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Unmasking the vulnerabilities of children exposed to HIV and/or antiretroviral drugs

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Key messages: HIV exposed and uninfected, children, surveillance

- In resource-limited settings, home to the majority of HIV exposed uninfected (HEU) children, HEU children have multiple exposures including maternal HIV infection, maternal/infant antiretroviral drugs (ARVs), and other ubiquitous environmental / household exposures that increase the risk of HEU and other children for poor health and developmental outcomes. Systematically identifying the exposures that place an additional health and/or developmental risk burden on HEU children is of paramount importance to catalyze progress towards ensuring the rapidly expanding HEU child population thrives and not merely survives.

- This will require nuanced data from in-depth studies, including long-term prospective cohort designs with appropriately powered sample sizes to understand risk factors and elucidate causal mechanisms associated with HEU child health and developmental disparities.

- The short and long-term routine monitoring of health outcomes of children exposed to HIV and/or ARVs is important and will require novel and collaborative approaches, particularly in high burden HIV settings.

Standfirst: "Vundli Ramokolo and colleagues argue that short and long-term monitoring of HIV and/or antiretroviral (ARV) exposure in children is critical to identifying ways of improving individual clinical care and developing responsive public health interventions ensuring that these children not only survive but thrive."

Competing interests statement: The authors have no competing interests

Contributorship: AG is a Clinician Scientist and Epidemiologist with more than a decades experience in clinical care and research. She has led national surveys to monitor PMTCT effectiveness. AG conceptualised the paper and contributed to its direction and finalization; VR is an Epidemiologist with over a decade of experience doing research on HIV exposed and unexposed children. She led the writing. ALS is a Paediatrician and Epidemiologist with more than a decade' experience in research with and clinical care of HIV -exposed children. KP is a Pediatrician and Internist and has been conducting clinical research in the health disparities of HIV and antiretroviral exposed but uninfected infants and children. She has been conducting maternal-child health research in Botswana, a high prevalence HIV setting, since 2008. KP has multiple publications related HIV-exposed uninfected children and has been an invited speaker at international conferences on this topic. All authors contributed to the ideas in the paper and the direction of the paper. All authors read the paper, contributed to all drafts and approved the final version of the paper.

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Introduction

The global number of HIV-exposed uninfected (HEU) children (0-14 years) has been steadily rising over the past two decades, largely due to the success of programmes to prevent peri- and post-natal HIV transmission, frequently known as Prevention of Mother to Child Transmission of HIV (PMTCT), and was estimated at 14.8 (10.7-19.2) million in 2017[1]. For example, the HEU population in South Africa grew from 1 million in 2002 to more than 3 million in 2017, as seen in Figure 1. Beyond preventing infant HIV acquisition, it is also important to ensure that HEU children thrive and reach their highest potential. Thus, this vulnerable population needs close monitoring to quantify the long-term effects of in-utero HIV and antiretroviral drug (ARV) exposure on their health and development and intervene when health or developmental disparities are identified. Failure to appropriately invest in HEU children now has significant longer term public health and human capital implications, particularly in high HIV burden settings[2].

Definition of exposure status

In research and operational/routine settings there is a need for exposures to be clearly defined as both the variation in how exposures are constructed and changes in ARV drug regimens over time limit the extent to which study results can be compared and consolidated. With the evolution of the HIV epidemic and triple antiretroviral therapy (ART) programmes, three HIV-related exposures are of paramount importance in children, namely in-utero or post-delivery HIV exposure, in-utero or post-delivery ARV exposure, and indirect/environmental HIV exposure through an HIV-affected household. The term "HEU child" typically refers to a child born to a mother living with HIV, where the child has been exposed to HIV infection in-utero or post-delivery. It is noteworthy that this HEU population is not homogenous, representing a population of children, some without in-utero or postnatal ARV exposure and others with both in-utero and postnatal ARV exposure with the nature of the ARV exposure varying by type, number and duration. Additionally, maternal physical and mental health, breastfeeding duration, household pathogens, and social challenges associated with poverty, such as food insecurity or poor water and sanitation contribute to the heterogeneity of exposures.

