The impact of health programmes to prevent vertical transmission of HIV. Advances, emerging health challenges and research priorities for children exposed to or living with HIV: Perspectives from South Africa

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Over the past three decades, tremendous global progress in preventing and treating paediatric HIV infection has been achieved. This paper highlights the emerging health challenges of HIV-exposed uninfected (HEU) children and the ageing population of children living with HIV (CLHIV), summarises programmatic opportunities for care, and highlights currently conducted research and remaining research priorities in high HIV-prevalence settings such as South Africa. Emerging health challenges amongst HEU children and CLHIV include preterm delivery, suboptimal growth, neurodevelopmental delay, mental health challenges, infectious disease morbidity and mortality, and acute and chronic respiratory illnesses including tuberculosis, pneumonia, bronchiectasis and lymphocytic interstitial pneumonitis. CLHIV and HEU children require three different categories of care: (*i*) optimal routine child health services applicable to all children; (*ii*) routine care currently provided to all HEU children and CLHIV, such as HIV testing or viral load monitoring, respectively, and (*iii*) additional care for CLHIV and HEU children who may have growth, neurodevelopmental, behavioural, cognitive or other deficits such as chronic lung disease, and require varying degrees of specialised care. However, the translation thereof into practice has been hampered by various systemic challenges, including shortages of trained healthcare staff, suboptimal use of the patient-held child's *Road to Health* book for screening and referral purposes, inadequate numbers and distribution of therapeutic staff, and shortages of assistive/diagnostic devices, where required. Additionally, in low-middle-income high HIV-prevalence settings, there is a lack of evidence-based solutions/models of care to optimise health amongst HEU and CLHIV. Current research priorities include understanding the mechanisms of preterm birth in women living with HIV to optimise preventive interventions; establishing pregnancy pharmacovigilance systems to understand the short-, medium- and long-term impact of *in utero* ART and HIV exposure; understanding the role of preconception maternal ART on HEU child infectious morbidity and long-term growth and neurodevelopmental trajectories in HEU children and CLHIV, understanding mental health outcomes and support required in HEU children and CLHIV through childhood and adolescence; monitoring HEU child morbidity and mortality compared with HIV-unexposed children; monitoring outcomes of CLHIV who initiated ART very early in life, sometimes with suboptimal ART regimens owing to medication formulation and registration issues; and testing sustainable models of care for HEU children and CLHIV including later reproductive care and support.

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Over the past three decades, tremendous global progress in preventing and treating paediatric HIV infection has been achieved.[1] In 2009, it was projected that 95% coverage of dual therapy to prevent vertical transmission of HIV with appropriate feeding choices could save 37 200 children's lives in 2015, using 2008 data as a baseline.[2] Although life-long triple antiretroviral therapy (ART) for pregnant and breastfeeding women has not been the panacea for eliminating vertical HIV transmission,[1] it has certainly brought this goal significantly closer.[1,3] Finally, we are seeing a shift to fewer perinatally acquired HIV infections; however, concomitantly, owing to sustained high antenatal HIV prevalence, the population of HIV-exposed uninfected (HEU) children is steadily increasing. Additionally we are seeing an ageing cohort of children living with HIV (CLHIV).[4]

