Pediatric HIV/AIDS Cohort Study (PHACS), IMPAACT 1074, and the HIV Research Network (HIVRN), and several studies that have now ended but for which data are still available for further analyses (PACTG 219C, LEGACY, and WITS). As mentioned above, the mortality rate in this population has declined substantially to less than 1% [1,60].

To date, the studies of PHIVA in the United States have been based in paediatric clinical settings, but as this population enters young adulthood, studies will need to be adapted to continue to follow these youth as they transition to adult-based care. Preliminary data and multiple anecdotes suggest that this transition can be very difficult for some, threatening their health and well-being [61].

Metabolic complications

Complications from chronic therapy and lifelong infection have emerged [62]. These include lipid abnormalities in approximately 20–25% and insulin resistance in 15% [63].
Low bone density has been reported in a number of studies, with boys potentially more affected than girls, but this finding may not be as severe as initially thought, since lower than expected height may explain a large part of the low BMD findings [55,64,65]. While concerns about renal impairment due to toxicity from prolonged ART have been raised, to date, studies have been reassuring that major renal toxicity is rare and much less common than was seen in in the era of suboptimal therapy [66]. Another organ system of concern for potential toxicity from long-term ART is the heart. Recent echocardiographic data have been reassuring that substantial cardiac disease is rare and much less common than was seen in in the pre-HAART era [67].

Neurocognitive complications and mental health issues

With effective ART, HIV encephalopathy has practically disappeared in the United States, but concerns for more subtle, but potentially profound central nervous system and mental health disorders have emerged [68]. In one study based in New York City, 61% of perinatally infected youth had a psychiatric disorder; a rate that was statistically significantly higher than the 49% rate seen in the HIV-exposed, uninfected comparison group [69]. However, follow-up data from this study and data from other studies have shown that rates of mental health disorders are not different between perinatally infected and exposed/uninfected or HIV-affected youth, though alarmingly high in both groups [70–72]. These findings suggest that HIV infection and its treatment may not be the major cause of these problems, but that other factors such as caregiver status, poverty, racism, stigma, exposure to violence, multiple losses and grief, are likely aetiologies. The co-occurrence of mental health problems, substance use, poor adherence to ART, and engagement in high risk activities threaten the health of PHIVA and increases the risk of HIV transmission to sexual partners and to infants [73,74].

Europe

Epidemiology

The UNAIDS estimate for the number of HIV-infected children under 15 years of age in Western and Central Europe in 2011 was 1600. As in the United States, this likely represents less than half of the perinatally infected population. The estimates for the number of deaths and new infections are similar to those for the United States. The perinatally infected population in Europe is likely slightly younger overall than in the United States and much more likely to have emigrated from abroad, as demonstrated by data from the Collaborative HIV Paediatric Study (CHIPS). In this study, which follows almost all HIV-infected children from 2006 onwards in the United Kingdom and Ireland, 55% were born abroad with 51% females, and 31% were 15 years of age or older in 2011 [http://www.chipscohort.ac.uk/default.asp]. As of March 2012, 1188 of the 1791 enrolled were alive and in active follow-up at a paediatric clinical site.

In France, the native-born perinatally infected population is followed until age 18 years in the French Perinatal Cohort study CO10 [http://cesp.insERM.fr/en/research/ongoing-studies/4716-anrs-epf-co1-co10-co11-en-gb.html]. Of the 702 enrolled, 211 had reached the age of 18 years (According to data on the website accessed on January 2, 2013). Researchers in Spain have established a Cohort of the Spanish Paediatric HIV Network (CoRISpe) that is following approximately 800 of the 1100–1200 HIV-infected children in Spain [75]. About one-quarter were born outside of Spain, and over one-third are at least 18 years of age. In addition, a number of other European countries have set up paediatric HIV cohorts [http://www.eurocord.net/cohort_registry.aspx].

The characteristics of the epidemic in Eastern Europe are quite different from that in Western and Central Europe. Here, the prevalence among adults is actually increasing, fuelled predominantly by intravenous drug use. According to UNAIDS, the number of infected children under 15 years of age in Eastern Europe and Central Asia is estimated to be 11,000, with more new paediatric infections and deaths among HIV-infected children than seen in the United States and other parts of Europe. The number less than 15 years of age has been relatively stable for most of the past decade suggesting that the number of newly infected infants equals the number of deaths plus the number who reach 15 years of age every year.

