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HIV Exposed Uninfected Children at School Age: Developing Country Context

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Abstract

With the success of chemoprophylaxis for the prevention of perinatal transmission of the human immunodeficiency virus (HIV), an increasing number of HIV-exposed but uninfected (HEU) children will have *in utero* and post-partum exposure to antiretroviral drugs and survive beyond infancy. The long term effect of antiretroviral drug exposure is however not fully understood. A few studies from developing countries have reported on growth, morbidity, mortality, nutrition, immunological profiles, neurodevelopment and behavioral disorders of HEU children. As the number of HEU children continues to increase worldwide, questions of clear public health importance need to be addressed: Is the health status and survival of HEU children into adolescence influenced by exposure to HIV-1 and /or combination antiretroviral therapy (cART) *in utero* or during infancy? To what extent is the long term neurodevelopmental outcomes influenced by being born into an HIV affected household. The aim of this review is to describe current evidence on health outcomes of HEU children, from resource constrained settings, as they mature into adolescence. Systemic review of literature (MEDLINE, PUBMED, Cochrane library, Google scholar,) published in 1999 to December 2015 was conducted. At school-aged HEU children had lower values of most anthropometric parameters than HIV unexposed uninfected (HUU) children at birth, all significant differences diminished after controlling for socioeconomic variables. Lower socioeconomic status is an independent risk factor for neurocognitive impairment and malnutrition in resource constrained settings. More research is required to assist healthcare workers in managing HEU children since this is an emerging problem.

Background

The millennium development goals have come and gone and yet the same threats to gains made on the child survival agenda of the 1980s remain undaunted. Globally an estimated 2.3 million children under the age of 14 years are living with HIV infection, 90% of whom acquired the infection antenatally, intrapartum or postnatally through breast feeding [1]. With the success of chemoprophylaxis for the prevention of perinatal transmission of the human immunodeficiency virus (HIV), an increasing number of HIV-exposed but uninfected (HEU) children will have *in utero* and post-partum exposure to antiretroviral drugs and survive beyond infancy. The proportion of HEU children who survive to school age is largely unknown and the majority live in sub-Saharan Africa [2]. The long term effect of antiretroviral drugs on children`s developing brains is not fully understood. A few studies from developing countries have reported on growth, morbidity and mortality outcomes of HEU children

despite the fact that these children were also at risk of perinatal insults, infectious disease, malnutrition and poverty related complications. As the number of HEU children continues to increase worldwide, questions of clear public health importance need to be addressed: Is the health status and survival of HEU children at adolescence influenced by exposure to HIV-1 and/or combination antiretroviral therapy (cART) *in utero* or during infancy? To what extent is the long term neurodevelopmental outcome influenced by being born into an HIV affected households. The aim of this review is to describe the evidence on health outcomes of HIV exposed uninfected children, from resource constrained settings, as they mature into adolescence.

Review Rationale

Although previous explorations of this research topic have been undertaken, this review aimed at extending those contributions by considering studies, 1) prospective studies among HIV exposed children, 2) across resource constrained settings, 3) reporting on intervention that prevent or postpone severe effects of infection, 4) effect of home environment, 5) were published in English language journal, 6) did not include a substantial proportion of participants exposed to *in utero* opiates, amphetamines or phencyclidine and included a comparison group.

Methodology

A systemic review of the literature (MEDLINE, PUBMED, Cochrane library and Google scholar,) published in 1999 to December 2015 was conducted.

Sixty nine of the 105 articles were reviewed by three authors: 18 cohort studies, 2 clinical trials, 11 reviews, and 74 cross sectional studies. The quality of studies was evaluated according to international guidelines.

Nutrition and Growth

Stunting and wasting remain problematic in children above 5 years from Africa [3-5] with high prevalence of mild stunting being demonstrated in South African rural children 8 to 11 years old [6]. A paradox of co-existence of over-nutrition and under-nutrition in 5 to 14 year old children from Pakistan has been reported [7]. Malnutrition affects growth, development, mental and physical capacity of children above 5 years [8]. In Brazil, socioeconomic factors, maternal height and birth weight influenced linear growth of children up to age 10years [9].

HIV infection and exposure has been noted to influence growth of children including those above 5 years. HEU children have lower weight and length z scores at birth compared to HIV unexposed uninfected (HUU) children [10,11] and also seem to have suboptimal postnatal growth even in breastfeeding populations from low income settings. The risk of small for gestational age in HEU children is higher than in HUU but lower than in HIV infected children [11]. This increased risk for small for gestational age in HEU could be a reflection of poor maternal health during pregnancy. The subsequent suboptimal postnatal growth [11,12] could also be reflecting the maternal ill health including subclinical mastitis, environmental and poor socio-demographics factors frequently found in low income settings. High income countries have demonstrated lower birth anthropometry in HEU but comparable postnatal growth with HUU [13].

