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A Challenging Knowledge Gap: Estimating Modes of HIV Acquisition Among Adolescents Entering HIV Care During Adolescence

John Humphrey, MD[1], Miranda Triedman, BS[2], Winstone Nyandiko, MBChB, MMed[3,4], Edwin Sang, MS[4], Emmanuel Kemboi, BS[4], Marsha Alera, MS[4], Vlad Novitsky, MD, PhD[2], Akarsh Manne, MS[2], Eslyne Jepkemboi, BS[4], Millicent Orido, BS[4], Edith Apondi, MBChB, MMed[4,5], Rachel Vreeman, MD[6], Kara Wools-Kaloustian, MD[1], and Rami Kantor, MD[2]

Abstract

Characterizing HIV acquisition modes among adolescents with HIV (AHIV) enrolling in care during adolescence is a challenging gap that impacts differential interventions. We explored whether primary data collection with targeted questionnaires may address this gap and improve understanding of risk factors and perceptions about adolescents' HIV acquisition, in Kenyan AHIV entering care at ≥10 years, and their mothers with HIV (MHIV). Clinical data were derived through chart review. Among 1073 AHIV in care, only 26 (2%) met eligibility criteria of being ≥10 years at care enrollment, disclosed to, and with living MHIV. Among 18/26 AHIV-MHIV dyads enrolled (median age of AHIV 14 years), none had documented HIV acquisition modes. Data suggested perinatal infection in 17/18 AHIV, with 1 reported non-perinatal acquisition risk factor, and some discordance between adolescent-mother perceptions of HIV acquisition. In this difficult-to-enroll, vulnerable population of AHIV-MHIV dyads, primary data collection can enhance understanding of AHIV acquisition modes.

Keywords

adolescent, HIV, mother-to-child transmission, HIV transmission mode, late care entry

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Background

The HIV epidemic among adolescents living with HIV (AHIV; 10-19 years of age) in sub-Saharan Africa is uniquely driven by perinatal and non-perinatal modes of HIV acquisition.[1] Epidemiologic studies suggest that most AHIV acquired HIV through perinatal transmission (mother-to-child transmission during pregnancy, delivery, or breastfeeding) and survived due to antiretroviral treatment (ART) access.[2-4] A third of infants with HIV may also have slow-progressing infection and survive a median of 16 years without ART.[5] Non-perinatal HIV acquisition (behavioral modes of transmission including sexual intercourse) is thought to account for an increasing proportion of infections among adolescents as they age.[3,6] However, there is no gold standard to distinguish perinatal and non-perinatal HIV acquisition among AHIV newly presenting to HIV services during adolescence.[2,7,8]

In some studies, perinatal HIV acquisition is assumed to have occurred for adolescents diagnosed with HIV when they were less than 10 or 15 years of age or if they

[1]Indiana University, Indianapolis, IN, USA
[2]Brown University, Providence, RI, USA
[3]Moi University College of Health Sciences, Eldoret, Kenya
[4]Academic Model Providing Access to Healthcare, Eldoret, Kenya
[5]Moi Teaching and Referral Hospital, Eldoret, Kenya
[6]Icahn School of Medicine at Mount Sinai, New York, NY, USA

Corresponding Author:
Dr. John Humphrey, Indiana University School of Medicine, 1120 W Michigan Street, Gatch Hall 578, 545 Barnhill Drive, EH 421, Indianapolis, IN 46202, USA.
Email: humphrjm@iu.edu

had mothers living with HIV (MHIV).[1,5,9-12] These assumptions may not be true for all adolescents enrolling in HIV care during adolescence, even if they have MHIV. Some AHIV could be long-term survivors following perinatal transmission or more recently infected through non-perinatal transmission.[5,13] Consider a hypothetical case of a 14-year-old girl in Kenya who enrolls in care following a new HIV diagnosis. She is sexually active and has a history of upper respiratory tract infections and suboptimal growth. Her mother's HIV status may be positive or unknown. How should the clinician council this adolescent as she grapples with how she contracted HIV?