Metabolic and neurocognitive complications

Metabolic and neurodevelopmental/behavioural findings in European PHIVA have been similar to those seen in PHIVA in the United States [76–78]. Data from the French CO10 cohort showed that school performance was comparable to national statistics [79]. However, Swiss and UK studies have illustrated that coping with HIV was an ongoing challenge for PHIVA as they became older, and that inconsistent disclosure and poor psychological adjustment had a negative impact on long-term adherence [80,81]. As mentioned above, a very important issue that needs to be addressed is how to continue to follow these youth as they transition to adult care, especially given that a number of the findings to date regarding hyperlipidemia, bone density, and the impact of mental health and other central nervous system disorders may not be fully expressed until later in adulthood. British researchers leading CHIPS are collaborating with the UK Register of HIV Seroconverters to be able to continue to follow PHIVA into adulthood. In addition, they have established a more intensive study, Adolescents and Adults Living with Perinatal HIV Cohort (AALPHI) [http://www.ctu.mrc.ac.uk/research_areas/study_details.aspx?st=258], on metabolic, neurocognitive, and other areas as these youth enter adulthood. Similarly, the French group has created the Cohort of Young Adults Infected With HIV Since Birth or During Childhood (CO19 COVERTE; ClinicalTrials.gov Identifier: NCT01269632) to follow PHIVA after they reach the age of 18 years and discontinue participation in CO10. As in the United States, preliminary data on the transition to adult care are sobering. Data presented from the United Kingdom in abstract form demonstrated an over five-fold higher rate of mortality in youth reaching the age of 21 years compared to their younger peers [82]. Importantly, poor adherence and end-stage AIDS conditions along with a high burden of mental health disorders were paramount.
Latin America and the Caribbean
Epidemiology and long-term complications

The 2011 UNAIDS estimates for Latin America and the Caribbean were 60,000 HIV-infected children under 15 years of age, 3300 new paediatric infections, and 3500 deaths [8]. The two countries with the most infected children in these regions are Brazil (20,000 infected children under 15 years of age), the largest economy in Latin America, and Haiti (13,000 infected children under 15 years of age), the poorest country in the Western hemisphere. Since 2009 the decline in new infections has been 32% in the Caribbean and 24% in Latin America, as PMTCT coverage approaches 80% in the Caribbean and over 50% throughout Latin America. As new infections are prevented and as perinatally infected children survive and mature into adolescence and young adulthood, the number of infected children under 15 years of age has declined from a peak of 22,000 in the Caribbean in 2004 to 18,000 in 2011. The peak in Latin America was 54,000 in 2005–6, down to 42,000 in 2011. Given these trends, the number under 15 years of age reported by UNAIDS is an underestimate of the total perinatally infected population, though not to the same extent as seen in the United States and Western and Central Europe.

Paediatric cohorts in these regions include the NICHD International Site Development Initiative (NISDI), which is now closed but has a database of over 1000 perinatally infected infants, children, and adolescents primarily in Brazil, but also several other Latin American countries [83]. CCASAnet, part of the leDEA network, is in the process of expanding its paediatric agenda. As in other regions, efforts should be made to follow PHIVA as they enter young adulthood and transition to adult-based care to continue to assess both complications and positive outcomes.

Findings from the NISDI study include a very low mortality rate, dyslipidemia in over a quarter, lower rates of insulin resistance than seen in the United States and Europe, low rates of opportunistic infections but higher than seen in comparable populations in the United States and Europe, and relatively low rates of renal and hepatic disease [83–87]. Two cross-sectional studies of BMD in Brazil demonstrated that between 17 and 32% of PHIVA studied had low BMD, though larger studies with appropriate comparison groups are clearly needed [88,89]. Data on neurocognitive and mental health problems for PHIVA in this region remain very limited.

Conclusions

Depending on the setting, the paediatric HIV epidemic has entered or is entering the next phase of its evolution as children grow up and face new challenges of living with HIV. PHIVA are a highly unique patient sub-population, having been infected before development of their immune systems, been subject to suboptimal ART options and formulations, and face transitioning from complete dependence on adult caregivers to becoming their own caregivers.

