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In utero/peripartum antiretroviral therapy exposure and mental health outcomes at 8–18 years old: A longitudinal comparative study of children with perinatally acquired HIV, children perinatally HIV exposed but uninfected, and children unexposed uninfected from Uganda

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Abstract

In utero/peripartum antiretroviral therapy (IPA) exposure type was examined in relationship to mental health symptoms among 577 children with perinatally acquired HIV (CPHIV), children perinatally HIV exposed but uninfected (CHEU), and children HIV unexposed uninfected (CHUU). IPA exposure was categorized for CPHIV and CHEU as none, single-dose nevirapine with or without zidovudine (sdNVP±AZT), sdNVP+AZT+lamivudine (3TC), or combination antiretroviral therapy (cART). Anxiety and depressive symptoms were reported at baseline, 6-, and 12-month follow-up per behavioral assessment system for children. Multivariable linear mixed models were used to estimate differences (b) with 95% confidence intervals (95% CI) for IPA exposure types versus CHEU without IPA exposure. Depressive and anxiety symptoms were lower in CHUU relative to CHEU and CPHIV but did not differ between CPHIV and CHEU. CHEU with sdNVP±AZT exposure had greater anxiety ($b = 0.51$, 95% CI: [0.06, 0.96]) and depressive symptoms ($b = 0.48$, 95% CI: [0.07, 0.89]) than CHEU without IPA exposure. CHEU with sdNVP+AZT+3TC exposure had higher anxiety ($b = 0.0.45$, 95% CI: [0.03, 0.86]) and depressive symptoms ($b = 0.72$, 95% CI: [0.27, 1.17]) versus CHEU without IPA exposure. Depressive and anxiety symptoms were not different for CHEU and CPHIV exposed to cART ($b = 0.12–0.60$, 95% CI: [−0.41, 1.30]) and CHEU and CHUU ($b = -0.04$ to 0.08, 95% CI: [−0.24, 0.29]) without IPA exposure. Among CHEU, peripartum sdNVP±AZT and sdNVP+AZT+3TC but not cART compared to no IPA exposure was associated with clinically important elevations in anxiety and depressive symptoms. Monitoring of mental health trajectory of HIV-affected children considering IPA is needed to inform mental health interventions. Patient Contribution: Caregivers and

their dependents provided consent for participation and collaborated with study team to identify mutually convenient times for protocol implementation.

KEYWORDS
antiretroviral therapy exposure, anxiety, children, depression, perinatal HIV status

1 | INTRODUCTION

The millions of HIV-affected children who either have perinatally acquired HIV (CPHIV) or are HIV-exposed but uninfected (CHEU) constitute a subgroup of highly vulnerable youth whose mental health outcomes require understanding to inform interventions. The relationship between HIV and mental health is often described as bidirectional; effects of living with HIV can increase risk of poor mental health outcomes, while poor mental health outcomes can affect neural pathways and predispose individuals to behaviors that increase risk of acquiring HIV (Betancourt et al., 2013; Mellins et al., 2011). Despite this complex interconnection, there is evidence that CPHIV experience poor mental health outcomes at higher rates than children who are perinatally HIV-exposed but uninfected (CHEU, i.e., mother-to-child transmission did not occur) or children who are HIV unexposed and uninfected (CHUU) (Buckley et al., 2020; Hoare et al., 2019; Mellins & Malee, 2013). Mental health morbidity is also magnified in CPHIV and CHEU as they may experience HIV-related stigma (Cluver et al., 2008) and higher rates of premature parental loss (Penner et al., 2020). Additionally, mental health symptoms adversely impact adherence to HIV treatment (Kacanek et al., 2015).

HIV may exacerbate psychiatric illness by infecting the central nervous system (Donenberg & Pao, 2005). HIV may also contribute to psychiatric illness through HIV-associated encephalopathy, which can occur even among immunocompetent CPHIV (Cooper et al., 1998; Tardieu et al., 2000). The increased use of in utero-peripartum antiretroviral therapy (IPA) has decreased the rate of vertical transmission of HIV from mothers with HIV and resulted in an expanding population of concomitantly HIV and ART-exposed infants (UNAIDS, n.d). Despite this decreased transmission, peripartum ART is associated with low birthweight (Goldstein et al., 2000; Schulte et al., 2007; Traore et al., 2013), metabolic dysregulations (Williams et al., 2016), mitochondrial toxicity (Fernandez Ibieta et al., 2010; Garcia-Otero et al., 2019; Hernandez et al., 2017; Jao et al., 2017; Noguera-Julian et al., 2015; Poirier et al., 2015; Watts et al., 2004), and neurotoxicity (Gill et al., 2015; Underwood et al., 2015), which are all factors that may induce or worsen psychiatric morbidity in HIV-affected children.

The relationship between early ART and mental health may vary according to perinatal HIV status. For example, among CPHIV, IPA is likely an exposure that improves long-term cognitive functioning and mental development (Mekmullica et al., 2009; Shanbhag et al., 2005; Smith et al., 2012). Not all IPA exposures are equal, however; the availability, quantity, and quality of peripartum ART have evolved substantially from their early use in 1996 (Ford et al., 2011). In resource-limited settings, there were large variations in the programmatic scale-up of IPA. As a result, millions of HIV-exposed children were either never exposed to ART or were subjected to varied qualities of peripartum ART exposures depending on their year of birth (Katabira et al., 2008). To date, the potential relevance of IPA exposure for long-term mental health outcomes in HIV-affected children has not been specifically studied. Thus, the purpose of this study is to determine the implications of these varied exposures for mental health in late childhood and adolescence. We hypothesize that IPA exposure type is associated with mental health outcomes, particularly that lack of exposure to cART will be associated with worse mental health outcomes among CPHIV and CHEU. We further hypothesize that the relationship of IPA exposure type to mental health outcomes may vary between CPHIV and CHEU as a result of factors that differ between individuals with HIV and individuals without HIV, such as HIV-related stigma. This study adds crucial data to understand possible variations in mental health outcomes by school-age and adolescence according to IPA exposure history and children's experience of HIV-related stigma.

2 | METHODS

2.1 | Study context and participants

We implemented a prospective cohort study among Ugandan school-aged (8–10 years old) and adolescent (11–18 years old) children ($n = 577$) and their adult caregivers ($n = 405$). The sample included CPHIV ($n = 198$), CHEU ($n = 191$), and CHUU ($n = 187$) recruited in Kampala district of Uganda between March 16, 2017, and August 18, 2021. Enrolled children are a subset of individuals enrolled in two larger prospective cohort studies of 750 school-aged and adolescent children for whom self-reported mental health measures could be defined. CPHIV and their adult caregivers were enrolled from active families connected to HIV care at Kawaala Health Center in Kampala, Uganda. CHEU were identified from the Early Infant Diagnosis registers and the outpatient department of the same hospitals as CPHIV. CHUU were enrolled from two sources: Kawaala Health Center outpatient department and social networks of the CPHIV and CHEU child-caregiver dyads already enrolled. Current HIV status for both CHEU and CHUU was ascertained using an HIV-rapid diagnosis test.

Each child-caregiver pair was followed at least 12 months or until loss to follow-up with study-related assessments implemented at enrollment, 6, and 12 months. The last enrolled participant in the

already completed parent study of 6–10-year-old children was evaluated on October 26, 2018. The follow-up interval for the ongoing second cohort of 11–18 years old adolescents was the same as in the completed study with exception of an additional assessment at 18 months. Data included from the adolescent cohort for this secondary analysis were restricted to evaluations on or before August 18, 2021.

2.2 | Eligibility/exclusion criteria

School-aged and adolescent children were eligible for the study if they were at least 8 years old so that self-reported mental health measures could be defined, and cared for by a primary caregiver living with HIV or living with perinatally acquired HIV themselves. Additional inclusion criteria included availability of data on HIV disclosure status from HIV-positive caregiver to coenrolled dependent child and/or the CPHIV's knowledge of personal HIV status. Children not born in a clinical setting and child-caregiver dyads without antenatal, delivery, or care records were ineligible because peripartum ART exposure and HIV status their pregnancy could not be ascertained.