Although the mode of HIV acquisition should not influence the decision to initiate ART, this case raises important considerations in understanding the mode of HIV acquisition among AHIV enrolling in care during adolescence. Clinically, knowledge that an adolescent acquired HIV perinatally implies that he or she has long-standing HIV infection. This knowledge can help guide clinicians in the evaluation of chronic HIV disease sequelae such as growth failure, pubertal delay, neurocognitive disease, lung and heart disease, or malignancy.[4,14-17] Growth delay and respiratory infections may suggest underlying HIV disease but are also prevalent in children without HIV in low- and middle-income countries. Conversely, knowledge that an adolescent acquired HIV non-perinatally can help clinicians provide tailored counseling and prevention services.[18,19] These AHIV may have higher rates of sexual activity and other peer-influenced behaviors that increase the risk of transmission to their partners or offspring.[20-23] At the program level, characterizing AHIV with non-perinatally acquired HIV may help tailor interventions to those at highest risk of HIV acquisition or onward transmission. At the epidemiology level, classifying the mode of HIV acquisition among AHIV presenting to care during adolescence is necessary to accurately model the adolescent HIV epidemic over time.[24]

HIV is the leading cause of death among adolescents 10 to 19 years in Eastern and Southern Africa.[25,26] By 2030, the HIV epidemic among adolescents in these regions is projected to increase by more than 20%.[1,27] Clinicians' limited ability to identify perinatal and non-perinatal HIV acquisition in AHIV who enter care during adolescence is an important knowledge gap that impacts care. Filling this gap can inform epidemic drivers and characteristics of AHIV needed to implement interventions at the individual and program levels. Epidemiologic studies have modeled likely modes of HIV acquisition in this population.[24,28] However, it is unclear whether primary data collection, that is, those directly collected from AHIV and their MHIV concerning their risk factors and perspectives about adolescent HIV acquisition, can help fill this gap. The objective of this study is to use primary data collection among AHIV who enrolled in care during adolescence and whose modes of HIV acquisition are unknown, and their MHIV, to better understand the extent of this gap and whether primary data collection can be used to fill it.

Methods

Study Design and Setting

This cross-sectional study was conducted at Moi Teaching and Referral Hospital (MTRH), the largest public healthcare facility in western Kenya and headquarters of the Academic Model Providing Access to Healthcare (AMPATH).[29,30] MTRH HIV clinics care for children and adults based on the Kenyan national guidelines and have a dedicated AHIV clinic, where participants were enrolled.[31] Patients are managed with an electronic medical record system including linkages between MHIV and their children.[32] This study was approved by the MTRH/Moi University College of Health Sciences Institutional Research and Ethics Committee and Indiana University IRB. Participants $\geq$18 years provided written informed consent. AHIV $<$18 years provided written assent with parental consent.

Participant Recruitment

Medical records were used to identify eligible AHIV and their MHIV enrolled at MTRH. First, we identified all AHIV 10 to 19 years active in care, defined as attending an appointment within 3 months of study start (February 1, 2019), or if censored, within 3 months of a scheduled appointment. Next, we excluded AHIV $<$10 years of age at enrollment in HIV care. This cutoff was selected because UNAIDS defines adolescence as 10 to 19 years and because HIV infection among children $<$10 years is equally distributed between boys and girls and largely restricted to those with MHIV, making perinatal transmission most likely.[16,33] We excluded adolescents with deceased mothers, those whose mothers did not have HIV (precluding perinatal transmission), those with unknown maternal HIV and vital statuses, and those who transferred to AMPATH after receiving care at non-AMPATH sites at $<$10 years of age. Finally, we did not recruit dyads in which the adolescent's HIV status was not disclosed to both adolescent and mother, to avoid risk of disclosure through participation. We aimed to sample the first 20 eligible AHIV-MHIV dyads.

Data Collection

Chart reviews derived documented modes of HIV acquisition, dates of enrollment in care and ART initiation, World Health Organization (WHO) stage and CD4 at ART initiation, and prior ART regimens and HIV viral loads. Date of enrollment into HIV care was considered the HIV diagnosis date unless the latter was known precisely, as diagnosis dates are not routinely available. Adolescent height-for-age *z*-scores at study enrollment were calculated using WHO growth reference charts.[34]

Questionnaires were administered privately to each participant between February 2019 and January 2020. AHIV were asked about how they believed they acquired HIV and exposures associated with HIV acquisition prior to diagnosis, including sexual intercourse, any sexual contact with an individual living with HIV, circumcision, sexually transmitted infections, blood transfusions or surgery, injection drug use, and use of other substances including alcohol, tobacco, marijuana, heroin, and inhalants. MHIV were asked about their breastfeeding practices and utilization of prevention of mother-to-child transmission (PMTCT) services, presence of other children living with HIV, and perceptions about how their adolescents acquired HIV.