HIV exposed uninfected children from the United States of America had better scores of bone mineral density [14] and higher total body fat compared to HIV infected children [15]. In Europe HEU children were 7 kg heavier and 7.5 cm taller than HIV infected children [16]. Advanced HIV infection impaired growth substantially. However, there were no major differences between HEU and the British growth standards from normal children. There is limited data of comparison of HUU, HEU and HIV infected children (HI) above 5 years from low income countries. In Uganda, both HEU and HIV infected pre-school children followed up to just above 5 years had sustained lower weight and height compared to WHO growth standards [17]. They had normal brain growth as reflected by normal head circumference for age. In Zimbabwe [18], HUU and HEU were 7.5 cm and 5.4 cm taller than HIV infected children above 5 years respectively. HUU and HEU children were 3.5 kg and 2.7 kg heavier than HIV infected children. HUU and HEU had mid-upper arm circumference 11 mm longer than the HIV infected children. There was also no difference in head circumference in these children above 5 years. In Zambia, HEU exposed to nevirapine at birth had lower values of most anthropometric variables compared to the HUU and main reason was poor socio-economic factors [19]. In the Dart trial carried out in Zimbabwe and Uganda, there was no evidence that *in utero* tenofovir affected growth after 2 years and no increase in congenital, renal, or growth abnormalities was observed [20].

Neurodevelopment

During the critical periods in childhood development, spanning from pregnancy to adolescence the developing nervous system is susceptible to psychological, environmental biological risk factors. Similar to adults, HIV type 1 in the paediatric population invades the CNS during primary infection and is often followed by compartmentation in sanctuary sites. This poses challenges to treatment modalities [21].

HIV infection and neurodevelopmental outcomes in infancy are determined by maternal and infant host factors both of which also influence HIV disease onset and severity. The timing of vertical

Table 1: Summary of studies reporting the effect of HIV on neurodevelopment among HEU children.

Study	Location	Study Type	Sample size	Participants	Age (range)	Developmental scale	Exposure to ARV	Findings HEU
Bisiachi et al. [25]	Italy	Cross section	42	29 HI 13 HEU	6 -15 yrs	Own tests	Not stated	Normal Normal range
Blanchette et al. [26]	Canada	Cross section	25	14 HI 11 HEU	5-12 yrs	WPPS	Yes	Normal function
Fishkin et al. [27]	US	Cross section	80	40 HI 40 HUU	3-5 yrs	WPPS	Yes	No report
Smith et al. [28]	US	Cohort	539	117 HI 422 HEU	3-7 yrs	MSCA	Yes	Normal function
Koekkoek et al. [29]	The Netherlands	Cross section	22	HI	6-13.5 yrs	SON-R	Yes,	No control
Bagendi et al. [30]	Uganda	Cohort	107	28 HI 42 HEU 37 HUU	6-12 yrs	K-ABC	No	No cognitive defects
Abubakar et al. [31]	Kenya	Cross section	367	31 HI 17 HEU 319 HUU	6-35 mnths	Kilifi Developmental Inventory	No	Similar motor function to HUEI
Lowick et al. [24]	South Africa	Cross section	60	35HI 30 Healthy unknown status	Preschool age	GMDS-ER	No	Normal function
Hoare et al. [32]	South Africa	Cross sectional	24	12 HI 12HUU	8-12 yrs	WASI	No	No report
Ruel et al. [33]	Uganda	Cross section	115	93HI 106 HUU	6-12 yrs	Test of Variables of Attention K-ABC, Bruininks-Oseretsky Test of Motor Proficiency	No	No report
Puthanakit et al. [34]	Thailand	RCT	623	284 HI 155 HEU 164 HUU	1-12 yrs	WISC-Thai	Yes	Normal function
Kandawasvika et al. [35]	Zimbabwe	Prospective	306	32 HI 121 HEI 153 HUU	6-8	MSCA	Yes	Similar to HIV uninfected

HI- Child with HIV infection; HEU- Child exposed but uninfected with HIV; HUU- Unexposed Uninfected; US- United States of America; RCT- Randomised Controlled Trial; KABC- Kaufman Assessment Battery for children; MSCA- McCarthy Scales of Children`s Abilities; SON-R- Snijders-Oomen nonverbal intelligence test for children and adolescents (abridged); WASI- Wechsler Abbreviated Scale of Intelligence; WPPSI- Wechsler Preschool and Primary Scale of Intelligence-Revised; WISC-R- Wechsler Intelligence Scale for Children- Revised; WISC- Thai Wechsler Intelligence Scale for Children Thai version; GMDS-ER- Griffiths Mental Development Scales-Extended Revised Version

infection also influences the rate of disease progression. Children infected with HIV who survived to school age were found to have neurodevelopmental deficits in general cognitive impairment, visual spatial, motor, language expression, perceptive performance and executive function [22-24].

