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Growth mixture modelling of HIV-exposed uninfected children under five in sub-Saharan Africa

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Abstract

Antiretroviral therapy scale-up has reduced vertical HIV transmission, expanding the population of HIV-exposed uninfected (HEU) children in sub-Saharan Africa. However, heterogeneity in their growth patterns and the influence of country context and maternal factors remain poorly understood. Longitudinal height-for-age (HAZ) and weight-for-age (WAZ) z-scores from HEU children (birth-60 months) in the multi-country PROMOTE cohort (Malawi, South Africa, Uganda, Zimbabwe) were derived. Growth mixture modelling with fractional polynomials was implemented using the Bolck-Croon-Hagenaars (BCH) method, incorporating country as a predictor, and maternal and household factors were examined in weighted multinomial models. Three distinct growth trajectories were identified for HAZ: severe stunting, 43.9%; mild-to-moderate, 39.9%; and adequate, 16.2%; and for WAZ: severe underweight, 23.6%; stable mild, 68.2%; and recovery, 8.1%. Moderate entropy (HAZ = 0.555; WAZ = 0.538) supported BCH weighting. Compared with Malawian children, South African children had significantly lower odds of severe underweight (aOR 0.57, 95% CI 0.37-0.88) and higher odds of being in the WAZ recovery trajectory (aOR 4.96, 95% CI 1.89-13.01). In multivariable analyses, private access to a flush toilet, maternal formal employment, and household electricity were associated with more favourable growth trajectories. Compared with PI-based regimens closer to delivery, EFV/NVP-based (aOR 0.44, 95% CI 0.27-0.73) and DTG-based (aOR 0.52, 95% CI 0.33-0.84) were associated with lower odds of mild-to-moderate stunting relative to adequate growth. Among HEU children, growth trajectories were more consistently associated with household infrastructure and country context than with maternal HIV disease severity. However, ART regimen type showed notable associations with growth trajectory membership, though these findings require confirmation in future research. These findings support the integration of social and structural interventions alongside ART programmes.

Keywords: HIV-exposed uninfected children, Growth mixture modelling, Growth trajectories, Sub-Saharan Africa, Child growth, Antiretroviral therapy

1. Introduction

The remarkable success of global antiretroviral therapy (ART) programmes has transformed maternal health, reducing vertical HIV transmission to under 5% in many settings and driving a rapid expansion in the population of HIV-exposed uninfected (HEU) children.[21] In sub-Saharan Africa, where over 15 million women of reproductive age live with HIV, this has

created a large and vulnerable paediatric cohort.[19] However, this public health achievement has unveiled a significant secondary concern: systematic reviews indicate HEU children experience a 30-50% higher risk of stunting and a 60-80% higher risk of wasting compared to their HIV-unexposed, uninfected peers, even in the context of universal maternal ART.[8, 10] These growth deficits threaten long-term health, cognitive development, and human capital potential.

The underlying cause of these growth impairments is complex and multifactorial, representing a dynamic interaction between biological exposures and structural determinants.[4,5] While ART regimens may play a contributory role, evidence from Eastern and Southern Africa underscores that stunting and wasting among HEU children remain strongly shaped by poverty, food insecurity, and limited access to healthcare.[4,5] This results in marked geographic heterogeneity; studies report median height-for-age z-score (HAZ) deficits ranging from -0.5 in some cohorts to -1.5 or more in others.[8,10] Conventional statistical approaches, which assume population homogeneity and estimate average effects, cannot capture this inherent heterogeneity and the distinct developmental pathways that may exist within the HEU population.[6]

To address this methodological and conceptual gap, this study employs growth mixture modelling (GMM), which identifies unobserved subgroups of children who follow particular growth patterns over time, rather than assuming all HEU children share a single, average trajectory.[7, 20] GMM moves beyond analysing population averages to identify unobserved subgroups (latent classes) that follow distinct developmental trajectories. Although GMM has been successfully applied in related fields such as nutrition and behavioral development[14], its use in studying HEU child growth patterns remains unexplored. This analytical advancement is critical for moving from a blanket understanding of HEU risks to a precise mapping of diverse growth experiences and their unique determinants.

Drawing on data from the multinational PROMOTE cohort across Uganda, Malawi, South Africa, and Zimbabwe, this study has two primary objectives: (1) to identify latent trajectories of height -for-age (HAZ) and weight-for-age (WAZ) z-scores among HEU children from birth through early childhood, and (2) to examine how maternal health indicators (e.g., viral load, ART regimen, CD4 count), socio-demographic characteristics, and crucially, geographic country context, predict membership in these distinct growth classes. By employing the Bolck-Croon-Hagenaars (BCH) method.[3, 9, 10], we directly model the country as a predictor of class membership, thereby formally integrating geographic variation into our analysis of heterogeneous growth patterns. To our knowledge, this is the first study to apply GMM to anthropometric data from a multi-country African cohort of HEU children. By clarifying these divergent growth pathways and their key drivers, our findings aim to provide a nuanced evidence base to inform targeted, context-specific interventions for this rapidly expanding and vulnerable population.

2. Materials and methods

2.1. Data description

PROMOTE (PROMise Ongoing Treatment Evaluation) is a PEPFAR-funded multi-country prospective observational cohort study designed to evaluate the long-term safety, adherence, and effectiveness of lifelong ART among HIV-infected pregnant and postpartum women and their HIV-exposed uninfected (HEU) children in sub-Saharan Africa.[15] The study extends follow-up of participants who were originally enrolled in the PROMISE (Promoting Maternal

and Infant Survival Everywhere) multi-country randomized trial (IMPAACT 1077BF/1077FF), which evaluated prevention of mother-to-child transmission (PMTCT) strategies for women with high CD4 counts.[1, 15] The PROMOTE study was conducted at eight research sites across four countries: Malawi (Blantyre and Lilongwe), South Africa (Soweto-Johannesburg and Umlazi-Durban), Uganda (MUJHU-Kampala), and Zimbabwe (Harare, Seke North, and St. Mary's).[16]

Enrollment into the PROMOTE study occurred between December 2016 and June 2017, following the termination and close-out of the PROMISE trial in 2015.[15, 16] Follow-up was planned to continue through 2021, providing approximately five years of extended follow-up [15, 16] A total of 1,987 HIV-infected mothers and 1784 children from the PROMISE trial were. enrolled into PROMOTE.[16] Additionally, children born during the PROMOTE follow-up period from subsequent (repeat) pregnancies were enrolled and followed with their mothers. [15] For the current analysis, 598 mothers who gave birth to 736 children during the study period were included. Data are presented for all deliveries during the study period, with maternal characteristics reported at each delivery or at the time of first enrolment.