2.3 | Ethical approval

Protocols for respective cohort studies were reviewed by the research ethics review boards of Kawaala Health Center. All caregivers gave written informed consent, and children provided assent or consent for study participation.

2.4 | Measures

IPA exposure type: Child IPA exposure was established from medical records, including birth mother's ART treatment card, antenatal or early infant diagnosis registers for CPHIV and CHEU at Kawaala Health Center. CHEU and CPHIV were exposed to one of four IPA types: (1) none, (2) intrapartum prophylactic single-dose nevirapine (sdNVP)± zidovudine (AZT), (3) intrapartum prophylactic sdNVP+AZT+lamivudine (3TC)—that is, sdNVP+AZT+3TC, and (4) combination ART (cART, including at least two ART drug classes). These children were compared to CHUU.

Child perinatal HIV status: Study participants were enrolled based on known HIV status verified for CPHIV via DNA PCR results documented in their medical record. Current HIV status of CHEU and CHUU was ascertained at enrollment using HIV-rapid diagnostic testing (Ezeamama et al., 2016).

Dependent child's knowledge of their caregiver's HIV-positive status (HIV disclosure): HIV disclosure was reported by HIV+ adult caregivers in response to two questions: "Have you ever shared your HIV status with anyone outside this study?" If affirmative, caregivers are then asked individual follow-up "yes or no" questions about the relational contexts in which disclosure has occurred: current sexual partner, mother, father, sister, brother, coenrolled child, other female/female relative, friend, or another person. HIV disclosure was indicated when caregivers affirmed that their coenrolled dependent child was among those aware of their positive HIV status.

Cumulative HIV-associated stigma burden: Two additional measures in adolescents were defined as summed indices of HIV-associated adverse social experiences that were present or absent. The first index is a sum of items: someone found out about the adolescent's HIV status against their wish, the adolescent experienced social isolation/discrimination or financial problems due to knowing their HIV status, and whether the adolescent shared their HIV status with someone. The second index included the experience of inter-personal social problems, conflict, or worry due to HIV-positive status such as: conflict with partner, break-up or separation from friends/partner, beating or other forms of physical violence, persistent worry about accidental HIV status disclosure leading to problems, being a burden on others, and isolation or lack of support from family or friends. Cumulative stigma was defined as the sum of respective indices. For analytic purposes, comparisons were made for 0, 1 compared to ≥2 cumulative HIV-associated stigma items.

Child-reported depression and anxiety symptoms: Self-reported symptoms of depression (feelings of loneliness, unhappiness, sadness, dejection, and overall feeling that nothing is going well or inability to enjoy life) and anxiety (feelings of nervousness, worry and fear, including the tendency to be overwhelmed by problems) were measured using 14 and 13 items from the Behavioral Assessment System for Children, Third Edition (BASC-3), respectively. Each item was scored using a four-point Likert scale (never, sometimes, often, and always) per manufacturer instructions (Dombrowski et al., 2004; Garcia-Barrera et al., 2011; Harrell-Williams et al., 2015; Kamphaus et al., 1999). In the absence of local norms for depression and anxiety metrics as defined by the BASC in Uganda, these measures were internally age and sex standardized to values obtained from demographically matched CHUUs as follows: (raw score—sample mean)/standard deviation (Ezeamama et al., 2016). Respective measures were then analyzed as continuous outcomes without further adjustment for age and sex.

Other covariates. Biological sex (male vs. female) and chronologic age (in years) were determined for caregivers and dependent children. For dependent children, age-based developmental stage was defined as school-aged (<10 years) versus adolescent (≥10 years). Caregiver demographics measured include age, sex, socioeconomic status, and caregiver HIV disclosure status. Caregiver functioning was measured as continuous variable per the Barkin Index of Maternal Function (Barkin et al., 2010).

2.5 | Statistical analyses

Means, standard deviations (SD), frequencies, and percentages were estimated within IPA exposure categories. Comparisons of child and caregiver sociodemographic, mental health, and well-being measures

were performed using analyses of variance for continuous variables and chi-square (X^2) tests for categorical variables. Hypothesis tests were two-sided, and statistical significance was achieved if p-value < 0.05. Multivariable linear mixed-effects models were performed by developmental stage, HIV exposure status, and caregiver HIV status to quantify associations between perinatal HIV status, IPA exposure type, and three repeated measures of depression and anxiety symptoms over 12 months. Random effects corresponded to nesting of repeated measures within the participant and nesting of participants within households (caregivers).

Time averaged least square means (LSMs) and standard errors (SE) were output from the models and were used to calculate standardized mean difference (SMD) values with 95% confidence interval (CI) using CHEU as a reference group to compare by perinatal HIV status and using CHEU with no IPA exposure as a reference group to compare by perinatal HIV status x IPA exposure (Tibshirani, 2011). |SMD| < 0.33, 0.33 ≤ |SMD | < 0.50, |SMD | ≥ 0.50 signified small, moderate, and large clinical importance following the existing precedent for measuring quality of life (QoL) outcomes (Haim Erder et al., 2003). Among CPHIV, associations between IPA exposure type and respective outcomes were investigated via multivariable mixed models adjusted for immune parameters and HIV-treatment-related factors, that is, ART regimen, age at ART initiation, and virologic suppression status.

Confounders such as child's age, sex, relationship with caregiver, and caregivers' age, sex, and socioeconomic status were adjusted for given subject matter knowledge. All analyses were implemented in Statistical Analysis Software version 9.4.

3 | RESULTS

A total of 577 children 8–18 years old including 320 girls and 266 boys with a mean age of 12.7 (standard deviation [SD] = 3.0) years were enrolled. Mean years of caregiver education differed across perinatal HIV status and IPA exposure groups with CHUU caregivers having the highest average level of education (mean [SD]: 7.3 [4.0]) and caregivers of children exposed to sdNVP+AZT+3TC having the lowest (mean [SD]: 7.3 [4.0] versus 5.7 [3.1]]. Age and sex standardized baseline depressive and anxiety symptoms differed according to IPA exposure groups with highest levels of both symptoms among children exposed to sdNVP±AZT and sdNVP+AZT+3TC. No other baseline variables differed across IPA exposure groups (Table 1).

3.1 | Perinatal HIV status in relation to time-averaged depressive and anxiety symptoms

Regardless of IPA exposure type, time-averaged depressive symptoms were similar for CPHIV (LSM = −0.05 ± 0.08) and CHEU (LSM = −0.07 ± 0.09) whereas anxiety symptoms were significantly higher among CHEU (LSM = 0.14 ± 0.08) compared to CPHIV (LSM = −0.01 ± 0.07) (Figure 1). Time-averaged depressive (SMD = −0.20 [0.41, 0.00]) and anxiety (SMD = −0.24 [−0.42, −0.05]) symptoms were significantly lower for CHUU in comparison with CHEU. However, time-averaged depression (SMD = 0.02 [−0.21, 0.24]) and anxiety (SMD = −0.15 [−0.34, 0.05]) symptoms did not differ for CPHIV in comparison to CHEU (Tables 2 and 3). Respective associations were generally strengthened in analyses restricted to adolescents (≥10 years old), HIV-exposed children, and dependent children of HIV+ caregivers (Tables 2 and 3).

3.2 | IPA exposure type and perinatal HIV status in relation to depressive and anxiety symptoms

Regardless of IPA exposure type, self-reported depressive symptoms were similar in CPHIV compared to CHEU with no IPA exposure. Depressive symptoms were significantly higher among CPHIV with no IPA exposure (SMD = 0.31 [0.05, 0.58]) than CHEU with no IPA exposure. Depressive symptoms among CPHIV exposed to cART (SMD = 0.60 [−0.10, 1.30]) were clinically significantly higher than CHEU with no IPA exposure (Table 2).