A few studies have reported on HEU and compared them to the reference population, in some studies unexposed uninfected peers of similar socioeconomic status. Studies have demonstrated conflicting results since controlling for confounding factors such as socioeconomic status, child stimulation in the home, care giver characteristic is problematic (Table 1).

Behavioral Problems

Conduct disorders in HEU children remains largely unknown in developing countries due unavailable data. Furthermore, there is lack of adapted and validated tools for assessing behavior in these settings [36,37]. In a study among 6-8 year old Zimbabwean children, HIV exposure did not influence prevalence of behavioral problems [35]. However a study among Ugandan adolescent orphans infected with HIV, a reported higher than normal rates of behavioral problems in that cohort [38].

Antiretroviral Exposure and Neurodevelopment

The relationship between cART and child neurodevelopment is extrapolated from evidence from developed world setting where PMTCT programs are wide spread and the infants are predominantly formula fed. The early initiation of cART has resulted in reduced the incidence of progressive encephalopathy by 50% in children infected perinatally with HIV, in a prospective study among 2389 American children [39]. In a South African study comparing the neurodevelopment of 27 infants infected with HIV to 29 infants exposed uninfected, the use of cART, prevented further deterioration in neurodevelopment function in the HIV infected group, but did not reverse the neurological damage already present [40].

Concerns remain regarding the safety of cART on the developing brain [40]. Evidence on the long term neurodevelopmental effects of antiretroviral therapy exposure is largely unknown. Maternal antenatal exposure to protease containing regimens was associated with increased risk of prematurity in an American PMTCT clinical trial comparing HIV transmission rates in the protease inhibitors group versus the non-reverse transcriptase inhibitor group [41]. A review of studies investigating the impact of HIV exposure and antiretroviral therapy or prophylaxis on neurodevelopmental outcomes reported subtle speech and language delay among children exposed uninfected with HIV [42]. Due to different methodologies used in assessing the effect of maternal cART exposure on neurodevelopment, comparison of the results is limited. Further studies on the long term neurodevelopment outcomes following maternal cART exposure in children without HIV infection are needed.

In a study by Barret et al. circumstantial evidence for mitochondrial dysfunction was found in HEU children exposed to antiretroviral therapy. All the children presented with neurological symptoms, often associated with abnormal magnetic resonance image (10 of 12) and/or a significant episode of hyperlactatemia (seven of 12). All had either a profound deficit in one of the respiratory chain complexes (11 of 12) and/ or a typical histological pattern (two of 12). All were perinatally exposed to antiretrovirals drugs. None of them had perinatal morbidity that could explain this symptomatology [43]. Hernandez et al. reported that mitochondrial parameters were reduced in HIV infected mothers and their newborn; especially newborn mitochondrial DNA levels, maternal and fetal mitochondrial protein synthesis and maternal glycerol-3-phosphate + complex III function without adverse perinatal outcome [44].

HIV or ARV exposure is associated with dysfunctional intermediary metabolism in newborns. Abnormal acylcarnitine levels were more frequent in ARV-exposed infants, suggesting that ARV may disturb fatty acid oxidation in some infants. Studies designed to validate and determine the clinical significance of these findings are needed [45].

Sociocultural Factors and Cognitive Development

The structure and cultural background of a family is critical in child development. Culture influences all aspects of child development and is reflected in child rearing practices. Protective cultural practices such breastfeeding are widely practiced in the developing communities [46]. It is the cultural norms that dictate the role of adults in child play, investment in child development and the degree to which society will embrace child protective practices such as child stimulation. Unfortunately, the AIDS epidemic has resulted in an increase in orphaned children as their parents succumb to HIV related illnesses. The family structure and dynamics have changed with more AIDS orphans growing up under the care of aged grandparents, older siblings or other relatives [47]. However, there is a lack of data on how the change in household composition impacts on child neurodevelopment, especially when the care givers change is due to death of a parent. In a case study among 193 Uganda orphans aged 15-19 years, 29% continued schooling undisrupted, 25% spent time off school and 45% dropped out of school and the least chance of continuing with education was reported in those fostered by grandparents (7%) [48].

Poverty and Child Development

Although definitions of poverty vary according to social, cultural and geographical location, the epidemiological perspective definition of low socioeconomic status, unemployment and low levels of education cuts across all cultures [49]. Universally, poverty increases the risk for emotional distress in families and children which may interfere with educational achievements. Poverty was correlated with increased maternal stress or depression and inadequate child stimulation in the home [50]. Studies demonstrated that the electrical brain activity of newborns of depressed mothers show reduced ability to learn from environment [51]. In the context of HIV infection, maternal mental health disorders compromise the parent-child interaction influencing cognitive stimulation. Poverty also negatively impact on the family's nutritional status. A study conducted in Kenya among children under 3 years living in poverty reported anthropometric measures such as height and weight as mediators of the relationship between socioeconomic status and psychomotor development [52].