Retention remained high throughout the 42-month follow-up period, at 89% for mothers and 85% for children, with visit completion rates exceeding 86%.[15, 16] The study design, baseline characteristics, and longitudinal data are reported elsewhere [15, 16]. At baseline, 97.8% of women reported currently using ART, and viral suppression at delivery was high (98.5% with viral load ≤40 copies/mL), reflecting high adherence to ART.[16] The median CD4 count at enrolment was 837 cells/µL (IQR 652–1045), and most women (96.4%) were in WHO clinical stage 1 or 2.[16]

The inclusion of Uganda, where HIV subtypes A and D predominate, alongside Southern African sites with subtype C, enables assessment of outcome generalizability across viral subtypes and ART contexts.[16] Women received country-standard ART regimens per national guidelines, with ART supplied as the prevailing standard of care in each country (efavirenz-based regimens in Malawi, Zimbabwe, and South Africa; protease inhibitor-based regimens in Uganda).[15, 16] The study provided laboratory testing and clinical management at no cost. Children found to be HIV-infected were started on ART per national guidelines, and mothers received counselling on adherence and health issues throughout the study.[15, 16] Further details on study procedures and ethical approvals have been published elsewhere. [16]

The PROMOTE study received ethical approval from all relevant institutional review boards (IRBs) and ethics committees in the U.S. and at collaborating sites in Uganda, Malawi, Zimbabwe, and South Africa.[16] Specifically, approval was obtained from: the Johns Hopkins University Institutional Review Board (Baltimore, MD, USA); the University of North Carolina at Chapel Hill Institutional Review Board (Chapel Hill, NC, USA); the Joint Clinical Research Centre IRB (Kampala, Uganda); the Uganda National Council for Science and Technology (Kampala, Uganda); the College of Medicine Research and Ethics Committee (Blantyre, Malawi); the National Health Sciences Research Committee (Lilongwe, Malawi); the Medical Research Council of Zimbabwe (Harare, Zimbabwe); the University of the Witwatersrand Human Research Ethics Committee (Johannesburg, South Africa); the University of KwaZulu-Natal Biomedical Research Ethics Committee (Durban, South Africa); and the South African Medical Research Council Ethics Committee (Cape Town, South Africa).[16] All women provided written informed consent to enroll and be followed with their children.[15, 16] All research was conducted in accordance with the ethical principles of the

Declaration of Helsinki and Good Clinical Practice guidelines. All methods were performed in accordance with the relevant guidelines and regulations.

2.2 Study variables

2.2.1. Outcome variable

Anthropometric measures such as HAZ, reflecting linear growth (stunting risk), and WAZ, reflecting weight gain (underweight risk), both serve as primary outcomes across the 0-60 month follow-up period. HAZ and WAZ were calculated using the World Health Organization (WHO) child growth standards (WHO SAS macro). Biologically implausible values, defined as HAZ <-4 or > 4 and WAZ <-4 or > 4, were excluded. The final analytic sample included all 736 children with at least one post-birth anthropometric measurement.

2.2.2. Explanatory variables

Maternal socio-demographic, clinical, and household characteristics that may influence child growth trajectories were collected at maternal study enrolment and treated as time-fixed covariates in subsequent latent class membership models. Maternal age was recorded in years. Maternal education level was categorized as no formal education, incomplete primary education, completed primary education, incomplete secondary education, completed secondary education, and college/university education. Marital status was classified as divorced, separated, widowed, married, no regular partner, or having a primary regular partner. Household socio-economic and environmental indicators included access to electricity and tap water (yes/no), ownership of a house or family home (yes/no), and travel time to the clinic (<30 minutes, 30-60 minutes, and >60 minutes).

Maternal clinical characteristics included antiretroviral therapy (ART) regimen at delivery or within a 10-day postpartum window, categorized as dolutegravir-based, lopinavir/ritonavir-based, or EFV/NVP-based regimens. Viral load measured at delivery or within the same 10-day window was categorized as undetectable (≤40 copies/mL), 41-199 copies/mL, 200-1000 copies/mL, and >1000 copies/mL. Maternal CD4 cell count at delivery or within the 10-day window was categorized as <350 cells/µL, 350-499 cells/µL, and ≥500 cells/µL. Maternal body mass index (BMI) was classified according to WHO categories: <18.5 kg/m², 18.5-24.9 kg/m², 25.0-29.9 kg/m², and ≥30 kg/m².

2.3 Statistical model

All analyses were performed using R version 4.3.0 (R Foundation for Statistical Computing) with the LCMM package version 1.9.5.

If we let t denote child age in months, and define the fractional polynomial terms as:

$$g_1(t) = t, \quad (1)$$
$$g_2(t) = \log(t+1), \quad (2)$$
$$g_3(t) = \frac{1}{t+1}, \quad (3)$$
$$g_4(t) = t^2, \quad (4)$$

The optimal number of latent classes was determined by comparing fit statistics (BIC, AIC, entropy), with the 3-class solution emerging as the best-fitting model.

For child i in latent class $k \in \{1,2,3\}$ at time t, the growth trajectory is modelled as:

$$Y_{itk} = \beta_{0k} + \beta_{1k}g_1(t) + \beta_{2k}g_2(t) + \beta_{3k}g_3(t) + \beta_{4k}g_4(t) + b_{0i} + b_{1i}g_1(t) + \epsilon_{itk}, \quad (5)$$

where:

- Y_{itk} is the growth outcome for child i at age t, within latent class k. This is the dependent variable representing the child's growth measurement at a specific time point.
- β_{0k} is the intercept for latent class k. It represents the baseline level of growth for children in class k, before considering the effects of age-related terms.
- β_{1k} is the coefficient for the age term $g_1(t) = t$, representing the linear effect of age (in months) on the growth outcome in latent class k. This captures how growth changes with the child's age.
- β_{2k} is the coefficient for $g_2(t) = \log(t + 1)$, capturing the logarithmic effect of age on growth in latent class k. This allows for diminishing returns, where growth slows as the child gets older.
- β_{3k} is the coefficient for $g_3(t) = \frac{1}{t+1}$, modeling an inverse effect of age on growth in latent class k. This term captures how the z-scores may decline as the child ages, reflecting slower growth relative to age-specific WHO standards rather than a reduction in absolute height.
- β_{4k} is the coefficient for $g_4(t) = t^2$, captures curvilinear acceleration or deceleration in growth with age in class k; a negative coefficient indicates growth decelerates over time, a positive coefficient indicates acceleration.
- b_{0i} is the random intercept for the child i, allow each child's trajectory to deviate from the class average, accounting for unmeasured individual characteristics. It is assumed to follow a normal distribution with a mean of 0 and a variance φ_{00}, reflecting variability in baseline growth across children.
- b_{1i} is the random slope for child i associated with age ($g_1(t) = t$), capturing the Individual-to-individual variability in growth rate. This term accounts for differences in how each child's growth trajectory evolves. Like the random intercept, it is assumed to follow a normal distribution with mean 0 and variance φ_{11}.
- $\epsilon_{itk} \sim N(0, \sigma_k^2)$, representing the residual error term with variance σ_k^2 specific to class k.