Regional data demonstrate that successful transition and HIV disease control are possible, but there are consequences of life-long HIV and ART – many of which we still do not understand. However, unless national HIV programmes and UNAIDS create mechanisms to count and keep track of the perinatally infected, we will not know how many of these children are and are not surviving into adulthood. Every year that goes by without dedicated global PHIVA surveillance means that tens of thousands of children could be lost in the crowd.

In addition, without longitudinal cohort studies, we would have few opportunities to characterize the consequences of HIV disease and treatment in order to find ways to prevent them. There are now multiple paediatric and adolescent cohorts scattered around the world. Although they vary with regards to both size and depth of data collection, global cohort collaborations could potentially generate the “big data” needed to answer common research questions. Providers and researchers will also have to transition into the next phase of the global paediatric epidemic in order to keep up with our patients.

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Competing interests

The authors report no competing interests.

Authors' contributions

Both authors have read and approved the final version and both authors drafted the manuscript.

References

1. Brady MT, Oleske JM, Williams PL, Elgie C, Mofenson LM, Dankner WM, et al. Declines in mortality rates and changes in causes of death in HIV-infected children during the HAART era. J Acquir Immune Defic Syndr. 2010;53(1):86–94.
2. Ferrand RA, Corbett EL, Wood R, Hargrove J, Ndhlovu CE, Cowan FM, et al. AIDS among older children and adolescents in Southern Africa: projecting the time course and magnitude of the epidemic. AIDS. 2009;23(15):2399–406.
3. Foster C, Judd A, Tookey P, Tudor-Williams G, Dunn D, Shingadia D, et al. Young people in the United Kingdom and Ireland with perinatally acquired HIV: the pediatric legacy for adult services. AIDS Patient Care STDS. 2009; 23(3):159–66.
4. Vijayan T, Benin AL, Wagner K, Romano S, Andiman WA. We never thought this would happen: transitioning care of adolescents with perinatally acquired HIV infection from pediatrics to internal medicine. AIDS Care. 2009;21(10): 1222–9.
5. Santos Cruz ML, Freimanis Hance L, Korelitz J, Aguilar A, Byrne J, Serchuck LK, et al. Characteristics of HIV infected adolescents in Latin America: results from the NISDI pediatric study. J Trop Pediatr. 2011;57(3):165–72.
6. Chokephaibulkit K, Karimnina A, Oberdorfer P, Nallusamy R, Bunupuradah T, Hansudeewachkul R, et al. For the TREAT Asia pediatric HIV observational database. Characteristics of perinatally HIV-infected adolescents in Asia: the TREAT Asia pediatric HIV observational database. 4th International Workshop on HIV Pediatrics, July 20–21, 2012, Washington, DC. Abstract P, 12.
7. Souza E, Santos N, Valentini S, Silva G, Falbo A. Long-term follow-up outcomes of perinatally HIV-infected adolescents: infection control but school failure. J Trop Pediatr. 2010;56(6):421–6.
8. WHO, UNAIDS, UNICEF. Global HIV/AIDS response: epidemic update and health sector progress towards universal Access, 2011 progress report. Geneva: World Health Organization; 2011.
9. Fogel JM, Mwatha A, Richardson P, Brown ER, Chiapeto T, Alexandre M, et al. Impact of maternal and infant antiretroviral drug regimens on drug resistance in HIV-infected breastfeeding infants, Pediatr Infect Dis J. 2013;32(4):e164–9.
10. Hunt GM, Covadiga A, Abrams EJ, Sherman G, Meyers T, Morris L, et al. HIV-1drug resistance at antiretroviral treatment initiation in children previously exposed to single-dose nevirapine. AIDS. 2011;25(12):1461–9.
11. de Mulder M, Yebra G, Navas A, de José MI, Gurbindo MD, González-Tomé MI, et al. High drug resistance prevalence among vertically HIV-infected...
patients transferred from pediatric care to adult units in Spain. PLoS One. 2012;7(12):e52155.
12. Hansudeewachakul R, Sirisanthana V, Kurniati N, Puthanakit T, Lumbiganon P, Saphonn V, et al. Antiretroviral therapy outcomes of HIV-infected children in the TREAT Asia pediatric HIV observational database. J Acquir Immune Defic Syndr. 2010;55(4):503–9.
13. Castro H, Judd A, Gibb DM, Butler K, Lodwick RK, van Sighem A, et al. Risk of triple-class virological failure in children with HIV: a retrospective cohort study. Lancet. 2011;377(9777):1580–7.
14. Wong FL, Hsu AJ, Plam RA, Siberry GK, Hutton N, Agwu AL. Antiretroviral treatment strategies in highly treatment experienced perinatally infected youth. Pediatr Infect Dis J. 2012;31(12):1279–83.
15. Ruel TD, Kamya MR, Li P, Pasutti W, Charlebois ED, Liegler T, et al. Early virologic failure and the development of antiretroviral drug resistance mutations in HIV-infected Ugandan children. J Acquir Immune Defic Syndr. 2011;56(3):44–50.
16. Davies MA, Boule A, Eley B, Mouttrie H, Technau K, Rabie H, et al. Accuracy of immunological criteria for identifying virological failure in children on antiretroviral therapy – the IeDEA Southern Africa Collaboration. Trop Med Int Health. 2011;16(11):1367–71.