Laboratory Methods

Whole blood samples were collected from all participants. Viral load testing was performed at the AMPATH research laboratory using the M2000 Realtime System from Abbott laboratories (Abbott park, Illinois, Chicago USA). Frozen plasma samples were batched and shipped at −80°C to the Kantor Laboratory at the Providence-Boston Center for AIDS Research. Three samples from AHIV with 3 viremia levels (ie, <1000, 1000-10 000, and >10 000 copies/mL) were selected for genotyping.

Analysis

The chart and questionnaire data were summarized using frequencies and medians with interquartile ranges (IQR). Viral suppression at study enrollment was defined using a threshold of <1000 copies/mL based on Kenya and WHO HIV treatment guidelines.[35] Drug resistance interpretation and predicted susceptibilities were evaluated using Stanford Database tools.[36] These data were graphed in the context of each subjects' ART regimens, viral loads, and CD4 counts since the date they enrolled in care.

Results

Among 1073 AHIV 10 to 19 years of age and active in HIV care at MTRH, 883 (82%) were excluded because they were <10 years when they enrolled in care (Figure 1, flow diagram of enrollment). Among the remaining 190 (18%) AHIV, 164 were ineligible because the mother was documented to be deceased for 113 (60%); 6 (3%) AHIV had mothers without HIV; 35 (18%) AHIV had unknown maternal HIV and vital statuses; 7 (4%) AHIV had transferred into MTRH from a non-AMPATH site at <10 years of age; and, 3 AHIV did not have their HIV status disclosed to them. Eighteen of the remaining 26 dyads were recruited during the study period, along with their 17 biological MHIV (1 mother was linked to 2 AHIV).

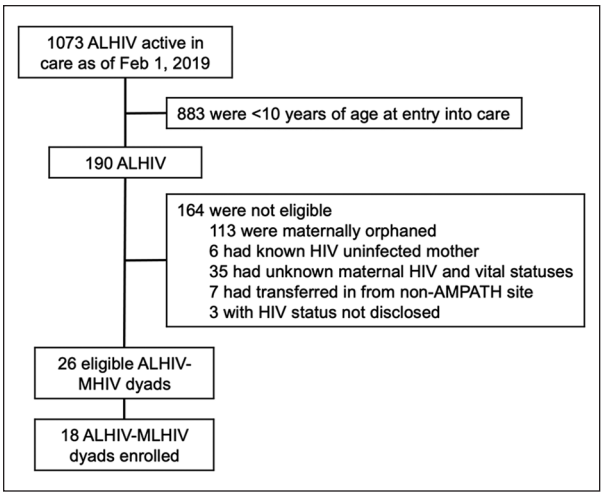

Figure 1. Flow diagram of enrollment.

Chart-Derived Characteristics of Enrolled AHIV

Among the 18 AHIV enrolled in the study, 56% were female and the median age at entry in HIV care at AMPATH was 12 years (IQR 11-12, oldest was 15; Table 1). Nine of the 18 enrolled AHIV were <12 years at entry into care, and of these, 3 had WHO stage 3 to 4 disease. None of the AHIV ≥12 years at entry in care had WHO stage 3 to 4 disease. At ART initiation, which occurred at a median of 2 weeks (IQR 0-33) after care enrollment, the median CD4 count was 566 cells/mm^3 and 55% had a CD4 >500 cells/mm^3. At study enrollment, 50% of AHIV were 15 to 19 years, the median height-for-age *z*-score was −2.0 (IQR −3.0 to 1.8), and 67% of AHIV had a *z*-score of ≤−2. Most AHIV (78%) were taking efavirenz-containing ART. However, 89% had switched to dolutegravir-containing ART by the end of the study. None of the enrolled AHIV had a documented mode of HIV acquisition in their medical records.

Table 1. Characteristics of Enrolled AHIV and MHIV Derived Through Chart Review and Viral Load Testing.