Researchers associated with the South African Medical Research Council (SAMRC) have conducted pivotal research, firstly to prevent MTCT and subsequently to attain EMTCT. The current SAMRC president, Glenda Gray, played a key role in the first multi-country PErinatal TRAnsmission (PETRA) tiral to investigate the efficacy of three short-course maternal and infant antiretroviral drug regimens to prevent MTCT.[5] The PETRA trial demonstrated that short-course, dual maternal antiretroviral (ARV) prophylaxis (from 36 weeks' gestation until 7 days postpartum) significantly reduced MTCT by 4 - 8 weeks postdelivery (63% efficacy), but had no significant 18-month benefits. This trial was followed by pivotal infant ARV post exposure prophylaxis research to obviate MTCT in women with no prior ART exposure.[6] Once South Africa (SA) adopted a policy to provide single-dose nevirapine to prevent vertical HIV transmission (PMTCT) in 18 pilot sites, the SAMRC was a key partner in evaluating the effectiveness of this policy: research in three purposively selected sites (Paarl, Rietvlei and Umlazi) demonstrated 8.6%, 13.7% and 11.9% MTCT at 3 - 4 weeks,[7] and 84%, 65% and 74% HIV-free survival at 9 months,[8] respectively, and poor infant feeding practices amongst HIV-negative and -positive mothers in the context of PMTCT.[9] After 8 years of national PMTCT scale-up, the SAMRC led 3 nationally representative evaluations in 2010, 2011 - 2012 and 2012 - 2013,[10,11] and 1 prospective observational cohort study[12] to measure 6-week and 18-month PMTCT effectiveness, respectively. These demonstrated a reduction in national 6-week MTCT to 3.5% with dual therapy (2008 PMTCT guidelines) and 2.6% with PMTCT Option A, and 4.3% at 18 months, with 6.3% 18-month MTCT or death. Since these surveys, a SAMRC-National Institute of Communicable Diseases (NICD) collaboration has established that national laboratory data provide valid estimates of early national MTCT.[13] With the adoption of PMTCT Option B+ (lifelong triple ART) for pregnant and breastfeeding women in 2015, and the release of global criteria to validate EMTCT, national short- and long-term PMTCT effectiveness needs to be monitored.[3,14,15] Despite a reduction in MTCT at national, provincial and district levels, SAMRC and partners report differential MTCT across provinces and districts, highlighting the gap between current case rates and the global target of 50 or fewer new paediatric HIV infections per 100 000 livebirths.[16] In 2019, the SAMRC led an analysis paper on whether elimination of MTCT is achievable in high HIV-prevalence settings, highlighting how maternal HIV prevalence drives the paediatric HIV case rate.[17]

By 2019, SA has stabilised antenatal HIV prevalence and been hugely successful in reducing MTCT.[16,18,19] Expressed as a percentage of all births to women living with HIV (WLHIV), modelling demonstrates that total MTCT (perinatal and postnatal HIV transmission to end of breastfeeding) decreased from 31.2% (95% confidence interval (CI) 28.7 - 34.3) in mid-2004/05, to 5.2% (95% CI 4.5 - 6.1) in mid-2016/17 (Thembisa model version 4.1). Overall, perinatal HIV transmission decreased from 18.7% (95% CI 18.2 - 19.2) in mid-2004/05 to 1.3% (95% CI 1.1 - 1.5) in mid-2016/17. Perinatal HIV transmission amongst mothers with known HIV infection was 0.84% (95% CI 0.78 - 0.90) in mid-2016/17. Consequently, given the stable antenatal HIV prevalence and reduction in MTCT, the number of HEU children aged 0 - 14 years increased from 1.3 million in 2004 to 3.2 million in 2017 – this is the highest number within any country globally, representing 21.5% of the global HEU child population.[4]

This paper highlights the emerging health challenges of HEU children and the ageing population of CLHIV, summarises programmatic opportunities for care, and highlights both current research underway and remaining research priorities in high HIV-prevalence settings, such as SA.

What are the emerging health challenges faced by HEU children and CLHIV?

Newborn outcomes

The newborn period presents a crucial opportunity for preventing perinatal and postnatal HIV transmission, through identification of all infants born to WLHIV and stratification of mother-infant pairs at high or low risk of HIV transmission with appropriate postnatal prophylaxis, depending on risk. Furthermore, all HIV-exposed newborns should receive HIV testing with a polymerase chain reaction (PCR) test to identify *in utero* HIV-infected infants as early as possible, as immediate initiation of infant ART improves survival and long-term outcomes. HIV-exposed newborns, both HIV-infected and HIV-uninfected, are more likely to start life as preterm infants, with lower birthweight and/or as small-for-gestational age, than their HIV-unexposed counterparts.[20] This effect differs by maternal ART regimen and timing of treatment initiation, although observed associations related to timing may be subject to selection bias.[21] Several studies have reported higher rates of preterm birth in infants born to women on ritonavir-boosted protease inhibitor-containing ART than other regimens.[22-24] These adverse birth outcomes persist even when pregnant WLHIV receive universal ART with current efavirenz or dolutegravir-based regimens,[25,26] and are probably associated with conception on ART, particularly in low- and middle-income countries.[27] These adverse birth outcomes are poorly understood but likely to influence HEU child outcomes beyond birth. Additionally, the potential for teratogenic effects of *in utero* drug exposures was recently highlighted by the preliminary signal in Botswana of a possible association between an increased risk for fetal neural tube defects and dolutegravir use at time of conception.[28] While more definitive data are awaited, this finding highlights the critical need for pregnancy pharmacovigilance systems in low- and middle-income countries, particularly those with a high HIV burden, such as SA.[29]