2.3.1 Latent class growth and growth mixture model specification and selection

To determine the optimal number of classes (K) and the functional form of age, we first estimated latent class growth models (LCGMs), following established recommendations for trajectory modelling in longitudinal studies. In this initial stage, the country was included as the only predictor of class membership.[11, 17, 20]

Based on the selected LCGM, the model was extended to a growth mixture model (GMM) by introducing within-class random effects, allowing individual trajectories to vary around the class-specific mean trajectory. [20]

Four alternative random-effects specifications were compared:

Model 1: Diagonal random-effects, common residual variance (homogenous):

$$\varphi = \begin{pmatrix} \varphi_{00} & 0 \\ 0 & \varphi_{11} \end{pmatrix},\ \sigma_k^2 = \sigma^2\ \forall_k. \qquad (6)$$

Assumes independent intercept and slope with identical residual variance across all latent classes

Model 2: Diagonal random-effects, class-specific residual variances (heterogeneous):

$$\varphi = \begin{pmatrix} \varphi_{00} & 0 \\ 0 & \varphi_{11} \end{pmatrix},\ \sigma_k^2 \text{ free by class} \qquad (7)$$

Assumes independent intercepts and slopes but allows different noise levels across latent classes.

Model 3: Unstructured random-effects, common residual variance:

$$\varphi = \begin{pmatrix} \varphi_{00} & \varphi_{01} \\ \varphi_{01} & \varphi_{11} \end{pmatrix},\ \sigma_k^2 = \sigma^2\ \forall_k \qquad (8)$$

Allows for correlated intercept and slope but assumes a common residual variance across latent classes.

Model 4: Unstructured random-effects, class-specific residual variances:

$$\varphi_k = \begin{pmatrix} \varphi_{00,k} & \varphi_{01,k} \\ \varphi_{01,k} & \varphi_{11,k} \end{pmatrix},\ \sigma_k^2 \text{ free by class} \qquad (9)$$

The most flexible specification, allowing both correlated intercept and slope, as well as class-specific residual variances.

Model selection was guided by AIC, BIC, entropy, minimum class size, and posterior classification probabilities, in accordance with the GRoLTS (Guidelines for Reporting on Latent Trajectory Studies) checklist to ensure transparent and comprehensive reporting of our trajectory analyses.[17] The Bolck-Croon-Hagenaars (BCH) three-step method was employed to investigate associations between latent growth trajectories and maternal characteristics while accounting for classification uncertainty.[3] First, a latent class model was fitted to repeated anthropometric measures that run concurrently with the class membership model, with country as the only predictor of latent class membership. Second, a classification error matrix was derived. Third, these weights were incorporated into a weighted multinomial regression model examining associations between latent class membership and maternal and sociodemographic factors. Variables that were not statistically associated with class membership in the bivariate analyses (Table S2) were excluded from the final multivariable model to preserve degrees of

freedom and reduce the risk of model overfitting. We selected Model 4 for HAZ and Model 3 for WAZ because they provided the lowest AIC and BIC and the highest entropy. The models offers the most flexible and realistic representation of the data, allowing correlated intercepts and slopes and acknowledging that the degree of individual variation around the mean trajectory may differ across latent classes (Table S3).

2 Results

Table 1. Maternal socio-demographic, clinical, and household characteristics at delivery and child growth indicators by country (Uganda, Malawi, Zimbabwe, and South Africa).

Variable	Uganda	Malawi	Zimbabwe	South Africa	Total
Maternal Characteristics					
Maternal characteristics, n	**117**	**234**	**172**	**75**	**598**
Maternal age years, Mean (SD)	31.44 (5.43)	31.57 (5.13)	32.75 (5.44)	32.51 (5.46)	32.32 (5.35)
Highest level of education*, n (%)					
No schooling	4 (3.4%)	20 (8.6%)	0	0	24 (4.0%)
Primary – partially completed	11 (9.4%)	33 (14.1%)	12 (7.0%)	1 (1.3%)	57 (9.5%)
Primary completed	33 (28.2%)	78 (33.3%)	8 (4.7%)	3 (4.0%)	122 (20.4%)
Secondary – partially completed	51 (43.6%)	70 (29.9%)	57 (33.1%)	38 (50.7%)	216 (36.1%)
Secondary completed	10 (8.6%)	27 (11.5%)	95 (55.2%)	22 (29.3%)	154 (25.8%)
College/University	8 (6.8%)	6 (2.6%)	0	11 (14.7%)	25 (4.2%)
Working status*, n (%)					
Not employed/housewife	45 (38.5%)	130 (55.6%)	85 (49.4%)	51 (68.0%)	311 (52.0%)
Self-employed (small business)	46 (39.3%)	76 (32.5%)	70 (40.7%)	3 (4.0%)	195 (32.6%)
Formal employed	26 (22.2%)	28 (12.0%)	17 (9.9%)	21 (28.0%)	92 (15.4%)

Variable	Uganda	Malawi	Zimbabwe	South Africa	Total
Owns or family owns a house	39 (33.4%)	99 (42.3%)	73 (42.4%)	59 (78.7%)	270 (45.2%)
Marital status*, n (%)					
No regular partner	7 (6.0%)	2 (0.9%)	3 (1.7%)	10 (13.3%)	22 (3.7%)
Primary regular partner	42 (35.9%)	3 (1.3%)	8 (4.7%)	55 (73.3%)	108 (18.1%)
Married	60 (51.3%)	195 (83.3%)	147 (85.5%)	9 (12.0%)	411 (68.7%)
Separated	8 (6.8%)	5 (2.1%)	6 (3.5%)	1 (1.3%)	20 (3.3%)
Divorced	0	11 (4.7%)	2 (1.2%)	0	13 (2.2%)
Widowed	0	18 (7.7%)	6 (3.5%)	0	24 (4.0%)
Electricity on the premises	93 (79.5%)	126 (53.9%)	102 (59.3%)	74 (98.7%)	395 (66.1%)
Tap water in the premises	44 (37.6%)	144 (61.5%)	98 (57.0%)	74 (98.9%)	360 (60.2%)
Type of toilet in the premises*, n (%)					
No toilet (open defecation)	3 (2.6%)	1 (0.5%)	2 (1.2%)	0	4 (0.7%)
Other	0	0	5 (2.9%)	0	5 (0.9%)
Pit latrine	102 (87.9%)	182 (94.3%)	34 (19.8%)	9 (12.0%)	327 (58.7%)
Private flush toilet	3 (2.6%)	6 (3.1%)	39 (22.7%)	48 (64.0%)	96 (17.2%)
Shared flush toilet	10 (8.6%)	4 (2.1%)	92 (53.5%)	18 (24.0%)	124 (22.3%)
Travel time from home to clinic, minutes*, n (%)					
< 30	4 (3.4%)	16 (6.8%)	79 (45.9%)	28 (37.3%)	127 (21.2%)
30–60	43 (36.8%)	123 (52.6%)	62 (36.1%)	32 (42.7%)	260 (43.5%)