Characteristic[a]	AHIV n (%) n = 18	MHIV n (%) n = 17
Age, median years (IQR)		
At enrollment in HIV care	12 (11, 12)	34 (29, 38)
At ART start	12 (11, 12)	35 (29, 40)
At study enrollment	14 (14, 16)	42 (36, 47)
Female	10 (56%)	17 (100%)
Height-for-age *Z*-score, median (IQR)	−2.0 (−3.0, −1.8)	N/a
Ever treated for active tuberculosis	2 (11%)	3 (18%)
WHO stage at ART initiation		
Stage 1-2	10 (55%)	8 (47%)
Stage 3-4	3 (17%)	7 (41%)
Missing	5 (28%)	2 (12%)
CD4 at ART initiation, median (IQR)[b]	566 (133, 762)	152 (113, 282)
Time (years) on ART, median (IQR)	4.0 (3.5, 5.1)	9.3 (5.6, 11.9)
First line ART	2.4 (1.8, 3.7)	3.1 (2.4, 4.6)
Seocnd line ART	1.0 (0.5, 1.5)	2.4 (0.5, 7.5)
ART base class at study enrollment		
EFV or NVP	14 (78%)	9 (53%)
ATV/r or LPV/r	3 (17%)	2 (12%)
DTG	1 (6%)	6 (35%)
Most recent ART base class prior to end of study period		
EFV or NVP	1 (6%)	1 (6%)
ATV/r or LPV/r	1 (6%)	4 (24%)
DTG	16 (89%)	11 (65%)
Viral load <1000 copies/mL	12 (67%)	15 (88%)

Abbreviations: AHIV, adolescents with HIV; ATV/r, atazanavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; IQR, interquartile range; LPV/r, lopinavir/ritonavir; MHIV, mothers with HIV; NVP, nevirapine.
[a]Some categories exceed 100% due to rounding.
[b]CD4 count available for 11 adolescents and 11 mothers.

Chart-Derived Characteristics of Enrolled MHIV

Among the 17 MHIV enrolled in the study, the median age at entry in HIV care was 34 years (IQR 29-38; Table 1). All MHIV enrolled in care after delivery of their child (ie, the adolescent participating in the study), 5 MHIV enrolled in care within 30 days of the date of the child's enrollment in care, and the remainder enrolled in care an average of 6 years (range 0.6-12 years) prior to the child's enrollment in care. There was no documentation that PMTCT services had been delivered for the mother or child, possibly because the mothers' HIV status was not yet known. At the mothers' ART initiation, which occurred a median of 8 weeks (IQR 2-42) after the mothers' care enrollment, the median CD4 was 152 cells/mm^3. At study enrollment, most MHIV (53%) were taking efavirenz-containing ART.

Questionnaire-Derived Data on Adolescent HIV Acquisition

MHIV reported that all AHIV were delivered vaginally, breastfed a median of 15 (IQR 12-24) months during infancy, and no MHIV were diagnosed with HIV before delivery (Table 2). Furthermore, no MHIV reported that they or their children had received PMTCT services, consistent with the lack of chart documented PMTCT service delivery. When MHIV were asked how they believed their adolescent acquired HIV, 13 stated perinatal transmission, 2 did not know, 1 stated that the adolescent was bitten by the adolescent's sibling who was living with HIV, and 1 stated that transmission occurred through forced sex. When AHIV were asked how they believed they acquired HIV, 10 stated mother-to-child transmission, 7 did not know, and 1 stated that she acquired HIV through forced sex at 10 years of age with an adult who was not her parent (which the mother also reported). Apart from this individual, no AHIV reported risk factors for non-perinatal HIV acquisition, either before or after their HIV diagnosis. There was discordance between some dyads' perceptions about the adolescent's HIV acquisition mode. Among 4 AHIV who did not know how they acquired HIV, 3 MHIV stated transmission occurred from mother-to-child and 1 stated it occurred from the adolescent's sibling. Conversely, 1 adolescent stated she acquired HIV through mother-to-child transmission,

Table 2. Results of Questionnaires Assessing the Modes of Adolescent HIV Acquisition.

Characteristic	AHIV n (%) n = 18
Ever breastfed	18 (100%)
Duration of breastfeeding, median months (IQR)	
Exclusive breastfeeding	6 (3-6)
Total breastfeeding	15 (12-24)
Timing of maternal enrollment in HIV care[a]	
Before or during delivery	0 (0%)
After delivery	17 (100%)
Mother received PMTCT services	0 (0%)
Mother has another child with HIV	2 (11%)
Adolescent risk factors for non-perinatal HIV acquisition[b]	0 (0%)
Perceived mode of adolescent HIV acquisition	
Perceptions of AHIV	
Perinatal	10 (56%)
Non-perinatal	1 (6%)
Unknown	7 (39%)
Perceptions of MHIV	
Perinatal	13 (76%)
Non-perinatal	2 (12%)
Unknown	2 (12%)

Abbreviations: AHIV, adolescents with HIV; IQR, interquartile range; MHIV, mother with HIV; PMTCT, prevention of mother-to-child transmission of HIV.
[a]Percentage among mothers (n = 17).
[b]Includes sexual intercourse, male circumcision, surgery, blood transfusion, injection drug use, history of sexually transmitted infection.

while her mother stated she did not know how the adolescent acquired HIV.