Growth

The synergistic interactions between infection, immunity and childhood malnutrition are well established.[30] Indeed, malnutrition is sometimes referred to as an immunodeficiency syndrome as it is a composite outcome of several inflammatory and metabolic pathways.[31] Infectious diseases such as HIV infection exacerbate undernutrition. In a prospective cohort study conducted prior to the availability of maternal ART, Ramokolo and colleagues reported worse postnatal growth velocity in SA CLHIV than HIV-unexposed and HEU children.[32] Consistent with other studies,[33] no significant differences in growth were observed between HIV-unexposed and HEU children. However, recent data show poorer early growth of HEU children, and notably suboptimal growth and failure to catch up postnatally in HEU infants born small for gestational age compared with HIV-unexposed infants.[34] This observation suggests a fetal origin to later poor HEU child outcomes that requires further interrogation.[35] Data also show that maternal HIV infection is associated with several adverse birth outcomes such as low birthweight, preterm birth, small-for-gestational age and stillbirth.[36-38] Additionally, HEU children in the era of Option B+ have poorer height growth compared with weight, and therefore higher BMI, and obesity remain a concern in adolescence and adulthood (du Plessis – in press). The mechanisms behind these observations remain unclear. Some speculate that immune

dysfunction induced by HIV exposure may partly explain the growth faltering.[39] There is also evidence that *in utero* exposure to maternal ART increases the risk of suboptimal birth outcomes, leading to poorer growth postnatally.[35,40] As countries adopt lifelong ART for pregnant and lactating women (WHO Option B+ policy), more women with higher CD4 counts will conceive on ART. Few data are available on these women and their children. Further research is therefore required to understand the interplay between HIV and growth in the current ART era to ensure that HIV-exposed children not only survive but also thrive.

Early neurodevelopment

Neurological, developmental and behavioural problems in CLHIV have been well-established as devastating consequences of HIV infection, ranging from cognitive deficits to HIV encephalopathy,[41-43] and these are associated with neuro-radiological findings.[44,45] Since the introduction of paediatric ART, studies have continued to document neurodevelopmental impairment.[46-48] Furthermore, there is growing evidence that HEU children may experience early developmental impairment. Previous reviews have reported some delays in cognitive, language or motor development,[47,49,50] although to a lesser extent than in CLHIV and mainly in low-resource settings.[47] A recent study from SA found motor and cognitive delay, particularly associated with preterm birth,[51] and a study from Zambia reported a later impact on school performance.[52] However, other studies in Botswana[53] and SA[54] have not found substantial differences when compared with HIV-unexposed children, although some language impairment was demonstrated, which has also been seen in high-income settings.[55] Further research and follow-up of both CLHIV and HEU children in the current ART era is needed to determine the nature of the developmental delay as well as the long-term implications. In addition, investigating the mechanisms behind the impaired development is important to prevent future developmental delay, and to understand the complex combination of HIV-related variables and illness, ART exposure and side-effects, and socioeconomic factors.