17. Westrip SP, Delong AK, Tray CS, Sophierin D, DuFort EM, Nerrienet E, et al. Prediction of treatment failure using 2010 World Health Organization guidelines is associated with high misclassification rates and drug resistance among HIV-infected Cambodian children. Clin Infect Dis. 2012;55(3):432–40.
18. Davies MA, Boule A, Technau K, Eley B, Mouttrie H, Rabie H, et al. The role of targeted viral load testing in diagnosing virological failure in children on antiretroviral therapy with immunological failure. Trop Med Int Health. 2012;17(14):1912–20.
19. Babiker A, Castro nee Green H, Compagnoucci A, Fiscus S, Giaquinto C, Gibb DM, et al. First-line antiretroviral therapy with a protease inhibitor versus non-nucleoside reverse transcriptase inhibitor and switch at higher versus lower viral load in HIV-infected children: an open-label, randomised phase 2/3 trial. Lancet Infect Dis. 2011;11(4):273–83.
20. Malee K, Williams P, Montepiedra G, McCabe M, Nichols S, Siros PA, et al. Medication adherence in children and adolescents with HIV infection: associations with behavioral impairment. AIDS Patient Care STDS. 2011;25(6):191–200.
21. Vreeman RC, Nyandiko WM, Ayapa SO, Walumbe EG, Marrero DJ, Inui TS. Mortality of infected and uninfected infants born to HIV-infected mothers in Harare, Zimbabwe. AIDS. 2004;18(2):273–80.
22. Ding H, Wilson CM, Modjarrad K, McGwin G Jr., Tang J, Vermund SH. Prevention of targeted viral load testing in diagnosing virological failure in children on antiretroviral therapy. J Acquir Immune Defic Syndr. 2012;56(4):369–76.
23. IeDEA Pediatric Working Group. A survey of paediatric HIV programmatic and clinical management practices in Asia and sub-Saharan Africa-the International epidemiologic Databases to Evaluate AIDS (IeDEA). J Int AIDS Soc. 2013;16(1):17998.
24. LaFont B, Cornell M, Grove D, Kidd M, Springer PE, Dobells E, et al. Early antiretroviral therapy improves neurodevelopmental outcomes in infants. AIDS. 2012;26(13):1685–90.
25. Violan A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, et al. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med. 2008;359(21):2233–40.
26. Lewick S, Sowry S, Meyers T. Neurodevelopmental delay among HIV-infected preschool children receiving antiretroviral therapy and healthy preschool children in Soweto, South Africa. Psychol Health. 2012;27(5):599–10.
27. Ruel TD, Bolvin MJ, Bose H, Bangirana P, Charlebois E, Havlir DV, et al. Neurocognitive and motor deficits in HIV-infected Ugandan children with high CD4 cell counts. Clin Infect Dis. 2012;54(7):1001–9.
28. Kamau JV, Kuria W, Mathai M, Awotwi L, Kangethe R. Psychiatric morbidity among HIV-infected children and adolescents in a resource-poor Kenyan urban community. AIDS Care. 2012;24(7):836–42.
29. McConnell MS, Chasombat S, Sanghooe U, Vukanpot N, Lolekha R, Pattarapayoon N, et al. National program scale-up and patient outcomes in a pediatric antiretroviral treatment program, Thailand, 2000–2007. J Acquir Immune Defic Syndr. 2010;54(4):423–9.
30. Zhao Y, Sun X, He Y, Tang Z, Peng G, Liu A, et al. Progress of the national pediatric free antiretroviral therapy program in China. AIDS Care. 2010;22(10):1182–8.
31. Karimpan A, Chokephaibulkit K, Pang J, Lumbiganon P, Hansudewechakul R, Amin J, et al. Cohort profile: the TREAT Asia pediatric HIV observational study. J Intern Med. 2011;269(4):15–24.
32. Aurpibul L, Puthanakit T, Lee P, Mangkabruks A, Sirisanthana T, Sirisanthana V. Lipidostrophy and metabolic changes in HIV-infected children on non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy. Antivir Ther. 2007;12(8):1247–54.
33. Aurpibul L, Puthanakit T, Sirisanthana T, Sirisanthana V. Haematological changes after switching from stavudine to zidovudine in HIV-infected children receiving highly active antiretroviral therapy. J Med Virol. 2008;80(5):517–21.
34. Aurpibul L, Puthanakit T, Taejaroenkul S, Sirisanthana T, Sirisanthana V. Recovery from lipodystrophy in HIV-infected children after substitution of stavudine with zidovudine in a non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy. Pediatr Infect Dis J. 2012;31(4):384–8.
35. Sawawiboon N, Wittawatmongkol O, Phongsart W, Prasitsuesai W, Lopprak R, Chokephaibulkit K. Lipodystrophy and reversal of facial lipoatrophy in perinatally HIV-infected children and adolescents after discontinuation of stavudine. Int J STD AIDS. 2012;23(7):497–501.
36. Karimpan A, Chokephaibulkit K, Fahey P, Karimpan A, Yuwfon N, Khunthi T, et al. Second-line protease inhibitor-based highly active antiretroviral therapy after failing non-nucleoside reverse transcriptase inhibitor-based regimens in Asian HIV-infected children. Antivir Ther. 2013 Jan 7.
54. Puthanakit T, Saksawad R, Bunupuradah T, Wittawatmongkol O, Chuanjaroen T, Uboiyam S, et al. Prevalence and risk factors of low bone mineral density among perinatally HIV-infected Thai adolescents receiving antiretroviral therapy. J Acquir Immune Defic Syndr. 2012;64(1):477–83.