Viral Suppression and Drug Resistance

Viral suppression at study enrollment was 67% among enrolled AHIV and 88% among enrolled MHIV (Table 1). Two- or three-class drug resistance was detected in each of the 3 adolescents' samples analyzed (Figure 2). These AHIV were 11 to 12 years of age at HIV care enrollment and ART initiation and 13 to 16 years at study enrollment. Two adolescents were viremic with resistance despite experiencing no prior ART regimen changes (#1 and #3 in Figure 2), 1 of which (#1) had low level viremia, not considered as failing per WHO guidelines; while 1 adolescent (#2 in Figure 2), a 16-year-old boy, experienced 5 unique ART regimens over a 3-year period.

Discussion

In this study, we tackle an important and challenging knowledge gap concerning the uncertain modes of HIV acquisition among AHIV who enrolled in care during adolescence and its potential impact. Using primary data collection through targeted questionnaires administered to AHIV and their MHIV to supplement their medical records, we derive several key findings. First, even in a large program with a robust electronic medical record, this unique population is difficult to enroll and has limited related documentation, requiring substantial analytical assumptions about adolescent HIV acquisition modes.[32,37,38] Second, primary data collection is essential; it can inform modes of HIV acquisition in this population and reduce misclassification of AHIV enrolling in care during adolescence. Third, the discordance in perceived mode of HIV acquisition among some AHIV versus their MHIV, and low rate of AHIV viral suppression and extensive drug resistance highlight the particular vulnerability of AHIV who enter into HIV care late, and the need for further research to understand their HIV acquisition modes and care needs.[39]

A core challenge in the use of routine program data to determine the mode of HIV acquisition among AHIV is the frequent lack of documented modes of infection and maternal HIV status. In a global analysis involving data from >10 000 AHIV ages 10 to 14 years at enrollment in care, transmission mode was documented in only 20% of cases.[24] This may be due to limitations in data collection platforms as well as clinician uncertainty regarding the mode of adolescent HIV acquisition. Either way, investigators must make significant assumptions about the likelihood of perinatal and non-perinatal transmission in this population. This problem is compounded by the large proportion of AHIV who are maternally orphaned and whose maternal HIV status cannot be determined. In our study, ~60% of AHIV who enrolled in HIV care at ≥10 years were maternally orphaned with no documentation of maternal HIV status. It is analytically assumed that most these deceased mothers had been living with HIV given that HIV is a leading cause of death among women and orphanhood is more common among AHIV compared to uninfected adolescents.[13,40-42] Still, this is a significant assumption that covers a large proportion of AHIV enrolled during adolescence, and it requires further attention.

Several studies have estimated the prevalence of perinatal and non-perinatal transmission among AHIV using routine program data, but these studies did not include primary data collection from AHIV.[24,28] Even in a very small sample, we found that chart review and simple questionnaires administered to AHIV and their MHIV can yield additional important information to understand their characteristics and HIV acquisition patterns. Our data suggest that most enrolled AHIV with living MHIV acquired HIV perinatally, supported by (i)