Variable	Uganda	Malawi	Zimbabwe	South Africa	Total
> 60	70 (59.8%)	95 (40.6%)	31 (18.0%)	15 (20.0%)	211 (35.3%)
Clinical indicators (denominator is number of children)	**147**	**279**	**205**	**105**	**736**
Duration of last ARTs used from pregnancy to delivery, months [a], n (%)					
< 1	6 (4.1%)	10 (3.6%)	12 (5.9%)	0	28 (3.8%)
1 to <3	22 (15.0%)	7 (2.5%)	14 (6.8%)	0	43 (5.8%)
3 to <6	36 (24.5%)	15 (5.4%)	7 (3.4%)	0	58 (7.9%)
6 to 9	83 (56.4%)	247 (88.5%)	172 (83.9%)	105 (100%)	607 (82.5%)
BMI at delivery or at 10-day window period, kg/m^2 [a] n (%)					
Underweight (<18.5)	37 (25.4%)	42 (15.0%)	40 (19.3%)	44 (41.9%)	163 (22.1%)
Normal weight (18.5-24.9)	68 (46.5%)	163 (58.4%)	114 (55.9%)	37 (35.0%)	382 (52.0%)
Overweight (25-29.9)	42 (28.2%)	74 (26.6%)	51 (24.8%)	24 (22.9%)	191 (25.9%)
Viral load at delivery or at 10-day window period, copies/mL [a], n (%)					
Undetectable (≤40)	140 (97.9%)	271 (98.5%)	203 (98.5%)	104 (99.0%)	718 (98.5%)
Low (41-199)	2 (1.4%)	3 (1.1%)	2 (1.0%)	0	7 (1.0%)
High (200-1000)	1 (0.7%)	1 (0.4%)	1 (0.5%)	1 (1.0%)	4 (0.5%)
Very High (>1000)	4 (2.7%)	6 (2.1%)	1 (0.5%)	0	11 (1.5%)
ART regimen at delivery or at 10-day window period, n (%)					

Variable	Uganda	Malawi	Zimbabwe	South Africa	Total
DTG-based	110 (74.8%)	222 (79.6%)	159 (77.6%)	8 (7.6%)	499 (67.8%)
EFV/NVP-based	18 (12.2%)	56 (20.1%)	38 (18.5%)	95 (90.5%)	207 (28.0%)
LPV/r, ATV/r, RTV based	19 (12.9%)	1 (0.4%)	8 (3.9%)	2 (1.9%)	30 (4.1%)
CD4 count at delivery or at 10-day window period, cells/µL, Median (IQR)	960.5 (714-1132)	773 (577-934)	898 (710-1090)	796 (617-943.5)	837 (652–1045)
Children's characteristics, n	**147**	**279**	**205**	**105**	**736**
Child gender, Male, n (%)	70 (47.4%)	128 (45.8%)	97 (47.4%)	57 (57.4%)	352 (47.8%)
Childbirth weight (kg), n (%)					
< 2.5	6 (3.8%)	5 (1.9%)	9 (4.6%)	5 (4.7%)	25 (3.4%)
2.5-4.0	128 (87.2%)	256 (91.6%)	188 (91.7%)	100 (95.3%)	671 (91.2%)
> 4.0	13 (9.0%)	18 (6.5%)	8 (3.7%)	0	39 (5.3%)
Length/height-for-age at delivery, n (%)					
Mean z-score	0.11	0.07	0.39	−0.10	0.14
SD for z-score	1.56	1.57	1.31	1.36	1.49
Proportion below 2 SD	9 (7.6%)	14 (6.4%)	7 (4.8%)	5 (7.7%)	35 (6.4%)
Proportion below 3 SD	3 (2.5%)	6 (2.7%)	1 (0.7%)	0	10 (1.8%)
Weight-for-age at delivery, n (%)					
Mean z-score	0.17	−0.07	−0.43	−0.22	−0.13
SD for z-score	1.23	1.09	1.00	0.97	1.10
Proportion below 2 SD	6 (5.0%)	7 (3.2%)	7 (4.8%)	2 (3.1%)	22 (4.0%)
Proportion below 3 SD	2 (1.7%)	1 (0.5%)	2 (1.4%)	1 (1.5%)	6 (1.1%)

SD = Standard Deviation; IQR = Interquartile Range; ART = Antiretroviral Therapy; DTG = Dolutegravir; EFV = Efavirenz; NVP = Nevirapine; LPV/r = Lopinavir/ritonavir; ATV/r = Atazanavir/ritonavir; RTV = Ritonavir; BMI = Body Mass Index.

Table 1 presents the baseline characteristics of 598 mothers living with HIV and their 736 HEU children across Uganda, Malawi, Zimbabwe, and South Africa. Descriptive differences in maternal socio-demographic and household characteristics were observed across countries, reflecting the heterogeneity of the study populations. Women in Zimbabwe and South Africa generally had higher educational attainment, while unemployment was most common in South Africa (68.0%) and Malawi (55.6%). Household living conditions were most favourable in South Africa, with the highest rates of access to electricity (98.7%), piped water (98.9%), and flush toilets (88.0%). Travel times to clinics were longest in Uganda, where 59.8% of women reported journeys exceeding 60 minutes. Maternal clinical profiles were generally favourable. Most pregnancies (82.5%) had a duration of last ART usage from pregnancy to delivery of 6 to 9 months, though this proportion ranged from 56.4% to 100% across subgroups. Viral suppression at delivery was high across countries (> 98.5% at ≤40 copies/mL). Median CD4 count was 837 cells/µL (IQR 652–1045). DTG-based regimens predominated overall (67.9%), although EFV/NVP-based regimens remained common in South Africa (90.4%). Among 736 children, 47.7% were male. Low birth weight (<2.5 kg) was uncommon (3.4%), and most infants (91.1%) had normal birth weight. Mean HAZ and WAZ at birth were close to the WHO reference population, with low prevalence of stunting (HAZ <-2 SD: 6.4%) and underweight (WAZ <-2 SD: 4.0%), indicating generally favourable growth status at birth across all countries. Entropy values for the selected three-class models were 0.555 for HAZ and 0.538 for WAZ (Table S5), indicating moderate classification certainty. The BCH three-step approach was used in all subsequent covariate analyses to mitigate bias from this uncertainty.