Relative to CHEU with no IPA exposure, self-reported anxiety symptoms were similar for CHEU exposed to cART (SMD = 0.18 [−0.14, 0.51]). However, CHEU exposed to sdNVP±AZT (SMD = 0.51 [0.06, 0.96]) and CHEU exposed to sdNVP+AZT+3TC (SMD = 0.45 [0.03, 0.86]) self-reported significantly higher anxiety at 6–18 years than CHEU with no IPA exposure, both clinically and statistically (Table 3). Both depressive (SMD = 0.08 [−0.12, 0.29]) and anxiety (SMD = −0.04 [0.24, 0.16]) symptoms were similar for CHUU versus CHEU with no IPA exposure (Tables 2 and 3).

The sdNVP+AZT+3TC-associated higher depression among CHEU remained consistent when the study size was constrained by child age, HIV exposure status, and caregiver HIV status. This similar association with regard to anxiety, however, only remained statistically significant when constrained by child age, despite the other constraints maintaining moderate clinical importance (Tables 2 and 3).

3.3 | Other variables in relation to depressive and anxiety symptoms among CPHIV

Among CPHIV, there were no differences in depressive or anxiety symptoms across IPA exposure types relative to CPHIV with no IPA exposure. Further adjustment for current ART regimen and socio-demographic confounders did not change this relationship. The use of protease inhibitor (PI) v. to nonnucleoside reverse transcriptase inhibitor-based cART, however, was associated with lower anxiety symptoms (SMD = −0.32 [0.59, −0.04]). The comparison of CPHIV without cART exposure at baseline (n = 5) with CPHIV with PI-based cART exposure at baseline suggests nontreatment with cART was associated with elevated risk of depressive symptoms (SMD = 0.91 [−0.58, 2.90]).

TABLE 1 Baseline description of study base of 577 Ugandan children 8–18 years and 405 caregivers according to in utero/peripartum antiretroviral therapy (IPA) exposure.

	sdNVP±AZT *N* = 81		sdNVP+AZT+3TC *N* = 62		cART *N* = 52		No IPA exposure *N* = 195		CHUU *N* = 187		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*p*-Value
Child demographic and psychosocial factors											
Female sex (*n*, %)	52.00	62.3	33	56.6	30	56.6	104	53.1	100	52.9	0.6080
Adolescent (*n*,%)	61.00	75.3	53	85.5	41	78.9	51	73.9	143	76.5	0.4368
Age (years)	13.00	3.11	12.9	2.7	12.3	2.9	12.6	3.1	12.8	2.9	0.6134
Acute stress (Perceived stress scale)	15.00	5.4	15.0	5.9	14.5	4.6	14.4	5.7	14.1	6.2	0.6779
Lifetime adversity score	3.60	3.6	3.1	4.0	3.5	2.9	3.4	3.8	3.5	4.0	0.9421
Anxiety	0.34	1.18	0.48	1.47	0.14	1.12	0.02	0.97	0.07	0.98	0.0219
Depression	0.25	1.33	0.43	1.63	0.19	1.41	0.06	1.18	−0.04	0.98	0.0783
	sdNV±AZT *N* = 72		sdNVP+AZT+3TC *N* = 50		cART *N* = 31		No IPA exposure *N* = 133		CHUU *N* = 119		*p*-Value
Caregiver socio-demographic factors											
Female sex (*n*, %)	58.00	86.60	42.0	85.7	28.0	93.3	118.0	89.4	106.0	89.9	0.8080
Ever alcohol use (*n*, %)	33.00	45.80	25.0	50.0	11.0	35.5	66.0	49.6	40.0	33.6	0.0720
Age (years)	38.8	11.00	40.5	11.7	40.7	13.3	40.5	11.7	38.1	11.2	0.4830
Years of education completed	6.90	3.30	5.7	3.1	6.2	4.5	6.1	3.8	7.3	4.0	0.0588
Currently lives with HIV	57.00	79.20	39.0	78.0	26.0	86.7	98.0	75.4	33.0	27.7	<0.0001
Years lived with HIV|HIV+	13.40	4.00	12.8	4.7	13.0	5.0	13.0	5.8	9.3	5.3	0.0046
Subjective social standing (McArthur scale)	3.20	1.30	3.3	1.2	3.6	1.7	3.4	1.5	3.6	1.4	0.1497
Acute stress (Perceived stress scale)	19.40	5.90	20.8	4.3	20.6	5.0	20.3	6.5	20.5	6.2	0.7520
Recent life stress (Recent life events questionnaire)	7.90	4.30	8.4	3.2	7.8	3.0	7.3	3.7	8.2	3.9	0.2860
Lifetime adversity score	2.00	2.30	2.5	2.7	2.3	2.0	2.0	2.1	2.0	2.0	0.6470
BMAT caregiving quality	58.60	9.72	61.2	9.0	59.7	7.7	58.0	8.51	58.5	10.5	0.1680
Depressed (Hopkins checklist) (*n*,%)	13.00	18.80	8.0	16.0	7.0	22.6	23.0	17.3	20.0	16.8	0.9450

Note: Values are expressed as mean (standard deviation) unless stated otherwise.

Abbreviations: cART, combination antiretroviral therapy; CHUU, children HIV unexposed uninfected. sdnvp±AZT, single-dose nevirapine with/without zidovudine; sdnvp+AZT+3TC, single-dose nevirapine with zidovudine with lamivudine.

No measure of CD4+ cell count (including CD4 nadir), predicted change in depressive or anxiety symptoms over 1 year (data not shown). However, experiencing <2 CD4+ cell count drops below 500 cells/μL was a clinically and statistically significant predictor of low depressive (SMD = −0.56 [−0.99, −0.14]) and low anxiety (SMD = −0.38 [−0.70, −0.06]) symptoms. Virologically suppressed CPHIV experienced statistically significant and clinically moderate reduction in depressive symptoms over 12 months relative to CPHIV with detectable viremia (SMD = −0.35 [−0.67, −0.04]). There was no association between virological suppression and anxiety symptoms (Table 4).

Among the 137 CPHIV adolescents with analyzable data, only 11 children reported experience of social stigma. This variable was not associated with either mental health outcome (Table 4). Similarly, CPHIV's knowledge of their caregivers' HIV-positive status was not clinically nor statistically associated with depressive (SMD = 0.27 [−0.12, 0.66]) and anxiety (SMD = −0.13 [−0.45, 0.20]) symptoms (data not shown).