55. Dimeligio LA, Wang J, Siberry GK, Miller TL, Geffen ME, Hara R, et al. Bone mineral density in children and adolescents with perinatal HIV infection. AIDS. 2013;27(2):211–20.

56. Puthanakit T, Ananworanich J, Vonthanak S, Kosalaraks P, Hansudewachakul R, van der Lugt J, et al. Cognitive function and neurodevelopmental outcomes in HIV-infected children older than 1 year of age randomized to early versus deferred antiretroviral therapy: the PREDICT neurodevelopmental study. Pediatr Infect Dis J. 2013 Jan 2.

57. Puthanakit T, Uprpbilul L, Louthrenoo O, Tapanya P, Nadasasarn R, Insee-ard S, et al. Poor cognitive functioning of school-aged children in Thailand with perinatally acquired HIV infection taking antiretroviral therapy. AIDS Patient Care STDs. 2010;24(3):141.

58. Prasitsuebsai W, Pang J, Hansudewachakul R, Razali K, Yusof N, Fong S, et al. Risk behaviors and treatment adherence among HIV-infected adolescents in the TREAT Asia Pediatric HIV observational database. 4th International Workshop on HIV Pediatrics, July 20–21, 2012, Washington, DC. Abstract P_18.

59. Whitmore S, Hughes D, Taylor A, Koening L. Estimated numbers and demographic characteristics of persons living with perinatally acquired HIV infection, 37 States, United States, 2007. XVII International AIDS Conference. Vienna, Austria. 2010.