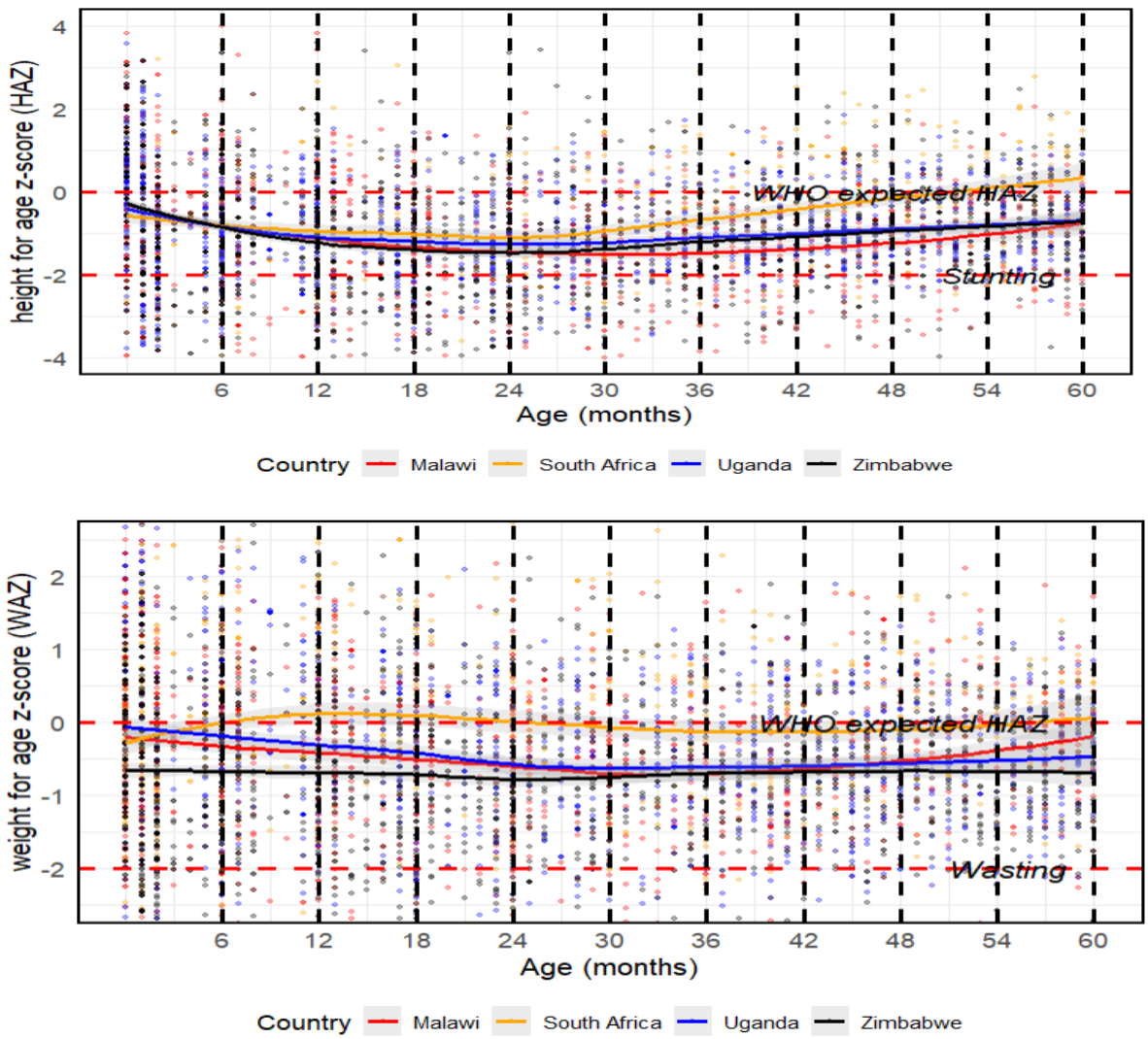

Fig. 1. Country-specific smoothed trajectories for height-for-age (HAZ; top) and weight-for-age (WAZ; bottom) from birth to 60 months.
Solid coloured curves represent country-level smooths with 95% uncertainty bands (shaded). Horizontal dashed lines mark 0 SD (WHO median) and -2 SD (stunting/underweight).

Across all four countries, mean HAZ trajectories remained below the WHO reference median (HAZ = 0) throughout follow-up and approached the stunting threshold (HAZ = -2) during early childhood (Figure 1). HAZ declined rapidly during the first 12-24 months, reaching its lowest levels between approximately 18 and 30 months, then gradually recovered. South Africa demonstrated the most favourable HAZ trajectory, with recovery toward the WHO median after 30 months, whereas Malawi and Uganda exhibited persistently lower HAZ values throughout the follow-up period. Zimbabwe showed an intermediate pattern. Despite some improvement with age, average HAZ remained below the WHO reference in all countries by 60 months, indicating sustained linear growth deficits. For WAZ, mean trajectories were generally closer to the WHO reference median and remained well above the underweight threshold (WAZ = -2) throughout follow-up. WAZ declined modestly during the first two years of life, followed by stabilisation and slight improvement after approximately 30 months. South Africa consistently exhibited the highest WAZ values, while Zimbabwe showed the lowest trajectory during early and mid-childhood. Differences between countries were less pronounced for WAZ than for HAZ.