Later mental health and neurocognitive development

The impact of perinatal HIV transmission is experienced well into adolescence, where HIV has historically been implicated in normative developmental challenges, including pubertal delays,[56] continued neurodevelopmental and cognitive problems[57,58] as well as greater social and emotional immaturity relative to same-age peers.[59] The most common mental health problems seem to be attention deficit hyperactivity disorder, mood disorder, anxiety disorder and substance use disorder.[60] However, not all adolescents living with HIV (ALHIV) experience the same level of vulnerability, as these disorders range from 8% to 60% in untreated HIV-infected adolescents.[60] The evidence from high-income settings suggests that CLHIV are at significant risk for mental health problems and substance use when entering adolescence.[61] Additionally, there is limited but growing research which suggests that youth living with perinatally acquired HIV infection may be equally, if not more, vulnerable to emotional and behavioural problems than HEU youth or HIV-uninfected youth living in households affected by HIV.[62,63] Recent SA data warned against conflating all HIV-infected adolescents: perinatally infected adolescents were more likely to be ART adherent, retained in healthcare and treated well by clinic staff than horizontally infected adolescents who display more mental health disorders than the former.[64] These better outcomes amongst perinatally infected adolescents are substantiated by a recent SA study which described a lower incidence of behavioural problems amongst perinatally acquired ALHIV, compared with uninfected adolescents.[65] In addition, the loss of adult caregivers to HIV, and poverty related to loss of income due to ill health, may also compromise the family's capacity to meet the needs of ALHIV.[66]

Infectious disease morbidity and mortality

Without ART, over 50% of CLHIV would die before age 2 years.[67] Recent studies indicate that, despite early introduction of ART, child mortality in CLHIV remains high and viral suppression is often suboptimal, with substantial implications for future health outcomes.[68,69] HEU children have also been found to have a higher mortality than HIV-unexposed children,[67,70] particularly in the first years of life, estimated to be ~double that of HIV-unexposed children, although reports vary across countries.[71,72] Data from SA suggest that the excess mortality in HEU children contributes substantially to total infant mortality.[73] HEU child mortality appears to be predominantly due to infectious causes,[74] and SA studies have shown that HEU infants have a higher incidence as well as greater risk for mortality from invasive pneumococcal disease and viral respiratory infections.[75,76] Prolonged breastfeeding, although with overwhelming benefits for improved nutrition and reduced diarrhoeal disease morbidity, did not prevent additional respiratory morbidity and mortality in HEU children from two different urban settings (Soweto and Paarl).[77,78] Furthermore, in studies from Botswana, cotrimoxazole prophylaxis did not reduce infectious morbidity or improve survival in HEU children in the first year of life.[79] Promising evidence from high-income settings suggests initiation of maternal ART before pregnancy may mitigate some of this infectious morbidity risk for HEU children; however, this still requires evaluation in HIV high-burden countries.[80]

Respiratory-related morbidity and mortality

Respiratory disease including tuberculosis and viral and bacterial infections remains the primary cause of hospital admissions in CLHIV despite early ART.[68] This finding is similar for HEU children, who also have increased rates of hospitalisation and suffer from more severe and unusual infectious diseases in the early years of life,[81,82] particularly pneumonia.[83] Although there is considerable difficulty estimating the association between HIV and pulmonary tuberculosis (PTB) in African children, the epidemiology of childhood TB and HIV overlap considerably.[84,85] Routine programmatic data from Cape Town prior to the paediatric ART roll-out reported a TB incidence of 1 596 per 100 000[86] in CLHIV, decreasing considerably following ART access,[87,88] and linked also to a reduction in associated hospitalisations.[89] HIV infection associated with multidrug-resistant (MDR) paediatric TB is a challenge, and SA studies reported a paediatric HIV prevalence of 54%, 77% and 43% amongst children with MDR TB in Johannesburg, KwaZulu-Natal and Cape Town, Western Cape in 2008, 2009 - 2010 and 2003 - 2008 respectively.[90-92] Amongst HEU children, data demonstrate that the incidence of TB is four times higher than in the general population.[84] Pneumocystis pneumonia (PJP) remains an important cause of severe pneumonia in HEU children and CLHIV: a prospective intervention study conducted in Steve Biko Academic Hospital, Pretoria, SA, demonstrated co-infection between PJP and cytomegalovirus (CMV), with a 30% mortality rate.[93] There is compelling evidence that infant ART decreases mortality from invasive pneumonia by 62.5% in SA and protects against hospitalisation and mortality from influenza.[84] Data are needed on the impact of PMTCT Option B+ and of early infant HIV diagnosis with early infant ART initiation on childhood respiratory diseases amongst CLHIV. Chronic lung disease (CLD), including bronchiectasis and lymphocytic interstitial pneumonitis, is