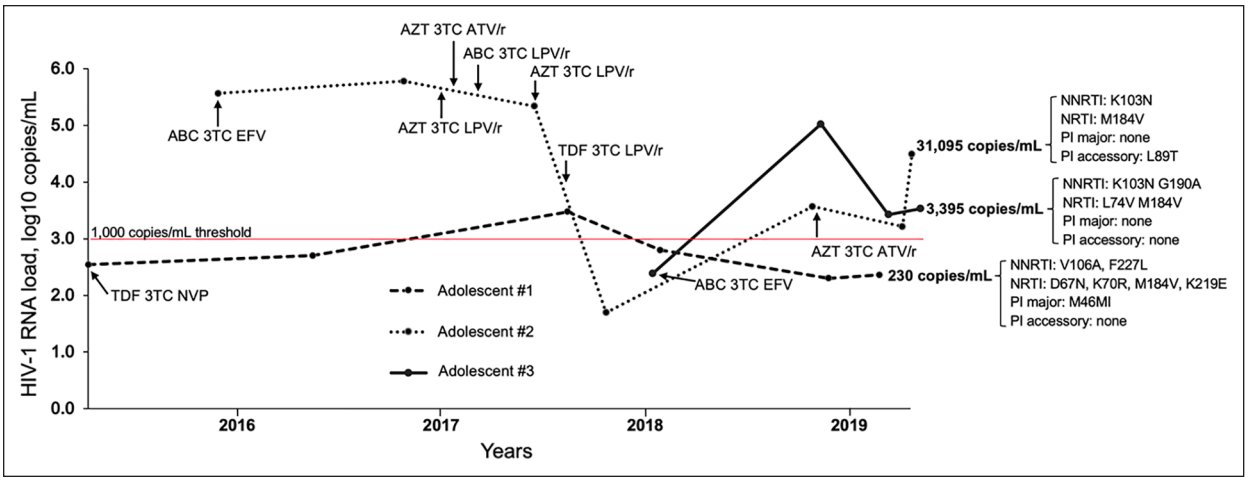

Figure 2. Timeline of clinical progression and detection of drug resistance for 3 adolescents.

94% of AHIV reported no risk factors for non-perinatal transmission; (ii) AHIV were younger at care entry, which makes sexual transmission less likely[24]; (iii) two-thirds of AHIV had a low height-for-age *z*-score that likely represents sequelae of perinatally-acquired HIV[16,34,43]; and (iv) all MHIV breastfeed their children and none received PMTCT services. Notably, 1 adolescent and her mother reported that the adolescent had acquired HIV through forced sex, and there was no documentation of her HIV status prior to this event. Reconsidering the hypothetical case presented above, without this information a clinician might have assumed the adolescent acquired HIV perinatally and overlook additional opportunities for treatment of the adolescent and family counseling, underscoring this important knowledge gap and the need to address it.

While prior studies have used a retrospective analysis approach to address the knowledge gap on adolescent HIV acquisition, primary data collection from AHIV and their MHIV illuminates important clinical aspects of this population and their care needs. First, 39% of AHIV said they did not know how they had acquired HIV and there was discordance between the adolescent's and mother's perceived HIV transmission mode in 27% of dyads. These data highlight the personal impact that uncertainty about HIV acquisition modes can have on these AHIV and their families, and their need for support. In addition, viral suppression among AHIV in our study was 67%, which is lower than the estimated 80% viral suppression rate among all AHIV in Kenya.[44] Multi-class resistance was identified in all AHIV for whom drug resistance was assessed, as has been previously reported by us and others.[45,46] Most mutations were linked to past antiretroviral exposures suggesting acquired resistance and 2 AHIV remained viremic after transitioning to dolutegravir-based ART. This further highlights the vulnerability of these AHIV and their need for support.

We recognize several limitations of our study. First, the sample size is small, which illustrates the difficulty of studying this population and the focused attention needed to do so. Second, the sample was not probability-based and excluded dyads in which disclosure had not occurred. Third, primary data collected through self-report, such as characteristics associated with non-perinatal transmission, may be subject to recall or social desirability biases.

Conclusions

AHIV enrolled in care during adolescence accounted for a considerable 18% of all AHIV in care at a large health facility in Kenya. Characterizing HIV acquisition modes in this population is an important and challenging knowledge gap with epidemiologic and clinical implications. Prediction tools are limited, and primary data collection among AHIV and MHIV can be used to better understand the likelihood of perinatal versus non-perinatal HIV acquisition, and recognize the care needs of this unique population. Knowledge of HIV acquisition modes can also inform effective prevention and treatment interventions, which might differ by acquisition mode; for example, enhancing PMTCT services to prevent perinatal HIV acquisition, and providing behavioral interventions in non-perinatal HIV acquisition. Awareness of this existing gap and efforts to mitigate it are essential to optimize care for these vulnerable AHIV.

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Author Contributions

J.H, W.N., and R.K. conceptualized and designed the study and had primary responsibility for interpretation of the data. J.H., M.T., E.S., V.N., A.M., E.J., and M.O. analyzed the data. J.H., M.T., W.N., E.A. J.H., M.T., W.N., K.W., and R.K. interpreted the data. J.H. wrote the first draft of the paper with assistance from R.K. All authors have read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval and Consent to Participate

This study was approved by the Moi University/Moi Teaching and Referral hospital Institutional Research and Ethics Committee in Kenya and the Indiana University Institutional Review Board in the United States. All experiments were performed in accordance with relevant guidelines and regulations. All participants provided written informed consent and the data were coded for analysis using unique study identification numbers assigned to each participant following enrollment, thus ensuring that the data could not be linked back to the participant except through the use of a linkage log.

Availability of Data and Materials

The dataset supporting the conclusions of this article is included within the article.

ORCID iDs

John Humphrey https://orcid.org/0000-0003-3156-1065
Rami Kantor https://orcid.org/0000-0003-3659-1108

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