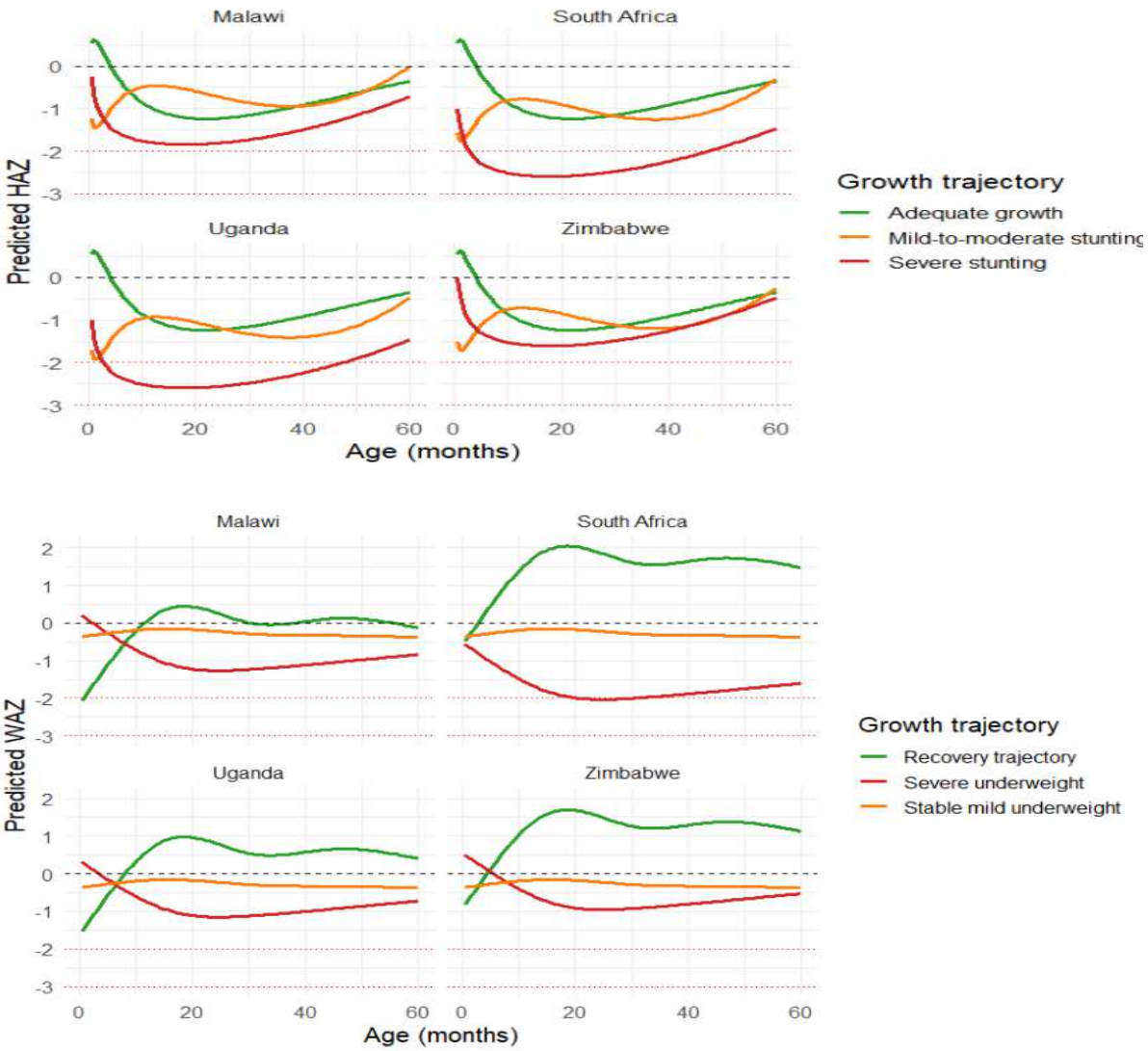

Fig. 2. Country-specific height-for-age (HAZ) and weight-for-age (WAZ) growth trajectory classes identified using growth mixture modelling. *The upper panels display predicted mean HAZ trajectories, and the lower panels display predicted mean WAZ trajectories.*

Figure 2 shows that for HAZ, a clear gradient is observed across classes: severe stunting remains below -2 SD throughout childhood, mild-to-moderate stunting shows partial recovery, and adequate growth approaches -1 to 0 SD after 24 months. South Africa shows the greatest separation between trajectory classes, while Malawi and Zimbabwe display more convergence at later ages. For WAZ, trajectories are more divergent over time. The recovery class shows substantial improvement toward normal z-scores, whereas severe underweight remains persistently low with minimal catch-up. The stable mild underweight class remains consistently below zero across childhood.

Table 2. Association between country and trajectory class membership (reference country: Malawi; reference trajectory: Adequate HAZ growth and stable mild underweight WAZ)

	Height for age z-score (ref: Adequate growth)				**Weight for age z-score (Stable mild underweight)**			
Predictor	**Severe stunting OR (95% CI)**	**p-value**	**Mild-to-moderate stunting OR (95% CI)**	**p-value**	**Recovery OR (95% CI)**	**p-value**	**Stable mild underweight OR (95% CI)**	**p-value**
Ref: Malawi	-	-	-	-	-	-	-	-
South Africa	0.73 (0.33-1.60)	0.441	0.47 (0.18-1.24)	0.131	0.57 (0.37-0.88)	0.017	4.96 (1.89-13.01)	0.001
Uganda	0.63 (0.32-1.25)	0.188	0.47 (0.19-1.18)	0.108	1.12 (0.65-1.93)	0.506	1.71 (0.63-4.64)	0.296
Zimbabwe	0.78 (0.39-1.56)	0.473	1.27 (0.60-2.66)	0.532	1.34 (0.82-2.30)	0.233	3.51 (1.45-8.52)	0.005

Table 2 presents that compared with Malawi, HEU children from South Africa had significantly lower odds of belonging to the severe underweight trajectory (OR 0.57, 95% CI 0.37-0.88; p=0.017), whereas children from South Africa and Zimbabwe had significantly higher odds of belonging to the recovery trajectory (South Africa: OR 4.96, 95% CI 1.89-13.01; Zimbabwe: OR 3.51, 95% CI 1.45-8.52). No significant country differences were observed for severe or mild-to-moderate stunting trajectories.

Table 3

Multivariable multinomial logistic regression of maternal socio-demographic, household, and treatment factors associated with child height-for-age (HAZ) and weight-for-age (WAZ) trajectory class membership, using persistent severe stunting as the reference trajectory

	Height for age z-score (Ref: Adequate growth)			
Predictor	**Severe stunting aOR (95% CI)**	**p-value**	**Mild-to-moderate stunting aOR (95% CI)**	**p-value**
Mother's level of education (Ref: Basic education)				
Higher education	1.14 (0.92-1.41)	0.232	1.26 (1.00-1.57)	0.046
Marital status (Ref: Has partner)				
Married	1.29 (1.01-1.63)	0.039	1.55 (1.20-1.99)	0.001

No partner	1.03 (0.75-1.42)	0.858	1.278 (0.92-1.78)	0.151
Employment status (Ref: Not employed)				
Formal employment	0.792 (0.624-1.004)	0.054	0.562 (0.436-0.723)	<0.001
Self-employed	1.199 (0.971-1.479)	0.091	0.948 (0.765-1.174)	0.624
Electricity in the premises (Ref: No)	1.186 (0.941-1.495)	0.149	0.757 (0.595-0.963)	0.023
Water in the premises (Ref: No)	0.919 (0.733-1.152)	0.462	0.958 (0.758-1.211)	0.719
Types of toilets in the premises (Ref: Other)				
Private flushed toilet	0.635 (0.483-0.834)	0.001	1.248 (0.948-1.642)	0.114
Shared flushed toilet	0.775 (0.604-0.994)	0.045	1.631 (1.271-2.092)	<0.001
CD4 count at delivery or at 10-day window period, cells/µL, n (%) (Ref: < 500)				
CD4 ≥500	1.361 (1.013-1.828)	0.041	1.167 (0.868-1.570)	0.306
BMI at delivery or at 10-day window period, kg/m^2 n (%) (Ref: < 18.5)				
BMI 18.5–24.9	1.724 (1.377-2.159)	<0.001	1.777 (1.407-2.244)	<0.001
BMI 25–29.9	1.063 (0.835-1.354)	0.619	1.224 (0.954-1.572)	0.112
Viral load at delivery or at 10-day window period, copies/mL, n (%) (Ref: Detected)				
Undetected	1.227 (0.937-1.607)	0.137	0.796 (0.614-1.034)	0.087
ART regimen at delivery or at 10-day window period, n (%) (Ref: PI-based)				
EFV/NVP-based	0.848 (0.508-1.416)	0.529	0.442 (0.268-0.727)	0.001
DTG-based	0.761 (0.468-1.237)	0.270	0.523 (0.327-0.836)	0.007
	Weight for age z-score (Ref: Recovery)			

