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Unmasking the vulnerabilities of HIV affected children

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Key messages:

- As of 2017 there are over 14 million HIV-exposed uninfected children aged 0-14 years in high HIV prevalence settings, with a more dramatic increase in this population in the last five years due to expanded access to more effective programmes to prevent vertical HIV transmission.
- HIV-exposed uninfected children living in resource-limited settings have multiple unique exposures including maternal HIV infection and maternal/infant antiretroviral drugs as well as ubiquitous environmental / or household exposures that have contributed to health disparities when compared with children born to women without HIV. These include higher rates of preterm birth, higher infectious morbidity incidence and severity, higher mortality, poorer growth and developmental delays.
- Research relying on systematic approaches to quantifying exposures attributable to outcome disparities among HIV-exposed uninfected children is urgently needed. This requires the collection of nuanced data from long-term, in-depth, appropriately powered prospective cohort studies that gather data on exposures, mediators, effect modifiers and outcomes to elucidate causal mechanisms and possible interventions.

- Whilst the research is underway to understand causal mechanisms affecting the health, growth and development of HIV-exposed uninfected children, routine health services in high burden HIV settings should be aware of HEU child vulnerability, for early and timely identification and management of adverse outcomes.

Standfirst: "Vundli Ramokolo and colleagues argue that in-depth studies of HIV-exposed uninfected children are needed to understand how multiple exposures affect this vulnerable population's short and long-term health and developmental outcomes. Additionally, high HIV prevalence settings need awareness of HEU child vulnerability in routine systems for early and timely identification and management of adverse outcomes; these will ensure that HIV-exposed uninfected children not only survive but thrive."

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Contributorship: AG is a Clinician Scientist and Epidemiologist with more than 15 years of 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 researching outcomes of HIV exposed and unexposed children. She led the writing. ALS is a Paediatrician and Epidemiologist with more than a decade of 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 for over a decade. 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 children (0-14 years) has been rising over the past two decades, and was estimated to include 14.8 (10.7-19.2) million children in 2017, of which 90% lived in sub-Saharan Africa(1). The growth of the HIV-exposed uninfected child population is largely due to the success of public health programmes to prevent peri- and post-natal vertical transmission of HIV. For example, the HIV-exposed uninfected population in South Africa grew from 1 million in 2002 to more than 3 million in 2017, as seen in Figure 1. However, the adoption of the World Health Organization's policy to provide life-long antiretroviral treatment to all pregnant women living with HIV(2) has resulted in an ever greater proportion of women living with HIV conceiving while on ART, with fetal exposure to antiretroviral drugs at a critical period of organogenesis in the first 10 weeks of a pregnancy. Beyond preventing infant HIV acquisition, it is important to ensure that HIV-exposed uninfected children also thrive, as research data have shown that these children are not only more likely to be born premature and small for gestational, but also tend to have poorer growth and developmental outcomes compared to their HIV unexposed counterparts(3). Thus, this vulnerable population needs close monitoring to quantify the short and long-term effects of in-utero HIV and ARV exposure, so effective interventions can be implemented where health or developmental disparities are identified. Failure to appropriately invest in HIV-exposed uninfected children now has significant longer term public health and human capital implications, particularly in high HIV burden settings(4). In this paper we analyze the exposures experienced by the HIV-exposed uninfected child population, suggest how research can inform current knowledge gaps, and highlight the importance of routinely monitoring this population through routine care for early identification and intervention to prevent adverse outcomes.

How do we define exposures in the HIV-exposed uninfected child population?