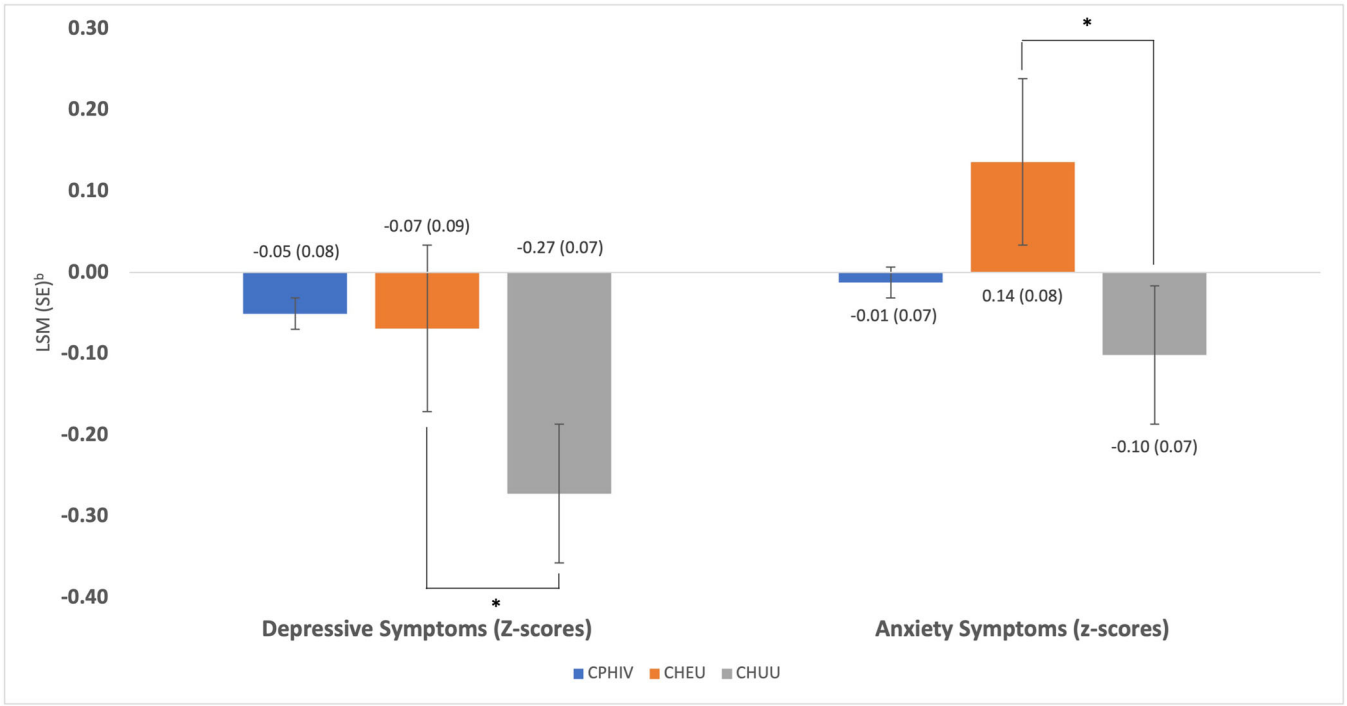

FIGURE 1 Time-averaged[a] depressive and anxiety symptoms according to perinatal HIV status in 8–18-year-old Ugandan children. [a]Depressive and anxiety symptoms were assessed at three time points over 12 months: baseline, 6 months, and 12 months. *indicates $p < 0.05$. CHEU, children HIV exposed but uninfected; CHUU, children HIV unexposed uninfected; CPHIV, children with perinatally acquired HIV; LSM, least square means; SE, standard error.

4 | DISCUSSION

We demonstrated important differences in anxiety and depressive symptoms by perinatal HIV status in 8–18-year-old Ugandan children. In line with observations in the Pediatric HIV/AIDS Cohorts Study (PHACS) (Malee et al., 2011; Smith et al., 2019) and adolescents from Kenya (Abubakar et al., 2017), we found that depression and anxiety symptoms were similar among CPHIV and CHEU. Compared to CHUU, HIV-exposed children had higher anxiety and depressive symptoms. Consistent with previously reported higher prevalence rates of emotional health problems among CHEU compared to CPHIV in the PHACS (Malee et al., 2011), we found anxiety symptoms were highest among CHEU. Our study suggests, however, that once adjusted for time and caregiver demographic factors, and further disaggregating outcomes according to IPA exposure type, depression and anxiety symptoms were similar for CPHIV with various IPA exposures relative to CHEU without IPA exposure.

Mental health outcomes were similar for CHUU compared to CHEU without IPA exposure. These group differences underscore the high vulnerability of HIV-exposed children to mental health challenges due to shared structural, environmental, and psychosocial risk factors (Betancourt et al., 2017; Nduwimana et al., 2017; Sherr et al., 2020). These differences also highlight the need to enhance risk stratification in this population by delineating predisposing risk factors for adverse mental health outcomes beyond perinatal HIV status. In contrast to other studies, except for caregiver educational level, no baseline sociodemographic, psychosocial, and caregiver stress/mental health variables differed across IPA exposure groups at baseline. This similar distribution of baseline characteristics among IPA exposure groups allowed us to confidently compare them without additional bias.

In line with our study hypothesis, we provided novel data showing that variations in anxiety and depression symptoms in 8–18-year-old Ugandan children over a 12-month follow-up period were related to IPA exposure type, especially among CHEU. Specifically, anxiety and depression symptoms were higher in CHEU exposed to sdNVP±AZT and sdNVP+AZT+3TC in comparison to CHEU without IPA exposure. While CHEU with sdNVP±AZT and sdNVP+AZT+3TC exposures had consistently higher clinically moderate to severe anxiety and depression symptoms, CHEU without IPA exposure reported similar mental health symptomatology as CHUU. Given the absence of HIV transmission in both groups, this finding suggests that HIV exposure without concomitant IPA exposure has little impact on mental health outcomes. Additionally, CHEU with cART exposure had similar mental health outcomes to CHEU without IPA exposure. These results suggest that among IPA-exposed children, different regimens may have disparate effects on mental health that remain poorly understood in HIV and IPA-exposed children.

The relative differences in association of various IPA regimens with mental health outcomes among CHEU were robust to sample restriction by age, HIV exposure status, and knowledge of HIV+

TABLE 2 Standardized mean differences in self-reported anxiety symptoms z-score among 8–18-year-old Ugandan children by perinatal HIV status and in utero/peripartum antiretroviral therapy (IPA) exposure type.

	Children ≥ 8 years old (*n* = 563)			Children ≥ 10 years old (*n* = 482)			HIV-exposed children[a] (*n* = 379)			Children of HIV+ caregivers (*n* = 361)		
	Multivariable model 1[b]			Multivariable model 1			Multivariable model 1			Multivariable model 2[c]		
Perinatal HIV status	***N***	**SMD**	**95% CI**	***N***	**SMD**	**95% CI**	***N***	**SMD**	**95% CI**	***N***	**SMD**	**(95% CI)**
CPHIV	195	−0.15	−0.34, 0.05	169	−0.14	−0.27, 0.23	195	−0.12	−0.32, 0.08	134	−0.15	−0.38, 0.09
CHEU	184	Ref		157	Ref		184	Ref		170	Ref	
CHUU	184	**−0.24**	**−0.42, −0.05**	156	**−0.26**	**−0.47, −0.05**	-	-		57	**−0.38**	**−0.61, −0.15**
CPHIV by IPA type												
sdnvp±AZT	48	0.06	−0.20, 0.31	42	0.16	−0.12, 0.45	48	0.07	−0.22, 0.35	36	0.11	−0.18, 0.40
dNVP+AZT+3TC	21	0.26	−0.27, 0.78	19	0.30	−0.29, 0.88	21	0.25	−0.38, 0.89	14	0.30	−0.40, 0.99
cART	16	0.12	−0.41, 0.64	15	0.19	−0.36, 0.75	16	−0.08	−0.67, 0.51	11	−0.11	−0.76, 0.55
None	110	0.00	−0.24, 0.23	93	0.07	−0.20, 0.34	110	−0.07	−0.32, 0.19	73	−0.02	−0.29, 0.25
CHEU by IPA type												
sdnvp ± AZT	29	***0.51***	***0.06, 0.89***	25	***0.63***	***0.10, 1.15***	29	***0.47***	***0.01, 0.93***	27	***0.53***	***0.06, 1.01***
dNVP+AZT+3TC	39	***0.45***	***0.03, 0.86***	37	***0.61***	***0.16, 1.00)***	39	*0.40*	*−0.03, 0.84*	33	*0.40*	*−0.03, 0.83*
cART	35	0.13	−0.22, 0.48	29	0.15	−0.25, 0.55	35	0.07	−0.28, 0.41	33	0.10	−0.27, 0.47
None	81	Ref		66	Ref		81	Ref		77	Ref	
CHUU	184	−0.04	−0.24, 0.16	156	0.01	−0.22, 0.24	-	-		57	−0.21	−0.45, 0.03

Note: Bolded values denote statistical significance; italicized values denote clinical significance.

Abbreviations: cART, combination antiretroviral therapy; CHEU, children HIV exposed but uninfected; CHUU, children HIV unexposed uninfected; CI, confidence interval; CPHIV, children with perinatally acquired HIV infected; dNVP+AZT+3TC, single-dose nevirapine with zidovudine with lamivudine; IPA, in utero/peripartum antiretroviral therapy; sdnvp±AZT, single-dose nevirapine with/without zidovudine; SMD, standardized mean difference.