Morbidity and Mortality

Prevention of Mother-to-Child HIV Transmission (PMTCT) programs in sub-Saharan Africa has been extremely successful in reducing the numbers of children infected with HIV. However, HEU children have substantially increased morbidity and mortality compared with children born to uninfected mothers HUU, predominantly from infectious causes. Moreover, a range of phenotypical and functional immunological differences between HEU and HUU children has been reported [53]. These differences have been reported particularly for infants below 2 years of age [31,54].

Possible reasons why the HIV exposed uninfected infants are at increased risk include less exposure to breast milk as mothers are either less able to breastfeed or stop breastfeeding early to protect their infant from HIV infection. Other contributing factors are parental illness or death resulting in inadequate care of the children, increased exposure to other infections and possibly exposure to antiretroviral drugs [55]. Maternal CD4 count predicts child mortality in HIV-uninfected children born to HIV-infected women [56]. Prematurity, teenage motherhood and symptomatic HIV-1 maternal disease were important predictors for post-neonatal mortality in a cohort of HIV-1 exposed uninfected infants according to a Kenyan study by Gichuhi [57]. These factors should be considered in monitoring and follow up in prevention of mother-to-child HIV-1 transmission (PMTCT) programs. In addition a broad approach for psychosocial support of HIV-affected families is needed to improve health of HIV-EU children. High quality programmatic research is needed to determine how to deliver such care [55].

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Although nutrition has been examined, the effects of CMV infection have not been evaluated in HEU children. The effects of CMV infection on the growth, development, and health of maternally HIV-exposed and unexposed infants in Zambia was studied. All CMV-seropositive infants had decreased length-for-age by 18 months compared with seronegative infants. In HIV-exposed infants CMV positive infants compared with those who were negative, had reduced head size and lower psychomotor development. HIV-exposed, CMV-viremic infants were more commonly referred for hospital treatment than CMV-negative infants. CMV seems to be a risk factor for poor child health in this region [58].

Infections may be more common and severe among HEU children than among unexposed children, which could contribute to both slower growth and higher mortality. A nearly study in Zaire (DRC) found that the incidence of persistent diarrhoea (> 14 days) among HIV-EU infants was twice that among HIV-unexposed infants [59]. An HIV exposure, rather than infection, based analysis of treatment failure among children with pneumonia to showed that failure odds among HIV-exposed uninfected infants were intermediate between their unexposed and infected counter parts [60]. The clinical and basic immunological findings of eight HIV-exposed uninfected infants hospitalized with serious infectious morbidity and referred for immunological evaluation showed that severe infections were likely. These included, Pneumocystis jiroveci pneumonia (three), cytomegalovirus colitis with perforation (one), Pseudomonas sepsis (two), hemorrhagic varicella (one) and Group A streptococcal meningitis and endocarditis (one). Five required intensive care, four for assisted ventilation and one for post-surgical care. The median age at presentation was 5.5 (1.5-15) months. Follow-up to 36 months suggested resolution of a transient immunodeficiency in two infants, one of whom had CD4 and the other B-cell depletion [61]. The HEU infants experience high rates of all-cause and infectious hospitalization (particularly gastroenteritis) and in-hospital mortality [62]. With cardiac function, non-HIV-infected infants born to HIV-infected mothers, fetal exposure to ART is associated with reduced Left Ventricular dimension, Left Ventricular mass, and septal wall thickness and with higher Left Ventricular fractional shortening and contractility during the first two years of life [63]. The important immune findings in HEU children are expanded memory T cell subsets and increased immune activation with increased apoptosis, reduced thymic function and fewer naïve T cells, accompanied by functional differences consistent with Th1/Th17 polarization and impaired APC function, in a setting of reduced transfer of maternal antibodies [64].

It is evident that few longitudinal studies have followed up HEU children to school age. In resource limited settings, future operational research studies are needed to inform HIV programmes on how best to promote the health of HEU children and their families in that context. Interventions to improve household family food security and assess availability of energy and micronutrient dense foods for school age children are a priority. Staple diets in Africa and other low income countries are frequently bulky with low energy and micronutrient density [65]. Cognitive stimulation therapy has been shown to improve cognitive function in HI children [66]. In HEU, there is need for further basic research using larger sample sizes and validated neurodevelopmental tools to assess the feasibility of including child cognitive stimulation intervention in child health programmes. More research is required to assist healthcare workers in managing HEU and their families. It is unclear if HEU children respond adequately to vaccines, need extra vaccine boosters, they benefit from antibiotic prophylaxis and the duration of such interventions. Strengthening family-centered HIV prevention and treatment programs will improve health outcomes and socioeconomic participation of HIV infected parents and their HEU children.

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