In research and operational (routine)settings, factors (i.e. exposures) that potentially influence or cause ill-health in HIV-exposed uninfected children need to be clearly defined to elucidate the etiologies of outcomes in these children. Furthermore, it has become increasingly important to clearly define the population of HIV-exposed uninfected children as variations in definitions limit direct comparability between studies and subsequently, evidence synthesis. The term *"HIV-exposed uninfected"* 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. Although defined by one term, there is much heterogeneity in this population,

both across time (due to changes in the HIV epidemic and antiretroviral drug regimens over the last two decades and within a fixed time period. During the early stages of the HIV epidemic, some infants were born to women living with HIV who did not receive antiretroviral drugs during pregnancy. These children do not have risks associated with in-utero antiretroviral drug exposure; however, they were likely exposed to high levels of maternal HIV viremia and systemic inflammation that could result in immune dysfunction (5, 6). This has direct implications for an HIV-exposed uninfected child's potential to survive and thrive as maternal viremia is also associated with lower motor and expressive language scores (7) and poorer growth outcomes(8). One of the largest cohort studies of HIV-exposed uninfected children (n=3125) was initiated in Zimbabwe in 1997 before any antiretroviral drugs were available.(5). Data from this study highlight the effect of HIV exposure alone on adverse birth outcomes such as preterm delivery, postnatal growth failure and mortality, thereby emphasizing the importance of primary HIV prevention.

Apart from HIV exposure, large scale-up of more effective programmes to prevent infant HIV acquisition has created further heterogeneity within the HIV-exposed uninfected population: some children were exposed to HIV and antiretroviral drugs at the time of conception; others later in gestation and yet others postnatally. Thus, depending on when their mothers living with HIV were diagnosed, an HIV-exposed uninfected child's antiretroviral exposure may vary by the timing of initiation, duration, dose and type of antiretroviral drugs. Recent data from a cohort study by Le Roux et. al. reports poorer growth among breastfed children exposed to HIV and antiretrovirals in-utero compared to HIV-unexposed uninfected children(9), thus highlighting the importance of further research on these children. Most recently antiretroviral drugs are now available as pre-exposure prophylaxis for HIV negative women at high risk of HIV acquisition. Some women on pre-exposure prophylaxis may conceive on and continue antiretroviral drugs during pregnancy and lactation(10). Their children will be HIV-unexposed but ARV-exposed in-utero, post-delivery or both. Monitoring systems are equally needed for this new population of HIV-unexposed but ARV-exposed children, a population that is currently limited in size but will likely grow.

In addition to in utero exposures, it is equally important to quantify household, community, societal and environmental factors, such as food insecurity or poor water and sanitation, factors that inevitably contribute to adverse child health and developmental outcomes. Therefore, beyond the direct physiological exposure to maternal HIV and antiretroviral drugs through pregnancy and breastfeeding, a broader definition of HIV affected children should be considered, as shown in Table 1. This would

encompass children living in households/environments that currently include or have included a person living with HIV. We refer to this population as environmentally HIV exposed children.

What research is needed to elucidate causal mechanisms and possible interventions to ensure HIV-exposed uninfected children survive and thrive?

There is a paucity of long-term follow-up data on HIV-exposed uninfected children, particularly in low- and middle-income countries, that have the highest burden of HIV, and especially more recently following increasing antiretroviral coverage that is often initiated pre-conception. Particularly as newer antiretroviral regimens are recommended for use during pregnancy and breastfeeding, contemporaneous cohort studies and surveillance systems of HIV-exposed uninfected children are urgently needed. Furthermore, while modelled estimates like the recently published UNAIDS estimates(1) are beneficial for describing and monitoring HIV-exposed uninfected child population trends, more nuanced data from in-depth studies are required to understand risk factors and causal mechanisms associated with HIV-exposed uninfected child health and developmental disparities. These studies require rigorous study designs, such as long-term prospective cohorts, with appropriately powered sample sizes that allow for complex analyses and should be conducted in settings where population prevalence of HIV-exposed uninfected children is highest.

Why do we need to strengthen the follow-up of HIV-exposed uninfected children in routine healthcare systems?

In many low- and middle-income country settings, the follow-up of HIV-exposed uninfected children in the routine vertical HIV transmission prevention programmes aligns with scheduled immunization visits and HIV testing time points and has historically concluded at 18 months postpartum. More recently, among HIV-exposed children who continue to breastfeed while their mothers receive antiretroviral treatment, the recommended follow-up period has been extended to 24 months to ensure exclusion of HIV-infection once all HIV-exposure has ended(11). Concurrently, with research efforts to understand causal mechanisms and relationships affecting the health, growth and development of HIV-exposed uninfected children, front-line healthcare providers in routine health services should be aware of HIV-exposed uninfected child vulnerabilities to ensure early and timely identification and management of adverse outcomes.