an unresolved challenge in CLHIV, despite ART. A Zimbabwean study by Ferrand *et al.*[94] demonstrated that ~45% of CLHIV aged 0 - 14 years receiving HIV-related care, have CLD, even at high CD4 cell counts and despite ART access. Data on acute and chronic lung disease in CLHIV in SA are sparse. Weber *et al.*[95] reporting on data from 56 children aged 5 years (interquartile range 2 - 8 years) demonstrated a significant association between CLD and lung hyperinflation and hyperpigmented skin lesions. Calligaro and Gray,[96] using data from Cape Town, SA, demonstrated increased airway resistance in HIV-infected v. HIV-uninfected children, and that an abnormal forced expiratory volume in one second (FEV1) was significantly correlated with high airway resistance. Like Ferrand *et al.*,[94] they concluded that lung involvement occurs early in CLHIV who do not access ART and that clinical and immunological correlates are poor predictors of lung involvement. More data are needed to understand these mechanisms. Additionally, data on the lung microbiome in CLHIV are limited, warranting further investigation.

What health services/ programmes exist to meet the needs of HEU children and CLHIV?

CLHIV and HEU children require three different categories of care.[97] The first entails optimal routine child health services applicable to all children, including immunisations, growth monitoring and nutritional support, as well as diagnosis and management of acute childhood illnesses. The second category pertains to the routine care currently provided to all HEU children and CLHIV, such as HIV testing at specified intervals (for HEU children), antiretroviral prophylaxis (for HEU children) or viral load monitoring (for CLHIV). Both these aspects of care are relatively well catered for and resourced through the Integrated Management of Childhood Illnesses (IMCI) strategy and supported by the *Road to Health* booklet (RTHB).The concept of what constitutes 'routine care' and 'success' in terms of the PMTCT programme, however, requires a paradigm shift in SA. The current major endpoint of the PMTCT programme is a child who is HIV free. A more progressive view of success would be a child who is HIV free, thriving, and has normal neurodevelopment, for which the third category of care is also required. The third category is additional care for CLHIV and HEU children who may have growth, neurodevelopmental, behavioural cognitive or other deficits such as chronic lung disease, and require varying degrees of specialised care. The new national PMTCT guideline (2019) identifies the HEU child as being at risk for poorer outcomes and recommends vigilance to identify vulnerabilities. The RTHB, the IMCI strategy, and the School Health Programme have included screening for developmental impairments in routine care for all children, including HEU children and CLHIV.[98] However, the translation thereof into practice has been hampered by various systemic challenges, including shortages of trained healthcare staff, suboptimal use of the patient-held RTHB for screening and referral purposes, inadequate numbers and distribution of therapeutic staff, lack of long-term follow-up of HEU children and adolescents, and shortages of assistive/diagnostic devices where required.[18]

What policy- and health system-related research has just been completed in SA or is underway?

The very early infant diagnosis study conducted at Kalafong hospital substantiates the current policy of universal rather than targeted birth HIV testing amongst HIV-exposed newborns. The study demonstrated that using a risk score (three- or four-risks) at a probability of 0.02 and 0.04, misses 20% and 24% of HIV-infected infants, respectively, at birth compared with universal testing.[99] A field-based evaluation of point-of-care testing for at-birth infant HIV diagnosis, conducted at Rahima Moosa Hospital, highlighted the additional staff needed to make this approach functional; however, the study highlighted the potential child health gains as time to infant ART initiation was reduced.[100] The PHANGISA study will assess the role of viral load and health systems factors in driving peripartum and postpartum MTCT, in the context of PMTCT Option B+, in Ehlanzeni, a rural district in SA (http://www.mrc.ac.za/intramural-research-units/HealthSystems-current-projects).