In South Africa the type and extent of the exposures, and thus the risk profiles of HEU children have changed since 2001, as PMTCT programming has evolved from offering single dose nevirapine to pregnant women living with HIV (WLHIV) as prophylaxis [3] to "Option B+" in 2015 that promotes lifelong ART to all pregnant and lactating WLHIV[4]. Furthermore, depending on the availability and efficiency of ARV drugs at

the time, the severity of the maternal HIV disease stage also varied. This has direct implications for an HEU child's potential to survive and thrive as maternal viremia is associated with lower motor and expressive language scores [5] and poorer growth outcomes[6]. Moreover, some infants are born to WLHIV who did not receive ARVs during pregnancy. Although these children do not have risks associated with in-utero ARV exposure, they were likely exposed to high levels of maternal HIV viremia and systemic inflammation that could result in immune dysfunction [7 8]. Systematically identifying the exposures that place HEU children at risk for poor health and developmental outcomes and ensuring that these exposures are accurately documented in research studies and health systems is of paramount importance to catalyze the implementation of appropriate interventions that ensure the HEU population not only survives, but also thrives.

Another point for consideration is that, improvements in ARV access and expanded programming are expected to result in an increasing proportion of women conceiving while on ARVs, given that ARVs are now available as pre-exposure prophylaxis (PrEP) for high risk women without HIV. Furthermore, some HIV negative women on PrEP pre-conception may continue ARVs during pregnancy and lactation now that PrEP is being tested for use in pregnant and lactating women[9] Their children will be HIV unexposed but ARV exposed (HUA) in-utero, post-delivery or both. Monitoring systems are equally needed for these HUA children.

Furthermore, beyond the direct physiological exposure to maternal HIV and ARVs through pregnancy and breastfeeding, a broader definition of HIV affected children should be considered. These are children who are affected by HIV as they live in households/environments that currently include or have included a person living with HIV. We refer to this population as environmentally HIV exposed (EHE) children. Evidence indicates that AIDS-orphans (children whose parents(s) have succumbed to AIDS), and children living in households with caregivers living with HIV experience vulnerabilities, such as poverty and depression, have an increased risk for poor mental health [10]. This suggests that all children living in HIV-affected households, irrespective of their direct HIV-exposure status, should be monitored as they may be exposed to interacting syndemics that increase their risk for poor health[11].

Prospective cohort studies of HIV exposed uninfected children

There is a paucity of long-term follow-up data on HEU children, particularly in low-to-middle income settings that carry the highest burden of the HIV pandemic. One of the largest cohort studies of HEU children (n=3125) was initiated in Zimbabwe in 1997 before any ARVs were available in this setting [12]. The

lack of ARV data in this study and many other similar cohorts precludes analysis of how ARV exposure amongst HEU children may reduce or contribute to adverse outcomes. Particularly as newer ARV regimens are recommended for use during pregnancy and breastfeeding, contemporaneous cohort studies and surveillance systems of HEU children are urgently needed. Furthermore, while modelled estimates like the recently published UNAIDS estimates[1] are beneficial for describing and monitoring HEU child population trends, more nuanced data from in-depth studies are required to understand risk factors and causal mechanisms associated with HEU child health and developmental disparities. Such studies require well thought through long-term prospective cohort study designs with appropriately powered sample sizes that allow for complex analyses.

Routine monitoring of children

In many low and middle-income settings, the follow-up of HEU children in routine clinical care aligns with scheduled immunization visits and HIV testing time points and has historically stopped at 18 months postpartum. More recently, an extension of follow-up to 24 months has been recommended as breastfeeding under ART cover, and therefore viral suppression, has been extended to 24 months[13]. Although programmes may be structured to follow-up HEU children until 18 or 24 months, HEU children will progress from childhood to adolescence and through to adulthood, when they are expected to be independently functioning and contributing members of society. A life-course approach to identifying and providing care for the most vulnerable HEU children through childhood, adolescence and adulthood is thus urgently needed. Ultimately, research and health systems data may demonstrate that HUA and EHE children may require similar specialized care. Outside of the routine immunization follow-up schedule, most often completed at age five years, most HEU, HUA and EHE children only visit health facilities for curative care when they are sick or re-enter the healthcare system again as adolescents or adults seeking services such as family planning or maternity care. This presents a challenge for understanding the health and long-term outcomes of these vulnerable groups of children and for monitoring ultimate PMTCT and HIV programme impact. Only when appropriately sized and structured HEU child data platforms are available, and when systems exist to routinely analyze such data, will it be possible to adequately inform health policies and programmes so that resources and interventions can be suitably allocated and designed. One such example is the “trigger-based” approach where, for instance, HEU children with specific events trigger two key activities: first, the referral of the child for additional clinical assessments and care and second, reporting of the event into a denominated database, comparable to the Evaluation

of the Khayelitsha AIDS Program (EKAPA) electronic health record for primary healthcare or TIER.Net electronic HIV register used in the Western Cape province of South Africa[14], to track population outcomes. This approach leverages the available detailed clinical data systems for improved individual clinical care, public health surveillance purposes and provides insights on risk factors for disease that may be used to develop future public health interventions[15].