Furthermore, the HIV-exposed uninfected child population is aging into adolescence and adulthood, requiring skills that result in independent functioning and contribution to society. A life-course approach to identifying and caring for the most vulnerable HIV-exposed uninfected children through childhood, adolescence and adulthood is thus urgently needed. 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 have an increased risk for poor mental health (12). Thus, all environmentally HIV exposed children, irrespective of their direct HIV or antiretroviral -exposure status, should be monitored as they may be exposed to interacting syndemics that increase risk for poor health(13). Ultimately, research and health systems data may demonstrate that children with in-utero exposure to HIV and/or early or long-term antiretroviral drug exposure may require specialized care and support and these services may also be needed for a portion of environmentally HIV exposed children. Outside of the routine immunization follow-up schedule, most often completed at age five years, children generally only experience health visit encounters for curative care when they are sick. They may re-enter the healthcare system 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 HIV exposed uninfected children, where simply understanding that they did not acquire HIV in infancy is no longer a sufficient end point of success.

Appropriately sized and structured routine child health data platforms, with systems to routinely analyze such data, will greatly facilitate evidence-informed health policies and programmes so that resources and interventions can be suitably allocated and designed. A practical application of this could be a "trigger-based" approach where, for instance, HIV-exposed uninfected children with specific events trigger two key activities: first, an alert to the clinician for referral of the child for additional clinical assessments and care and second, reporting of the event into a denominated database(14). One such example is in the Western Cape Province of South Africa where individual health records are linked through use of a unique identifier from birth into adulthood(15), importantly with concomitant linking of the mother-child dyad(16), 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 disease risk factors needed to develop future public health interventions(17). The scale-up of this system to other parts of the country will require investments in infrastructural and human capacity development,

data quality improvement mechanisms, and standardization and interoperability to ensure data transferability between new and existing software(16).

Multisectoral and ethical considerations for HIV affected children

Over 90% of HIV-exposed uninfected children live in countries with overburdened healthcare systems with competing priorities, and a quadruple burden of disease including communicable, non-communicable, perinatal and maternal, and injury-related disorders (18).The increasing evidence that a portion of HIV and antiretroviral exposed uninfected children have poorer neurodevelopmental outcomes than HIV unexposed children (19), substantiates the urgent need for a multisectoral approach. For example, tracking of educational outcomes at population level by a child's HIV exposure status is needed. However, careful thought and planning are necessary to ensure that applicable exposures or interventions are adequately captured to account for differences in academic performance. Such a strategy may necessitate HIV exposure status disclosure to the child or adolescent and to key personnel including health care providers and educators charged with monitoring outcomes and/or providing interventions to ensure the child thrives. Notwithstanding the health benefits of documenting the in-utero HIV and antiretroviral exposure status of children for healthcare and educational purposes, key questions are: Do the benefits of disclosure, beyond the breastfeeding period, outweigh or balance potential harms such as stigma or trauma? Does this impinge on the mother's or child's right to privacy? Some would argue that the benefits of disclosing the mother's HIV status to healthcare providers during breastfeeding are justified because interventions that prevent breastmilk transmission can be implemented and modified during this period, but that disclosure should stop with breastfeeding cessation as the child is no longer at risk of vertical HIV acquisition(20). Others argue that the HIV and/or antiretroviral exposed child population, as well as environmentally HIV exposed children, are at risk throughout their lifetime, regardless; thus, based on article 24 of the International Convention on the Rights of the Child(21), specific health care providers need access to their HIV and / or ARV exposure status throughout their lives.