Predictor	Severe underweight aOR (95% CI)	p-value	Stable mild underweight aOR (95% CI)	p-value
Mother's level of education (Ref: Basic education)				
Higher education	0.814 (0.618-1.072)	0.143	0.668 (0.517-0.864)	0.002
Employment status (Ref: Not employed)				
Formal employment	0.637 (0.484-0.840)	0.001	0.632 (0.494-0.809)	<0.001
Self-employed	0.746 (0.588-0.947)	0.016	0.673 (0.539-0.840)	<0.001
Electricity in the premises (Ref: No)	0.615 (0.466-0.813)	0.001	0.799 (0.615-1.037)	0.091
Water in the premises (Ref: No)	0.888 (0.678-1.165)	0.392	1.137 (0.883-1.464)	0.318
Types of toilets in the premises (Ref: Other)				
Private flushed toilet	0.795 (0.589-1.074)	0.134	0.559 (0.425-0.735)	<0.001
Shared flushed toilet	0.834 (0.636–1.094)	0.190	0.571 (0.445-0.733)	<0.001
ART regimen at delivery or at 10-day window period, n (%) (Ref: PI-based)				
EFV/NVP-based regimen	0.435 (0.245-0.773)	0.005	0.573 (0.336-0.979)	0.042
DTG-based regimen	0.750 (0.436-1.290)	0.298	0.661 (0.397-1.102)	0.112

*Note: other toilets on the premises include no toilet (open defecation), and pit latrine. Higher education includes secondary – partially completed, secondary completed, and college/university; basic education includes no schooling, primary - partially completed and primary compl*eted

Table 3 shows that for HAZ trajectories, higher maternal education was significantly associated with increased odds of mild-to-moderate stunting compared to adequate growth (aOR: 1.26, 95% CI: 1.00-1.57; p=0.046). Being married was significantly associated with higher odds of severe stunting (aOR: 1.29, 95% CI: 1.01-1.63; p=0.039) and mild-to-moderate stunting (aOR: 1.55, 95% CI: 1.20-1.99; p=0.001). Formal employment was significantly associated with reduced odds of mild-to-moderate stunting (aOR: 0.56, 95% CI: 0.44-0.72; p<0.001). Household electricity was significantly associated with reduced odds of mild-to-moderate stunting (aOR: 0.76, 95% CI: 0.60-0.96; p=0.023). Private flushed toilets were significantly associated with lower odds of severe stunting (aOR: 0.64, 95% CI: 0.48-0.83; p=0.001), while shared flushed toilets were associated with lower odds of severe stunting (aOR: 0.78, 95% CI: 0.60-0.99; p=0.045) but higher odds of mild-to-moderate stunting (aOR: 1.63, 95% CI: 1.27-2.09; p<0.001). Maternal BMI 18.5-24.9 kg/m² was significantly associated with increased odds of both severe stunting and mild-to-moderate stunting (both p<0.001). CD4 ≥500 cells/µL

was significantly associated with higher odds of severe stunting (aOR: 1.36, 95% CI: 1.01-1.83; p=0.041).

In bivariate analyses, EFV/NVP-based and DTG-based ART regimens were associated with lower odds of mild-to-moderate stunting compared with PI-based regimens. In multivariable analyses adjusting for maternal, household, and clinical factors, these associations remained significant: EFV/NVP-based regimens were associated with significantly lower odds of mild-to-moderate stunting compared with PI-based regimens (aOR 0.44, 95% CI 0.27-0.73; p=0.001), as were DTG-based regimens (aOR 0.52, 95% CI 0.33-0.84; p=0.007). For WAZ trajectories, EFV/NVP-based regimens were associated with significantly reduced odds of severe underweight (aOR 0.44, 95% CI 0.25-0.77; p=0.005) and stable mild underweight (aOR 0.57, 95% CI 0.34-0.98; p=0.042) compared to the recovery trajectory. DTG-based regimens showed no statistically significant associations with WAZ trajectory membership (severe underweight: aOR 0.75, 95% CI 0.44-1.29; p=0.298; stable mild underweight: aOR 0.66, 95% CI 0.40-1.10; p=0.112). However, these associations should be interpreted with caution given the observational design and potential confounding by treatment indication, as ART regimen allocation differed across countries and calendar periods.

For WAZ trajectories, compared to recovery, higher maternal education was significantly associated with reduced odds of stable mild underweight (aOR: 0.67, 95% CI: 0.52-0.86; p=0.002). Formal employment (aOR: 0.64, 95% CI: 0.48-0.84; p=0.001) and self-employment (aOR: 0.75, 95% CI: 0.59-0.95; p=0.016) were significantly associated with reduced odds of severe underweight. Household electricity was significantly associated with reduced odds of severe underweight (aOR: 0.62, 95% CI: 0.47-0.81; p=0.001). Private and shared flushed toilets were both significantly associated with lower odds of stable mild underweight (aOR: 0.56, 95% CI: 0.43-0.74; p<0.001 and aOR: 0.57, 95% CI: 0.45-0.73; p<0.001, respectively).

Discussion

To our knowledge, this is the first study to apply growth mixture modelling to longitudinal anthropometric data from HIV-exposed uninfected (HEU) children across four countries in sub-Saharan Africa. Three distinct latent trajectories were identified for both height-for-age (HAZ) and weight-for-age (WAZ), demonstrating substantial heterogeneity in growth patterns during the first five years of life. Although most children followed persistently suboptimal trajectories, only a small proportion experienced adequate linear growth or weight recovery. These findings extend previous studies, which have largely reported average growth differences among HEU children, by identifying clinically meaningful subgroups with distinct developmental pathways.[8, 9, 10, 12]

Country context emerged as an important determinant of weight growth trajectories. Compared with children in Malawi, children in South Africa had significantly lower odds of severe underweight and substantially higher odds of belonging to the recovery trajectory. In comparison, children from Zimbabwe also showed higher odds of recovery. These findings suggest that differences in socioeconomic development, health-system capacity, and household living conditions across countries contribute importantly to child nutritional outcomes. In contrast, no significant country differences were observed for HAZ trajectories, suggesting that chronic linear growth deficits may be influenced by early-life exposures common across these settings.[7, 18]

Household socioeconomic conditions were among the strongest predictors of favourable growth trajectories. Access to electricity, improved sanitation, and maternal formal employment were consistently associated with lower odds of adverse HAZ and WAZ trajectories. These findings support previous evidence that structural determinants, including household infrastructure and socioeconomic status, remain major drivers of child growth even in the era of widespread maternal antiretroviral therapy. Poor sanitation is known to increase the risk of recurrent enteric infections and environmental enteric dysfunction, both of which impair nutrient absorption and child growth.[2] Collectively, these findings suggest that improving household living conditions should complement HIV-specific interventions to optimize child growth outcomes.