The Way Forward

In reality, most HEU children live in countries with competing priorities, such as South Africa that is facing a quadruple burden of disease including communicable, non-communicable, perinatal and maternal, and injury-related disorders [16]. The long-term monitoring of morbidity, quality of life and mortality of HEU, HAU and EHE children will require novel and collaborative approaches, particularly in high burden HIV settings where the health sector is already overtaxed. The solution will require the use of unique identifiers, linking an individual's health records from childhood into adulthood. The increasing evidence that HEU children with ARV exposure have poorer neurodevelopmental outcomes than HIV unexposed children [17], argues for a multisectoral approach. For example, there may be merit in tracking educational outcomes at population level by a child's HIV exposure status, controlling for educational and social interventions such as grants, where appropriate. This will need careful thought and planning to ensure that applicable exposures or interventions are adequately captured to account for differences in academic performance. Inevitably, any longer term or broader monitoring carries with it the need to address disclosure, both to the child or adolescent of their HEU status, to those who monitor outcomes and to those who provide interventions. Notwithstanding the health benefits of documenting the in-utero HIV and ARV exposure status of the HEU / HUA child for healthcare purposes, this status discloses the mother's HIV and ARV-risk status and therefore presents an ethical dilemma. More specifically, there are concerns about whether the benefits of disclosure outweigh or balance potential harms such as stigma or trauma and whether this impinges on the mother's or child's right to privacy. Some may argue that the benefits of disclosing the mother's HIV status during breastfeeding are justified because interventions that prevent breastmilk transmission of HIV can be modified during this period, but that disclosure should stop when breastfeeding stops as the child is no longer at risk of HIV acquisition. Others may argue that HEU, HUA and EHE children are at risk throughout their lifetime, regardless; thus, based on the International Convention on the Rights of the Child, specific health care providers need access to their HIV and / or ARV exposure status throughout their lives. In conclusion, despite concerns about disclosure, both short and

long-term monitoring of HIV and/or ARV exposed children is critical to identify ways to ensure that these children thrive.

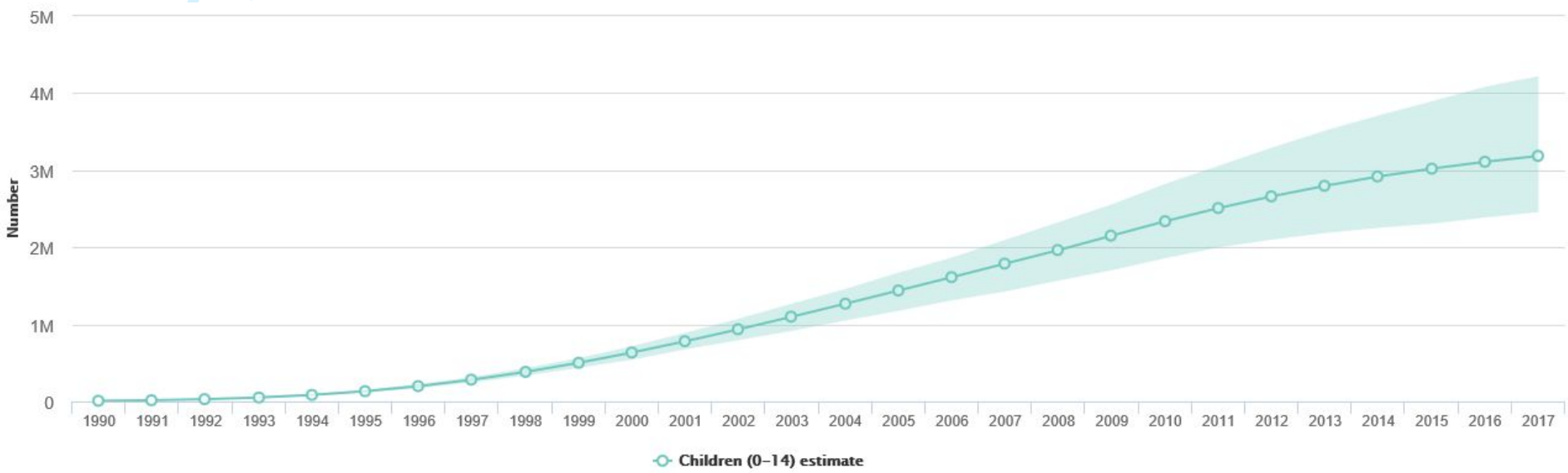

Figure 1: Number of HIV exposed uninfected children in South Africa[1]

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