Research priorities in high HIV-prevalence settings

CLHIV and HEU children experience unique health challenges that require vigilance and ongoing, long-term surveillance. This need is especially important, given the increasing HEU child population in SA and globally. Care needs to be provided in a non-stigmatising way, and front-line health workers should be aware of the vulnerabilities of these populations.

Several research gaps exist for CLHIV and HEU children in high HIV-prevalence settings (Fig. 1), including understanding mechanisms of preterm birth in WLHIV, to optimise preventive interventions;

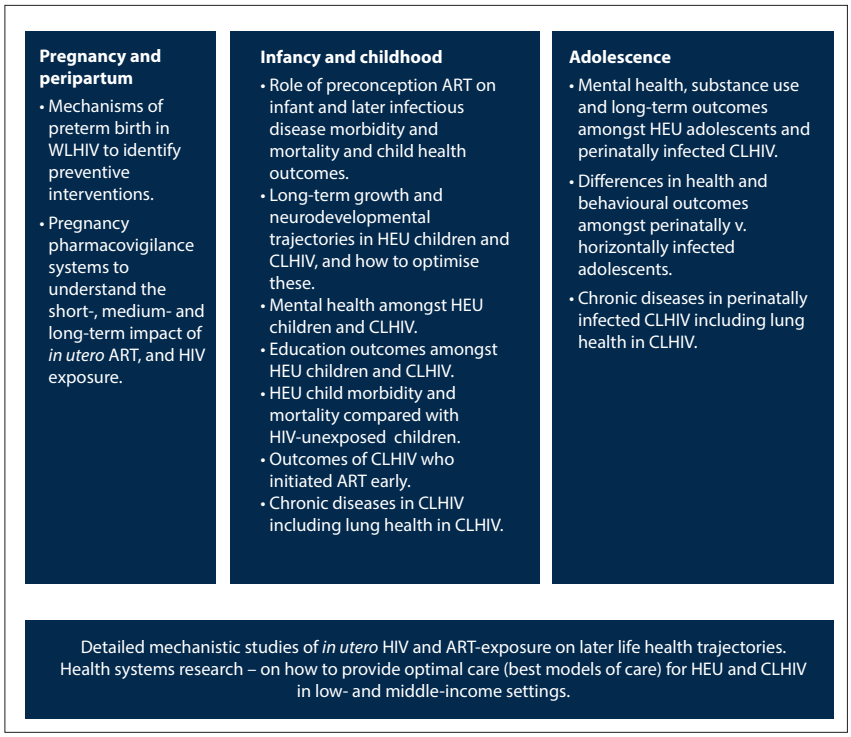

Fig. 1. Research priorities in high HIV-prevalence settings. (WLHIV = women living with HIV; ART = antiretroviral therapy; HEU = HIV-exposed uninfected; CLHIV = children living with HIV.)

establishing pregnancy pharmacovigilance systems to understand the short-, medium- and long-term impact of *in utero* ART and HIV exposure; understanding the role of preconception maternal ART on infant infectious morbidity, understanding the role of preconception maternal ART on HEU children's infectious morbidity and long-term growth and neurodevelopmental trajectories in HEU children and CLHIV; understanding mental health outcomes and support required in HEU children and CLHIV through childhood and adolescence; monitoring HEU child morbidity and mortality compared with HIV-unexposed children; monitoring outcomes of CLHIV who initiated ART very early in life, sometimes with suboptimal ART regimens due to medication formulation and registration issues; and testing sustainable models of care for HEU children and CLHIV including later reproductive care and support. Lastly, we must not lose sight of the urgent need to reduce maternal HIV prevalence, as this is the most important way to reduce the numbers of CLHIV and HEU.

Conclusion

More than one in five children in SA are HIV- and ART-exposed *in utero*; never before has there been exposure to an infectious disease or associated medication use of this magnitude during pregnancy. SA needs to lead the way in better understanding the vulnerabilities of HEU children and CLHIV, to optimise their short- and long-term outcomes.

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