Maternal HIV-related clinical characteristics were generally weaker predictors of trajectory membership than socioeconomic factors. Maternal viral suppression and CD4 count showed limited independent associations after multivariable adjustment, suggesting that successful ART programmes have reduced the influence of maternal HIV disease severity on child growth. Instead, persistent growth inequalities among HEU children appear to be driven predominantly by social and environmental factors rather than maternal HIV disease itself. These findings are consistent with recent studies showing that, despite universal maternal ART, HEU children continue to experience growth disadvantages associated with broader contextual factors.[4, 17]

Although EFV/NVP- and DTG-based regimens were associated with lower odds of adverse growth trajectories compared with PI-based regimens in our analyses (HAZ mild-to-moderate stunting: EFV/NVP-based aOR 0.44, 95% CI 0.27-0.73, p=0.001; DTG-based aOR 0.52, 95% CI 0.33-0.84, p=0.007), these associations should be interpreted with considerable caution given the observational design and potential confounding by treatment indication. ART regimen allocation differed substantially across countries and calendar periods, with PI-based regimens predominantly used in Uganda (where these regimens were standard of care) and EFV/NVP- and DTG-based regimens in Malawi, Zimbabwe, and South Africa. This systematic variation makes it difficult to disentangle regimen effects from country-level factors, including differences in healthcare quality, nutrition programs, socioeconomic development, and health system infrastructure. Residual confounding by unmeasured maternal, household, or health system characteristics cannot be excluded. Consequently, these associations should be considered hypothesis-generating rather than evidence of causal treatment effects.[1, 15] Future research, ideally employing randomized designs or large observational studies with comprehensive adjustment for baseline characteristics and treatment indications, is needed to confirm or refute these findings.

This study has several strengths, including its multinational longitudinal design, repeated anthropometric measurements over the first five years of life, and the application of growth mixture modelling with the BCH three-step approach to account for uncertainty in latent class assignment. Nevertheless, several limitations should be acknowledged.

First, the observational design precludes causal inference. While we adjusted for a range of potential confounders, the possibility of residual confounding cannot be excluded. This is particularly relevant for the ART regimen findings, where treatment allocation was not randomized and differed systematically by country and calendar period. Women receiving PI-based regimens were predominantly from Uganda, while those receiving EFV/NVP-based or DTG-based regimens were predominantly from other countries, making it difficult to

disentangle regimen effects from country-level factors such as healthcare quality, nutrition programs, and socioeconomic conditions.

Second, important determinants of child growth, including infant feeding practices (breastfeeding duration and exclusivity), dietary diversity, household food security, maternal mental health, and childhood morbidity (particularly diarrhoeal and respiratory infections), were unavailable and may have resulted in residual confounding. These factors are known to be strongly associated with child growth and may have confounded the observed associations.

Third, the study did not include a comparator group of HIV-unexposed uninfected (HUU) children, limiting our ability to determine the extent to which the observed growth trajectories were attributable specifically to HIV and antiretroviral exposure versus broader contextual factors common to the study settings. Without this comparison, we cannot quantify the excess risk attributable to HIV exposure per se.

Fourth, HAZ and WAZ were modelled separately rather than jointly, despite both outcomes occurring simultaneously within the same child. Joint modelling of these correlated longitudinal outcomes may better capture their interrelationship and provide a more comprehensive understanding of child growth patterns. Future research employing joint trajectory modelling could provide additional insights.

Fifth, the moderate entropy values (HAZ = 0.555; WAZ = 0.538) indicate some uncertainty in trajectory classification. While we used the BCH three-step method to mitigate bias from this uncertainty, some misclassification may remain, potentially attenuating associations with covariates. The use of BCH weighting, however, is considered a robust approach for handling classification uncertainty.[3]

Sixth, several covariates were treated as time-fixed at enrolment, although maternal health status, socioeconomic conditions, and ART regimens may change over the follow-up period. Time-varying covariates could provide more precise estimates of these associations, though our approach reflects the available data and is consistent with standard practice in trajectory modelling studies.

Seventh, the study was conducted at research sites with high retention rates and comprehensive clinical support, which may not be representative of routine programmatic settings in the same countries. The findings may therefore reflect outcomes under optimal conditions and may not generalise to settings with lower retention or less comprehensive support.

Finally, the relatively small number of children in some trajectory classes (e.g., WAZ recovery, 8.1%) limited statistical power for some subgroup analyses and may have resulted in imprecise estimates for certain covariate associations.

3 Conclusion

Distinct growth trajectories exist among HIV-exposed uninfected children during the first five years of life, with household socioeconomic conditions, country context, and ART regimen type all showing important associations with trajectory membership. These findings highlight the multifactorial nature of growth outcomes in this population and suggest that integrated interventions combining effective HIV care with improved living conditions and nutritional support may be needed to optimize child growth. However, given the observational design, the findings related to ART regimen require confirmation in future research. Growth mixture

modelling offers a valuable approach for identifying vulnerable subgroups and their associated determinants, which can inform targeted child health interventions. Future studies should incorporate comprehensive data on infant feeding, dietary diversity, and household food security, and ideally include HIV-unexposed comparator groups to better quantify the excess risk attributable to HIV exposure.

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Data Availability Statement*:* The data that support the findings of this study are available from the PROMOTE study investigators, but restrictions apply to the availability of these data, which were used under approval from the relevant institutional review boards for the current study. Data are not publicly available due to participant privacy and confidentiality protections.

De-identified data may be made available from the corresponding author upon reasonable request and with the appropriate ethical approvals and data use agreements. Requests for data access should be directed to the corresponding author, who will facilitate the request in accordance with study governance policies. The PROMOTE study baseline findings are available at https://doi.org/10.1371/journal.pone.0208805.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this manuscript, the authors used Notion AI to assist with planning and organizing the manuscript structure, Elicit AI to identify and retrieve relevant and up-to-date scientific literature, ChatGPT and Claude to assist with improving statistical analysis code and enhancing the clarity, organization, and flow of the manuscript, and DeepSeek to review the statistical analysis workflow and suggest alternative analytical approaches and code improvements. All AI-generated outputs and retrieved information were critically reviewed, verified against the sources where appropriate, and edited by the authors. The authors take full responsibility for the accuracy, integrity, and content of the published article.

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