60. Kapogiannis BG, Soe MM, Nesheim SR, Abrams EJ, Carter RJ, Farley J, et al. Mortality trends in the US perinatal AIDS Collaborative transmission study (1986–2004). Clin Infect Dis. 2011;53(10):1024–34.

61. Agwu A, Althoff K, Rusten K, Korthuis PT, Berry S, Gaur A, et al. Factors associated with falling out of care for older adolescents in the HIV research network. Abstract MOPE061. XIX International AIDS Conference, Washington, DC, 2012.

62. Hazra R, Siberry GK, Mofenson LM. Growing up with HIV: children, adolescents, and young adults with perinatally acquired HIV infection. Annual Rev Med. 2010;61:169–85.

63. Geffen ME, Patel K, Miller TL, Hara R, Silio M, Van Dyke RB, et al. Factors associated with insulin resistance among children and adolescents perinatally infected with HIV-1 in the pediatric HIV/AIDS cohort study. Horm Res Paediat. 2011;76(6):386–91.

64. Hazra R, Gafni RI, Malarelli F, Balis FM, Tullio AN, DeCarlo E, et al. Tenofivirus disopiroxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy for pediatric HIV infection. Pediatrics. 2005;116(6):e846–54.

65. Jacobson DL, Lindsey JC, Gordon CM, Myoe J, Hardin DS, Mulligan K, et al. Total body and spinal bone mineral density across Tanner stage in perinatally HIV-infected and uninfected children and youth in PACTG1045. AIDS. 2010;24(5):887–96.

66. Jacobsen DL, Lindsey JC, Gordon CM, Myoe J, Hardin DS, Mulligan K, et al. Tenofivirus treatment duration predicts proteasein in a multi-ethnic United States cohort of children and adolescents with perinatal HIV-1 infection, Pediatr Infect Dis J. 2012 Dec 17.

67. Lipshultz SE, Williams PL, Wilkinson JD, Leister EC, Van Dyke RB, Shearer WT, et al. for the Pediatric HIV/AIDS Cohort Study (PHACS). Cardiac status of HIV-infected children treated with long-term combination antiretroviral therapy: results from the adolescent master protocol of the NIH multicenter pediatric HIV/AIDS cohort study, JAMA Pediatr. 2013;122(1):1–8.

68. Patel K, Ming X, Williams PL, Robertson KR, Olesek JM, Seage GR 3rd. Impact of HAART and CNS-penetrating antiretroviral regimens on HIV encephalopathy among perinatally infected children and adolescents. AIDS. 2009;23(14):1893–901.

69. Mellins CA, Brackis-Cott E, Leu CS, Ellington KS, Doeleka C, Wiznia A, et al. Rates and types of psychiatric disorders in perinatally human immunodeficiency virus-infected youth and survivors. J Child Psychol Psychiatry Allied Disciplines. 2009;50(9):1311–8.

70. Mellins CA, Ellington KS, Leu CS, Santamaria EK, Doeleka C, Wiznia A, et al. Prevalence and change in psychiatric disorders among perinatally HIV-infected and HIV-exposed youth. AIDS Care. 2012;24(8):953–62.

71. Malea KM, Tasiopoulos K, Huo Y, Sibbery G, Williams PL, Hara R, et al. Mental health functioning among children and adolescents with perinatal HIV infection and perinatal HIV exposure. AIDS Care. 2011;23(12):1533–44.

72. Gadov KD, Chernoff M, Williams PL, Brouwers P, Morse E, Heston J, et al. Co-occurring psychiatric symptoms in children perinatally infected with HIV and peer comparison sample. J Dev Behav Pediatr. 2010;31(2):116–28.

73. Mellins CA, Tasiopoulos K, Malea K, Moscicki AB, Patton D, Smith R, et al. Behavioral health risks in perinatally HIV-exposed youth: co-occurrence of sexual and drug use behavior, mental health problems, and nonadherence to antiretroviral treatment. AIDS Patient Care STDs. 2011;25(7):413–22.

74. Tasiopoulos K, Moscicki AB, Mellins C, Kacanek D, Malea K, Allison S, et al. Sexual risk behavior among youth with perinatal HIV infection in the United States: predictors and implications for intervention development. Clin Infect Dis. 2012;54(2):283–90.