[a]Includes CHEU+CPHIV.

[b]Multivariable model 1 is adjusted for time and caregiver demographics (age, sex, and socioeconomic status).

[c]Multivariable model 2 is adjusted for all variables in model 1 plus caregiver HIV disclosure status.

TABLE 3 Standardized mean differences in self-reported depressive symptoms z-score among 8–18-year-old Ugandan children by perinatal HIV status and in utero/peripartum antiretroviral therapy (IPA) exposure type.

	Children ≥ 8 years old (*n* = 563)			Children ≥ 10 years old (*n* = 482)			HIV-exposed children[a] (*n* = 379)			Children of caregivers living with HIV (*n* = 361)		
	Multivariable model 1[b]			Multivariable model 1			Multivariable model 1			Multivariable model 2[c]		
Perinatal HIV Status	***N***	**SMD**	**95% CI**	***N***	**SMD**	**95% CI**	***N***	**SMD**	**95% CI**	***N***	**SMD**	**95% CI**
CPHIV	195	0.02	−0.21, 0.24	169	0.02	−0.27, 0.23	195	0.04	−0.19, 0.27	134	0.04	−0.23, 0.31
CHEU	184	Ref		157	Ref		184	Ref		170	Ref	
CHUU	184	**−0.20**	**−0.41, −0.00**	156	**−0.21**	**−0.02, 0.42**	-	-		57	**−0.30**	**−0.55, −0.06**
CPHIV by IPA type												
sdnvp±AZT	48	0.26	−0.04, 0.57	42	***0.36***	***0.04, 0.69***	48	*0.30*	*−0.02, 0.61*	36	0.31	−0.06, 0.68
sdnvp+AZT+3TC	21	0.16	−0.23, 0.55	19	0.07	−0.34, 0.48	21	0.17	−0.24, 0.58	14	*0.35*	*−0.21, 0.90*
cART	16	0.60	−0.10, 1.30	15	*0.54*	*−0.17, 1.25*	16	*0.59*	*−0.09, 1.28*	11	*0.63*	*−0.30, 1.56*
None	110	**0.31**	**0.05, 0.58**	93	***0.40***	***0.12, 0.68***	110	***0.33***	***0.06, 0.60***	73	0.28	−0.03, 0.58
CHEU by IPA type												
sdnvp±AZT	29	***0.48***	***0.07, 0.89***	**25**	***0.54***	***0.12, 0.97***	29	***0.48***	***0.07, 0.90***	27	***0.50***	***0.04, 0.96***
sdnvp+AZT+3TC	39	***0.72***	***0.27, 1.17***	**37**	***0.87***	***0.39, 1.35***	39	***0.73***	***0.29, 1.19***	33	***0.65***	***0.23, 1.08***
cART	35	0.29	−0.15, 0.73	29	*0.33*	*−0.16, 0.82*	35	0.28	−0.16, 0.71	33	*0.34*	*−0.11, 0.79*
None	81	Ref		66	Ref		81	Ref		77	Ref	
CHUU	184	0.08	(−0.12, 0.29)	156	0.08	−0.12, 0.29	-	-		57	−0.03	−0.28, 0.22

Note: Bolded values denote statistical significance; italicized values denote clinical significance.

Abbreviations: cART, combination antiretroviral therapy; CHEU, children HIV exposed but uninfected; CI, confidence interval; CPHIV, children with perinatally acquired HIV infected; dNVP+AZT+3TC, single-dose nevirapine with zidovudine with lamivudine; IPA, in utero/peripartum antiretroviral therapy; sdnvp±AZT, single-dose nevirapine with/without zidovudine; SMD, standardized mean difference.

[a]Includes CHEU+CPHIV.

[b]Multivariable model 1 is adjusted for time and caregiver demographics (age, sex, and socioeconomic status).

[c]Multivariable model 2 is adjusted for all variables in model 1 plus caregiver HIV disclosure status.

TABLE 4 Correlates of depressive and anxiety symptoms among 8–18-year-old Ugandan children with perinatally acquired HIV (CPHIV).

	N	Depressive symptoms in CPHIV[a] (*n* = 195)		Anxiety symptoms in CPHIV[a] (*n* = 195)	
		SMD[c]	95% (CI)	SMD	95% CI
IPA[b] *exposure status*					
sdnvp±AZT[d]	48	0.07	−0.26, 0.40	0.13	−0.11, 0.35
sdnvp+AZT+3TC[e]	21	−0.13	−0.43, 0.35	0.31	−0.18, 0.81
cART[f]	16	0.26	−0.47, 0.80	0.12	−0.34, 0.58
None	110		Ref	Ref	
IPA exposure status adjusted for current ART regimen					
sdnvp±AZT	48	−0.12	−0.42, 0.19	−0.02	−0.25, 0.22
sdnvp+AZT+3TC	21	−0.16	−0.60, 0.28	0.32	−0.20, 0.84
cART	16	0.20	−0.51, 0.91	0.11	−0.41, 0.62
None	110		Ref	Ref	
Current cART exposure status					
NNRTI[g] (EFV[h]/NVP[i] inclusive)	90		Ref	Ref	
NRTI[j] (Abacavir or TDF[k] inclusive)	50	0.21	−0.21, 0.63	0.15	−0.15, 0.44
PI[l]	43	−0.15	−0.71, 0.17	**−0.32**	**−0.59, −0.04**
None/unknown	5	0.91	−0.58, 2.90	−0.01	−0.86, 0.83
CD4+ history[m] *(n = 187)*					
0	68	−0.35	−0.73, 0.04	−0.20	−0.52, 0.13
1	64	**−0.56**	**−0.99, −0.14**	**−0.38**	**−0.70, −0.06**
2+	55		Ref	Ref	
Virologically suppressed (n = 160)					
Yes	63	**−0.35**	**−0.67, −0.04**	−0.17	−0.42, 0.08
No	97		Ref	Ref	
Experienced stigma (n = 137)					
Yes	11	−0.49	−1.20, 0.22	0.20	−0.20, 0.58
No	126		Ref	Ref	

Note: Bolded values indicate statistically significant differences.

[a]Multivariable model adjusted for time, caregiver demographics (age, sex, and socioeconomic status), and HIV factors (ART regimen, age at ART initiation, and virologic suppression status);

[b]IPA: in utero/peripartum antiretroviral therapy.

[c]SMD: standardized mean difference.

[d]sdnvp±AZT: Single-dose nevirapine with/without zidovudine.

[e]sdnvp+AZT+3TC: Single-dose nevirapine with zidovudine with lamivudine.

[f]cART: combination antiretroviral therapy.

[g]Nonnucleoside reverse transcriptase inhibitor.

[h]Efavirenz.

[i]Nevirapine.

[j]Nucleoside reverse transcriptase inhibitor.

[k]Tenofovir disoproxil fumarate.

[l]Protease inhibitor.

[m]CD4+ history is the number of times an individual's CD4+ cell count <500 cells/μL.

caregivers' status. We found that associations between certain IPA exposures and increased severity of mental health symptoms were not explained by active HIV infection, differences in caregiving environment, or sociodemographic factors already controlled for in this study. In support of the potentially disparate mental health effect of various IPA regimens, preclinical in vitro and animal studies (McHenry et al., 2019; Schnoll et al., 2021) have linked exposure to antiretroviral drugs with lower maturation, survival, and worse myelination in oligodendrocytes (Jensen et al., 2015). Further, evidence from mouse studies has indicated the associations of in utero AZT+3TC exposure to atypical behaviors in adolescent period of mouse life (Calamandrei et al., 1999; Venerosi et al., 2000, 2001, 2003). These preclinical observations align with the premise that any IPA exposure may modulate social, emotional, and mental well-being in humans across the life course, and certain IPA exposures may exacerbate these modulations (Calamandrei et al., 1999; Venerosi et al., 2000, 2001, 2003).