The Way Forward

Research is needed to understand the mechanisms leading to short and long-term health and developmental disparities in HIV-exposed uninfected children. In high burden HIV settings, the long-term close follow-up of HIV affected children to track vulnerabilities and monitor morbidity, quality of life and mortality will require novel and collaborative approaches, such as harmonized data collection with data

pooling for analyses between countries, recognizing that these settings already have an overburdened health sector. Furthermore, strategies such as the promotion of timely capturing of complete and accurate facility-level data and the training of data stewards will need to be adopted to strengthen the quality of routine data for effective monitoring. As health care providers and educators, our responsibility is to ensure that these children not only survive, but also thrive, achieving optimal productivity in adolescence and adulthood.

Exposures	Sub-groups of HIV affected children		
	HIV exposed uninfected child	**HIV unexposed, ARV exposed child**	**Environmentally HIV exposed children**
Exposure to maternal HIV: varies by timing of maternal infection, drug type, maternal viral load and disease stage	Yes	No	No
Exposure to maternal ARVs: varies by timing of initiation; drug type dosages and duration	Yes	Yes	No
Exposure to infant ARVs: varies by timing of initiation; drug type dosages and duration	Yes	No	No
Exposure to a household with people living with HIV	Yes	Maybe	Yes
Ubiquitous environmental exposure: poverty, poor sanitation and water, food security etc.	Yes	Yes	Yes

Table 1: Sub-groups of HIV-affected children

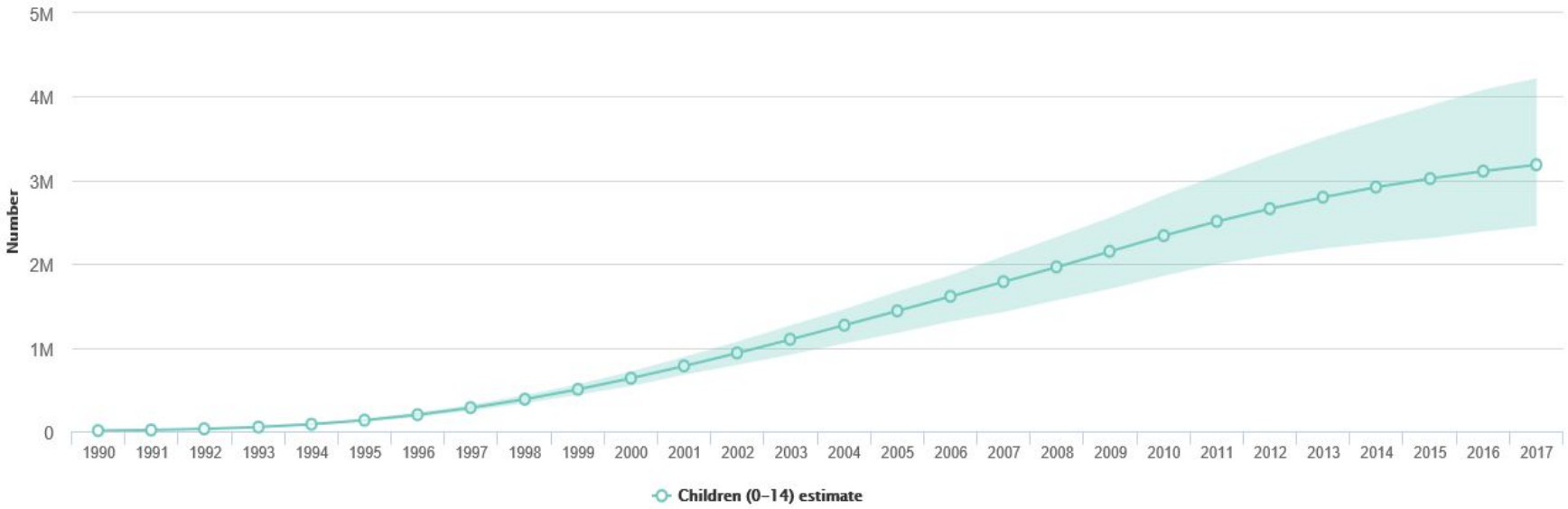

Figure 1: 2018 UNAIDS estimates of the number of HIV-exposed uninfected children in South Africa(1)

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