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Global estimates of viral suppression in children/adolescents and adults on antiretroviral therapy adjusted for missing viral load measurements: a multi-regional study from 31 countries

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RESEARCH IN CONTEXT

Evidence before this study

To support "Undetectable=untransmittable (U=U)" and treatment-as-prevention strategies, accurate estimation of the third 95 target of UNAIDS's 95-95-95 is critical. While routine viral load (VL) testing is the standard of care in high-income countries, VL testing has been slow to expand in low- and middle-income countries (LMICs). We searched PubMed database on March 18, 2020, for studies published in English after December 31, 1999, using the terms "HIV", "viral suppression", "loss to follow-up", "tracing", "viral load", and "reconnected to care". We identified only one tracing study which integrated the viral suppression proportion among a random sample who were lost to follow-up (LFTU) from Zambia. The study found that the HIV viremia, defined by VL ≥1,000 copies/mL, was present in 18.1% (95% CI 14.0%-22.3%) of people living with HIV (PWH) in care, and 71.3% (95% CI 58.2%-84.4%) of individuals lost to follow up. After incorporating tracing outcomes and VL results among those who were LTFU and traced into the cohort, the study provided an overall prevalence of HIV viremia of 24.7% (95% CI 21.0%–29.3%).

Added value of this study

To our knowledge, this is the first study using multiregional HIV cohort databases to estimate the viral suppression proportions accounting for missing VL measurements of PWH both in and out of care. We found that 76% of children/adolescents and 90% of adults, who were in follow-up and had VL measurements were suppressed at 3 years after ART initiation. After adjusting for missing VL measurements among those who transferred, were lost to follow-up, or were in follow-up but with no VL testing, 9177 (59%) of 15,667 children/adolescents and 115,260 (65%) of 178,458 adults were virally suppressed at 3 years after ART initiation. The estimated proportions varied widely across regions from 37% to 83% in children/adolescents and from 21% to 90% in adults.

Implications of all the available evidence

Reports on viral suppression proportions that do not account VL for the sizeable proportion of LTFU PWH who are connected to care elsewhere and still receiving ART or VL estimates that do not account for PWH in care who are not tested are unlikely to reflect the actual proportion of virally suppressed among the PWH population who are accessing care. In the era of "U=U", strategies and increased efforts for better retention in care and more systematic routine VL testing could be helpful in estimating the actual suppressed population. Although adults with HIV are approaching the UNAID 95% target, progress among children/adolescents is slower and estimates are still behind the target.

SUMMARY

Background

As countries move towards the UNAIDS's 95-95-95 targets and with the strong evidence of "Undetectable=untransmittable," it is increasingly important to assess whether those receiving antiretroviral therapy (ART) achieve viral suppression. We estimated the proportions of viral suppression among children/adolescents and adults at 1, 2 and 3 years after initiating ART.

Methods

Seven regional cohorts from the International epidemiology Databases to Evaluate AIDS (IeDEA) consortium contributed data from individuals initiating ART between 2010 and 2019 at 148 sites in 31 countries with annual viral load (VL) monitoring. Data up to March 2020 were analyzed. We estimated the proportions of children/adolescents and adults with viral suppression (VL<1000 copies/mL) using an intention-to-treat (ITT)-like approach and an adjusted approach which accounted for missing VL measurements.

Findings

A total of 21,594 children/adolescents from 106 sites in 22 countries (55% female) and 255,662 adults from 143 sites in 30 countries (64% female) were included. Among those who were in follow-up and had VL testing, 4287 (76%) of 5641 children/adolescents and 57,970 (90%) of 64,487 adults were virally suppressed 3 years after ART initiation. In the ITT analyses, 4287 (24%) of 17,589 children/adolescents and 57,970 (29%) of 201,124 adults were virally suppressed 3 years after ART initiation. After adjusting for missing VL measurements among those who transferred, were lost to follow-up, or in follow-up without VL testing, 9177 (59%) of 15,667 children/adolescents and 115,260 (65%) of 178,458 adults were virally suppressed at 3 years following ART initiation. These estimates varied widely across IeDEA regions from 37% to 83% in children/adolescents and from 21% to 90% in adults.

Interpretation

While adults with HIV are approaching the global target of 95% viral suppression, progress among children/adolescents is much slower. Substantial efforts are still needed for reaching the viral suppression target for children/adolescents.