In analyses restricted to HIV-exposed children (CPHIV and CHEU), we observed that regardless of IPA exposure type, CPHIV on average had elevated depressive symptoms of modest to large clinical significance compared to CHEU without IPA exposure. Across IPA exposure groups, this association was statistically significant only for CPHIV without IPA exposure compared to CHEU without IPA exposure. Since both groups were HIV exposed, this prevailing difference suggests that HIV infection itself or unique experiences associated with CPHIV status were driving the observed adverse mental health trajectory. Further adjustment of this association for HIV disclosure status weakened association to nonsignificance, suggesting that children's knowledge about the HIV status of themselves or their caregiver may modify mental health outcomes among HIV-exposed children.

Among CPHIV, the most vulnerable demographic in this study, we found no difference in anxiety or depression symptoms according to IPA exposure. However, CPHIV currently on protease inhibitor-based cART had significantly lower anxiety relative to CPHIV currently on NNRTI-based cART. Further, depression and anxiety symptoms were inversely correlated with CD4+ cell count and lack of virologic suppression, underscoring the importance of effective HIV treatment for improvement of mental health outcomes in persons living with HIV (Nachman et al., 2012; de Vega et al., 2019).

The observational design of this study limits our ability to remove residual confounding by unmeasured covariates. Further, the sample includes children born between 2000 and 2009, and the associations described apply to IPA regimen in use at time of birth. Therefore, results obtained here are generalizable to surviving children born from that era of the global HIV pandemic. Hence, the novel IPA-related variations in depression and anxiety reported remain associative in nature. Further interrogation of this relationship in carefully designed future studies will be important to confirm these observations in perinatally HIV and ART-exposed children of HIV-positive women. In addition, the effects of peripartum exposure to modern ART regimens on mental health outcomes of contemporary CPHIV and CHEU remains an open question. Finally, although we included many socioeconomic variables for both children and caregivers, there are limitless additional variables that could have been explored such as income level, food or housing insecurity, employment, literacy, and many others. Future research is needed for comprehensive assessment of the role of these variables to inform differences between CHEU and CPHIV.

The strengths of the present investigation include its large sample size, the longitudinal design including multiple assessments of mental health, the use of validated self-report measures of depression and anxiety (Riley, 2004), the application of a rigorous analytic strategy that controlled for important confounders, and inclusion of sensitivity analyses to examine stability of associations across defined samples. Further strengths that increase confidence in the reported findings include objective determination of IPA and HIV exposure/transmission status via medical records and specific testing upon enrollment, and the presence of robust comparative groups that permit isolation of mental health associations due to IPA type, HIV exposure/transmission status, and HIV-affected environment.

In conclusion, we provided novel data indicating important differences in mental health outcomes of CHEU at 8–18 years of age associated with peripartum sdNVP±AZT and sdNVP+AZT+3TC. Equally important, peripartum cART exposure was not adversely associated with depression or distress, and CHEU without IPA exposure reported mental health symptomatology similar to CHUU. This data lays the foundation for understanding the long-term emotional and mental health effects of IPA exposure. Further, findings underscore the importance of monitoring the mental health trajectory of HIV-exposed children to glean information that could be leveraged to ensure that these vulnerable children not only survive but thrive throughout childhood and into adulthood.

AUTHOR CONTRIBUTIONS

Audrey Coventry: Writing—original draft preparation; writing—review and editing. **Alla Sikorskii**: Formal analysis; writing—review and editing. **Sarah K. Zalwango**: Writing—review and editing; project administration. **Itziar Familiar-Lopez**: Writing—review and editing. **Vanessa N. Cardino**: Writing—review and editing. **Bruno Giordani**: Writing—review and editing. **Amara E. Ezeamama**: Conceptualization; formal analysis; data curation; writing—original draft preparation; writing—review and editing; project administration; funding acquisition.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available on request due to privacy/ethical reasons.

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REFERENCES

Abubakar, A., Van de Vijver, F. J. R., Hassan, A. S., Fischer, R., Nyongesa, M. K., Kabunda, B., Berkley, J. A., Stein, A., & Newton, C. R. (2017). Cumulative psychosocial risk is a salient predictor of depressive symptoms among vertically HIV-infected and HIV-affected adolescents at the Kenyan coast. *Annals of Global Health*, *83*(5–6), 743–752. https://doi.org/10.1016/j.aogh.2017.10.024

Barkin, J. L., Wisner, K. L., Bromberger, J. T., Beach, S. R., Terry, M. A., & Wisniewski, S. R. (2010). Development of the Barkin Index of maternal functioning. *Journal of Women's Health*, *19*(12), 2239–2246. https://doi.org/10.1089/jwh.2009.1893

Betancourt, T. S., Meyers-Ohki, S. E., Charrow, A., & Hansen, N. (2013). Annual research review: Mental health and resilience in HIV/AIDS-affected children—A review of the literature and recommendations for future research. *Journal of Child Psychology and Psychiatry*, *54*(4), 423–444. https://doi.org/10.1111/j.1469-7610.2012.02613.x

Betancourt, T. S., Ng, L. C., Kirk, C. M., Brennan, R. T., Beardslee, W. R., Stulac, S., Mushashi, C., Nduwimana, E., Mukunzi, S., Nyirandagijimana, B., Kalisa, G., Rwabukwisi, C. F., & Sezibera, V. (2017). Family-based promotion of mental health in children affected by HIV: A pilot randomized controlled trial. *Journal of Child Psychology and Psychiatry*, *58*(8), 922–930. https://doi.org/10.1111/jcpp.12729

Buckley, J., Otwombe, K., Joyce, C., Leshabane, G., Hornschuh, S., Hlongwane, K., Dietrich, J., Grelotti, D. J., & Violari, A. (2020). Mental health of adolescents in the era of antiretroviral therapy: Is there a difference between HIV-infected and uninfected youth in South Africa. *Journal of Adolescent Health*, *67*(1), 76–83. https://doi.org/10.1016/j.jadohealth.2020.01.010

Calamandrei, G., Venerosi, A., Branchi, I., & Alleva, E. (1999). Effects of prenatal zidovudine treatment on learning and memory capacities of preweanling and young adult mice. *Neurotoxicology*, *20*(1), 17–25.

Cluver, L. D., Gardner, F., & Operario, D. (2008). Effects of stigma on the mental health of adolescents orphaned by AIDS. *Journal of Adolescent Health*, *42*(4), 410–417. https://doi.org/10.1016/j.jadohealth.2007.09.022

Cooper, E. R., Hanson, C., Diaz, C., Mendez, H., Abboud, R., Nugent, R., Pitt, J., Rich, K., Rodriguez, E. M., & Smeriglio, V. (1998). Encephalopathy and progression of human immunodeficiency virus disease in a cohort of children with perinatally acquired human immunodeficiency virus infection. *The Journal of Pediatrics*, *132*(5), 808–812. https://doi.org/10.1016/S0022-3476(98)70308-7

Dombrowski, S. C., Kamphaus, R. W., & Reynolds, C. R. (2004). After the demise of the discrepancy: Proposed learning disabilities diagnostic criteria. *Professional Psychology: Research and Practice*, *35*(4), 364–372. https://doi.org/10.1037/0735-7028.35.4.364

Donenberg, G. R., & Pao, M. (2005). Youths and HIV/AIDS: Psychiatry's role in a changing epidemic. *Journal of the American Academy of Child & Adolescent Psychiatry*, *44*(8), 728–747. https://doi.org/10.1097/01.chi.0000166381.68392.02

Ezeamama, A. E., Guwatudde, D., Wang, M., Bagenda, D., Brown, K., Kyeyune, R., Smith, E., Wamani, H., Manabe, Y. C., & Fawzi, W. W. (2016). High perceived social standing is associated with better health in HIV-infected Ugandan adults on highly active antiretroviral therapy. *Journal of Behavioral Medicine*, *39*(3), 453–464. https://doi.org/10.1007/s10865-015-9710-x

Fernández Ibieta, M., Bellón Cano, J. M., Ramos Amador, J. T., González-Tomé, M. I., Guillén Martín, S., Navarro Gómez, M., de José, M. I., Beceiro, J., Iglesias, E., Prieto, L., Santos, M. J., Martínez Guardia, N., Roa, M. A., & Regidor, J. (2010). Exposición a antirretrovirales y toxicidad mitocondrial en una cohorte de niños no infectados hijos de madres VIH positivas. *Anales de Pediatría*, *73*(4), 180–188. https://doi.org/10.1016/j.anpedi.2010.02.004

Ford, N., Calmy, A., & Mills, E. J. (2011). The first decade of antiretroviral therapy in Africa. *Globalization and Health*, *7*, 33.