75. de Jose MJ, Jimenez de Ory S, Espiau M, Fortuy C, Navarro ML, Soler-Palacín P, et al. A new tool for the paediatric HIV research: general data from the Cohort of the Spanish Paediatric HIV network (CoRISpe). BMC Infect Dis. 2013;13:2.

76. European Paediatric Lipodystrophy Group. Antiretroviral therapy, fat redistribution and hyperlipidaemia in HIV-infected children in Europe. AIDS. 2004;18(10):1443–51.

77. Berengszaszi M, Dolloff C, Levine M, Faye A, Dehmoun S, Bellai N, et al. Longitudinal evaluation and risk factors of lipodystrophy and associated metabolic changes in HIV-infected children. J Acquir Immune Defic Syndr. 2005;40(2):161–8.

78. Koeklok S, de Sonville DM, Wolfs TF, Lich R, Geelen SP. Neurocognitive function profile in HIV-infected school-age children. Eur J Paediatr Neurol. 2008;12(4):920–7.

79. Dolloff C, Le Chenadec J, Faye A, Blanche S, Briand N, Rouzioux C, et al. Long-term outcomes in adolescents perinatally infected with HIV-1 and followed up since birth in the French perinatal cohort (EPF/ANRS C003). Clin Infect Dis. 2010;51(2):214–24.

80. Michaud PA, Suris JC, Thomas R, Gnehm HE, Cheseaux J. Coping with an HIV infection. A multicenter qualitative survey on HIV positive adolescents’ perceptions of their disease, therapeutic adherence and treatment. Swiss Med Wksy. 2010;140(17–18):247–53.

81. Sopena S, Evangel M, Dodge J, Melvin D. Coping and psychological adjustment in adolescents with vertically acquired HIV. AIDS Care. 2010;22(10):1252–8.

82. Foster C. Mortality amongst HIV-infected young people following transition to adult care: an HIV Young Persons Network (HYPNet) audit. Abstract 06. 18th Annual Conference of the British HIV Association. Birmingham, UK, 2012.

83. Hazra R, Stozsek SK, Freimanis Hance L, Pinto J, Marques H, Peixoto M, et al. Cohort profile: NICHD International Site Development Initiative (NISDI): a prospective, observational study of HIV-exposed and HIV-infected children at clinical sites in Latin American and Caribbean countries. Int J Epidemiol. 2009;38(5):1207–14.

84. Brewinski M, Megazzini K, Hance LF, Cruz MC, Pavia-Ruz N, Dellla Negra M, et al. Dyslipidemia in a cohort of HIV-infected Latin American children receiving highly active antiretroviral therapy. J Trop Pediatr. 2011;57(5):324–32.

85. Hazra R, Hance LF, Monteiro JP, Pavia Ruz N, Machado DM, Saavedra M, et al. Insulin resistance and glucose and lipid concentrations in a cohort of perinatally HIV-infected Latin American children, Pediatr Infect Dis J. 2013 Jan 28.

86. Alarcon JO, Freimanis-Hance L, Kraus M, Reyes MF, Cardoso CA, Mussi-Pinhata MM, et al. Opportunistic and other infections in HIV-infected children in Latin America compared to a similar cohort in the United States. AIDS Res Hum Retroviruses. 2012;28(3):282–8.

87. Siberry G, Cohen R, Harris D, Santos Cruz ML, Oliveira R, Peixoto MF, et al. Non-invasive estimate of liver fibrosis prevalence and risk factors in Latin American perinatally HIV-infected children. 3rd International Workshop on HIV Paediatrics. Rome, Italy, 2011. Abstract PP_11.

88. Schotscherbyna A, Pinheiro MF, Mendonca LM, Gouveia C, Luiz RR, Machado ES, et al. Factors associated with low bone mineral density in a Brazilian cohort of vertically HIV-infected adolescents. J Infect Dis. 2012;206(12):e872–8.

89. de Lima LR, da Silva RC, Giuliano Ide C, Sakuno T, Brincas SM, de Carvalho AP. Bone mass in children and adolescents infected with human immunodeficiency virus. J Pediatr (Rio J). 2013;89(1):91–9.