Garcia-Barrera, M. A., Kamphaus, R. W., & Bandalos, D. (2011). Theoretical and statistical derivation of a screener for the behavioral assessment of executive functions in children. *Psychological Assessment*, *23*(1), 64–79. https://doi.org/10.1037/a0021097

García-Otero, L., López, M., Guitart-Mampel, M., Morén, C., Goncé, A., Esteve, C., Salazar, L., Gómez, O., Martínez, J. M., Torres, B., César, S., Garrabou, G., Crispi, F., & Gratacós, E. (2019). Cardiac and mitochondrial function in HIV-uninfected fetuses exposed to antiretroviral treatment. *PLoS One*, *14*(3), e0213279. https://doi.org/10.1371/journal.pone.0213279

Gill, A. J., Kovacsics, C. E., Vance, P. J., Collman, R. G., & Kolson, D. L. (2015). Induction of heme oxygenase-1 deficiency and associated glutamate-mediated neurotoxicity is a highly conserved HIV phenotype of chronic macrophage infection that is resistant to antiretroviral therapy. *Journal of Virology*, *89*(20), 10656–10667. https://doi.org/10.1128/JVI.01495-15

Goldstein, P. J., Smit, R., Stevens, M., & Sever, J. L. (2000). Association between HIV in pregnancy and antiretroviral therapy, including protease inhibitors and low birth weight infants. *Infectious Diseases in Obstetrics and Gynecology*, *8*(2), 94–98. https://doi.org/10.1155/S1064744900000089

Haim Erder, M., Santanello, N., & Hays, R. D. (2003). Assessing the clinical significance of patient-reported outcomes: Examples drawn from a recent meeting of the drug information association (DIA). *Clinical Therapeutics*, *25*, D12–D13. https://doi.org/10.1016/S0149-2918(03)80252-7

Harrell-Williams, L. M., Raines, T. C., Kamphaus, R. W., & Dever, B. V. (2015). Psychometric analysis of the BASC-2 behavioral and emotional screening system (BESS) student form: Results from high school student samples. *Psychological Assessment*, *27*(2), 738–743. https://doi.org/10.1037/pas0000079

Hernández, S., Catalán-García, M., Morén, C., García-Otero, L., López, M., Guitart-Mampel, M., Milisenda, J., Coll, O., Cardellach, F., Gratacós, E., Miró, Ò., & Garrabou, G. (2017). Placental mitochondrial toxicity, oxidative stress, apoptosis, and adverse perinatal outcomes in HIV pregnancies under antiretroviral treatment containing zidovudine. *Journal of Acquired Immune Deficiency Syndromes*, *75*(4), e113–e119. https://doi.org/10.1097/QAI.0000000000001334

Hoare, J., Phillips, N., Brittain, K., Myer, L., Zar, H. J., & Stein, D. J. (2019). Mental health and functional competence in the Cape Town adolescent antiretroviral cohort. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *81*(4), e109–e116. https://doi.org/10.1097/QAI.0000000000002068

Jao, J., Powis, K. M., Kirmse, B., Yu, C., Epie, F., Nshom, E., Abrams, E. J., Sperling, R. S., Leroith, D., Geffner, M. E., Kurland, I. J., & Côté, H. C. F. (2017). Lower mitochondrial DNA and altered mitochondrial fuel metabolism in HIV-exposed uninfected infants in Cameroon. *AIDS*, *31*(18), 2475–2481. https://doi.org/10.1097/QAD.0000000000001647

Jensen, B. K., Monnerie, H., Mannell, M. V., Gannon, P. J., Espinoza, C. A., Erickson, M. A., Bruce-Keller, A. J., Gelman, B. B., Briand, L. A., Pierce, R. C., Jordan-Sciutto, K. L., & Grinspan, J. B. (2015). Altered oligodendrocyte maturation and myelin maintenance: The role of antiretrovirals in HIV-associated neurocognitive disorders. *Journal of Neuropathology & Experimental Neurology*, *74*(11), 1093–1118. https://doi.org/10.1097/NEN.0000000000000255

Kacanek, D., Angelidou, K., Williams, P. L., Chernoff, M., Gadow, K. D., & Nachman, S. (2015). Psychiatric symptoms and antiretroviral

nonadherence in US youth with perinatal HIV: A longitudinal study. *AIDS*, *29*(10), 1227–1237. https://doi.org/10.1097/QAD.0000000000000697

Kamphaus, R. W., Petoskey, M. D., Cody, A. H., Rowe, E. W., Huberty, C. J., & Reynolds, C. R. (1999). A typology of parent rated child behavior for a national US sample. *Journal of Child Psychology and Psychiatry*, *40*(4), 607–616. https://doi.org/10.1017/S0021963098003771

Katabira, E. T., Kamya, M. R., Kalyesubula, I., & Namale, A. (2008). *National Antiretroviral treatment and care guidelines for adults, adolescents, and children*. Ministry of Health.

Malee, K. M., Tassiopoulos, K., Huo, Y., Siberry, G., Williams, P. L., Hazra, R., Smith, R. A., Allison, S. M., Garvie, P. A., Kammerer, B., Kapetanovic, S., Nichols, S., Van Dyke, R., Seage, G. R., & Mellins, C. A., for the Pediatric HIV/AIDS Cohort S. (2011). Mental health functioning among children and adolescents with perinatal HIV infection and perinatal HIV exposure. *AIDS Care*, *23*(12), 1533–1544. https://doi.org/10.1080/09540121.2011.575120

McHenry, M. S., Balogun, K. A., McDonald, B. C., Vreeman, R. C., Whipple, E. C., & Serghides, L. (2019). In utero exposure to HIV and/or antiretroviral therapy: A systematic review of preclinical and clinical evidence of cognitive outcomes. *Journal of the International AIDS Society*, *22*(4), e25275. https://doi.org/10.1002/jia2.25275

Mekmullica, J., Brouwers, P., Charurat, M., Paul, M., Shearer, W., Mendez, H., Diaz, C., Read, J. S., Mondal, P., Smith, R., & McIntosh, K. (2009). Early immunological predictors of neurodevelopmental outcomes in HIV-infected children. *Clinical Infectious Diseases*, *48*(3), 338–346. https://doi.org/10.1086/595885

Mellins, C. A., & Malee, K. M. (2013). Understanding the mental health of youth living with perinatal HIV infection: Lessons learned and current challenges. *Journal of the International AIDS Society*, *16*, 18593. https://doi.org/10.7448/IAS.16.1.18593

Mellins, C. A., Tassiopoulos, K., Malee, K., Moscicki, A. B., Patton, D., Smith, R., Usitalo, A., Allison, S. M., Van Dyke, R., & Seage for the Pediatric HIV-AI III, G. R. (2011). Behavioral health risks in perinatally HIV-exposed youth: Co-occurrence of sexual and drug use behavior, mental health problems, and nonadherence to antiretroviral treatment. *AIDS Patient Care and STDs*, *25*(7), 413–422. https://doi.org/10.1089/apc.2011.0025

Nachman, S., Chernoff, M., Williams, P., Hodge, J., Heston, J., & Gadow, K. D. (2012). Human immunodeficiency virus disease severity, psychiatric symptoms, and functional outcomes in perinatally infected youth. *Archives of Pediatrics & Adolescent Medicine*, *166*(6), 528–535. https://doi.org/10.1001/archpediatrics.2011.1785

Nduwimana, E., Mukunzi, S., Ng, L. C., Kirk, C. M., Bizimana, J. I., & Betancourt, T. S. (2017). Mental health of children living in foster families in rural Rwanda: The role of HIV and the family environment. *AIDS and Behavior*, *21*(6), 1518–1529. https://doi.org/10.1007/s10461-016-1482-y

Noguera-Julian, A., Morén, C., Rovira, N., Garrabou, G., Catalán, M., Sánchez, E., Cardellach, F., Miró, Ó., & Fortuny, C. (2015). Decreased mitochondrial function among healthy infants exposed to antiretrovirals during gestation, delivery and the neonatal period. *Pediatric Infectious Disease Journal*, *34*(12), 1349–1354. https://doi.org/10.1097/INF.0000000000000894

Penner, F., Sharp, C., Marais, L., Shohet, C., Givon, D., & Boivin, M. (2020). Community-based caregiver and family interventions to support the mental health of orphans and vulnerable children: Review and future directions. *New Directions for Child and Adolescent Development*, *2020*(171), 77–105. https://doi.org/10.1002/cad.20352

Poirier, M. C., Gibbons, A. T., Rugeles, M. T., Andre-Schmutz, I., & Blanche, S. (2015). Fetal consequences of maternal antiretroviral nucleoside reverse transcriptase inhibitor use in human and nonhuman primate pregnancy. *Current Opinion in Pediatrics*, *27*(2), 233–239. https://doi.org/10.1097/MOP.0000000000000193

Riley, A. W. (2004). Evidence that school-age children can self-report on their health. *Ambulatory Pediatrics*, *4*(4), 371–376. https://doi.org/10.1367/A03-178r.1

Schnoll, J. G., Temsamrit, B., Zhang, D., Song, H., Ming, G., & Christian, K. M. (2021). Evaluating neurodevelopmental consequences of perinatal exposure to antiretroviral drugs: Current challenges and new approaches. *Journal of Neuroimmune Pharmacology*, *16*(1), 113–129. https://doi.org/10.1007/s11481-019-09880-z

Schulte, J., Dominguez, K., Sukalac, T., Bohannon, B., & Fowler, M. G. (2007). Declines in low birth weight and preterm birth among infants who were born to HIV-infected women during an era of increased use of maternal antiretroviral drugs: Pediatric spectrum of HIV disease, 1989–2004. *Pediatrics*, *119*(4), e900–e906. https://doi.org/10.1542/peds.2006-1123

Shanbhag, M. C., Rutstein, R. M., Zaoutis, T., Zhao, H., Chao, D., & Radcliffe, J. (2005). Neurocognitive functioning in pediatric human immunodeficiency virus infection: Effects of combined therapy. *Archives of Pediatrics & Adolescent Medicine*, *159*(7), 651–656. https://doi.org/10.1001/archpedi.159.7.651

Sherr, L., Yakubovich, A. R., Skeen, S., Tomlinson, M., Cluver, L. D., Roberts, K. J., & Macedo, A. (2020). Depressive symptoms among children attending community based support in South Africa—Pathways for disrupting risk factors. *Clinical Child Psychology and Psychiatry*, *25*(4), 984–1001. https://doi.org/10.1177/1359104520935502

Smith, R., Chernoff, M., Williams, P. L., Malee, K. M., Sirois, P. A., Kammerer, B., Wilkins, M., Nichols, S., Mellins, C., Usitalo, A., Garvie, P., & Rutstein, R. (2012). Impact of HIV severity on cognitive and adaptive functioning during childhood and adolescence. *Pediatric Infectious Disease Journal*, *31*(6), 592–598. https://doi.org/10.1097/INF.0b013e318253844b

Smith, R., Huo, Y., Tassiopoulos, K., Rutstein, R., Kapetanovic, S., Mellins, C., Kacanek, D., Malee, K., Yogev, R., Ann Sanders, M., Malee, K., Hunter, S., Shearer, W., Paul, M., Cooper, N., Harris, L., Purswani, M., Baig, M. M., Villegas, A., … Cuadra, A. (2019). Mental health diagnoses, symptoms, and service utilization in US youth with perinatal HIV infection or HIV exposure. *AIDS Patient Care and STDs*, *33*(1), 1–13. https://doi.org/10.1089/apc.2018.0096

Tardieu, M., Le Chenadec, J., Persoz, A., Meyer, L., Blanche, S., & Mayaux, M. J. (2000). HIV-1-related encephalopathy in infants compared with children and adults. *Neurology*, *54*(5), 1089–1095. https://doi.org/10.1212/Wnl.54.5.1089

Tibshirani, R. (2011). Regression shrinkage and selection via the lasso: A retrospective. *Journal of the Royal Statistical Society Series B: Statistical Methodology*, *73*, 273–282.

Traore, H., Meda, N., Nagot, N., Somé, E., Neboua, D., Kankasa, C., Hofmeyr, J., Tumwine, J., Vallo, R., Ye, D., Tylleskar, T., & Van de Perre, P. (2013). Déterminants du faible poids de naissance chez des enfants nés de mères séropositives pour le VIH, non éligibles au traitement antirétroviral, en Afrique. *Revue d'Épidémiologie et de Santé Publique*, *61*(5), 413–420. https://doi.org/10.1016/j.respe.2013.05.022

UNAIDS. *Global HIV & AIDS statistics—Fact sheet*. https://www.unaids.org/en/resources/fact-sheet

Underwood, J., Robertson, K. R., & Winston, A. (2015). Could antiretroviral neurotoxicity play a role in the pathogenesis of cognitive impairment in treated HIV disease? *AIDS*, *29*(3), 253–261. https://doi.org/10.1097/QAD.0000000000000538

de Vega, L., Effendy, E., & Camellia, V. (2019). Screening of mental disorders related CD4 count of people living with HIV/AIDS with anti-retroviral treatment in Medan, Indonesia. *Open Access Macedonian Journal of Medical Sciences*, *7*(16), 2647–2651. https://doi.org/10.3889/oamjms.2019.818

Venerosi, A., Cirulli, F., Capone, F., & Alleva, E. (2003). Prolonged perinatal AZT administration and early maternal separation: Effects on social and emotional behaviour of periadolescent mice. *Pharmacology, Biochemistry and Behavior*, *74*(3), 671–681. https://doi.org/10.1016/s0091-3057(02)01068-7

Venerosi, A., Cirulli, F., Lil'p, I. G., Fiore, M., Calamandrei, G., & Alleva, E. (2000). Prolonged perinatal exposure to AZT affects aggressive behaviour of adult CD-1 mice. *Psychopharmacology*, *150*(4), 404–411. https://doi.org/10.1007/s002130000455

Venerosi, A., Valanzano, A., Alleva, E., & Calamandrei, G. (2001). Prenatal exposure to anti-HIV drugs: Neurobehavioral effects of zidovudine (AZT) + lamivudine (3TC) treatment in mice. *Teratology*, *63*(1), 26–37. https://doi.org/10.1002/1096-9926(200101)63:1%3C26::AID-TERA1005%3E3.0.CO;2-G

Watts, D. H., Balasubramanian, R., Maupin, Jr., R. T., Delke, I., Dorenbaum, A., Fiore, S., Newell, M. L., Delfraissy, J. F., Gelber, R. D., Mofenson, L. M., Culnane, M., & Cunningham, C. K. (2004). Maternal toxicity and pregnancy complications in human immunodeficiency virus-infected women receiving antiretroviral therapy: PACTG 316. *American Journal of Obstetrics and Gynecology*, *190*(2), 506–516. https://doi.org/10.1016/j.ajog.2003.07.018

Williams, P. L., Hazra, R., Van Dyke, R. B., Yildirim, C., Crain, M. J., Seage, 3rd, G. R., Civitello, L., Ellis, A., Butler, L., & Rich, K. (2016). Antiretroviral exposure during pregnancy and adverse outcomes in HIV-exposed uninfected infants and children using a trigger-based design. *AIDS*, *30*(1), 133–144. https://doi.org/10.1097/QAD.0000000000000916

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