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Keywords: HIV, viral suppression, children, adults, viral load

Introduction

In 2020, an estimated 26 million people, or nearly 70% of all people living with HIV (PWH) worldwide, were receiving antiretroviral therapy (ART).[1] With increasing access to ART, the number of PWH receiving treatment is expected to continue to increase. Consistent adherence to an effective ART regimen suppresses viral load (VL) to undetectable levels, limits transmission, and improves health outcomes and associated health care costs.[2-4]

In 2013, the World Health Organization (WHO) recommended routine VL testing as the preferred way to improve monitoring and earlier identification of treatment failure.[5] The Joint United Nations Program on HIV/AIDS (UNAIDS) established the 95-95-95 targets with the goal of achieving viral suppression in 95% of all people taking ART by 2030.[6] To track progress, the goal has placed increased emphasis on the need for short- and long-term data on virologic outcomes. In 2016, WHO recommended to conduct VL testing at 6 and 12 months after ART initiation and then every 12 months thereafter if the person is stable on ART.[5] To support "Undetectable=untransmittable (U=U)" and treatment-as-prevention strategies, accurate estimation of the third 95 target is critical. While routine VL testing is the standard of care in high-income countries, VL testing has been slow to expand in low- and middle-income countries (LMICs).[7] Consequently, in settings that have only recently implemented VL testing for routine monitoring of PWH on ART, data on viral suppression are limited.[8-12]

The International epidemiology Databases to Evaluate AIDS (IeDEA) (https://www.iedea.org) is a global research network established in 2006 by the US National Institutes of Health. IeDEA merges and analyzes routinely collected data from large and diverse populations of PWH across seven international regions: Central Africa; East Africa; Southern Africa; West Africa; Asia-Pacific; Caribbean, Central and South America (CCASAnet); and North America (NA-ACCORD). In the present study, we analyzed data from IeDEA treatment sites that provided at least annual routine VL monitoring to estimate the proportions of children/adolescents and adults who achieved viral suppression at 1, 2, and 3 years after initiating ART.

Methods

Study population

Children/adolescents and adults with HIV who initiated ART between 2010 and 2019 at an IeDEA site with routine VL monitoring were eligible for inclusion in the analysis. Clinical management, selection of initial ART regimen, laboratory tests, or interventions were performed according to local guidelines. Routine VL monitoring was defined as at least 1 annual VL test per person as reported by each participating region. Only PWH who started ART after the time a site started routine VL monitoring were included. If no information was provided regarding VL testing frequency and its start date, we calculated the number of tests for each patient at each calendar year after ART start, and obtained the

median number of tests per site, per year. Sites were considered as having routine VL from the year when a median of at least one annual VL test per person was observed. Data from the subsequent calendar years were included irrespective of their median values. We excluded from the analyses PWH who were not ART-naïve at clinic enrolment, PWH who had less than 6 months of follow-up after the first visit, and those who did not have a known date of ART initiation. The final analysis database included data available up to March 2020. The date of database closure differed for each of the participating sites ranging between September 2012 and March 2020 (10% before 2017, 22% between 2017 and 2018, 68% between 2019 and 2020).

Ethics review

Primary data collection by all participating sites and the pooling of the data in collaborative analyses were approved by their respective ethics committees or institutional review boards. Each participating IeDEA region had separate ethics approvals to contribute data to this analysis. Consent requirements and procedures were determined by the local regulatory bodies, and adherence to those standards was the responsibility of each site.

Children/adolescents were defined as individuals <18 years of age and adults as those ≥18 years at ART initiation. The main endpoints analyzed were the unadjusted and adjusted proportions of children/adolescents and adults with viral suppression (i.e, VL <1000 copies/mL) at 1, 2, and 3 years after ART initiation. For VL, we selected the single closest value reported during a window of ±6 months from the specified time point, and then classified this measurement as suppressed or not suppressed. PWH were considered active at each time point if they had a clinic visit on the specified time point or later. Only active PWH were included in the numerator to examine the proportions with and without VL testing at year 1, year 2 and year 3. PWH without evidence of contact with the clinic for more than 6 months before site-specific closure dates were classified as lost to follow-up (LTFU), with their follow-up period ending at the date of last clinic visit.

For laboratory and clinical measurements at ART initiation, we used the measurement closest to ART start within a window of 6 months before and 1 week after ART start, with the pre-ART measurement used in the case of two measurements with the same number of days before and after the ART date. Severe HIV-associated immunodeficiency was defined according to WHO criteria as CD4% <25% (age <1 year), <20% (age 1 to <3 years), <15% (age 3 to 5 years), and <15% or <200 cells/mm^3 (age ≥5 years).[13] We calculated height-for-age z-score using the WHO 2006/2007 child growth standards[14] and weight-for-age z-score using the WHO 1977 standards[15].

Statistical methods

We conducted separate analyses for children/adolescents and adults. We used descriptive statistics to summarize patient characteristics at ART initiation, stratified by IeDEA region. We first used the intention-to-treat (ITT)-like approach to include all PWH started who ART with or without VL outcomes. Quantifying the viral suppression rates among all PWH who have started ART, including those with missing VL measurements due to LTFU or transfers, is an important indicator in HIV care programs, especially in the era of treatment-as-prevention or "U=U". Therefore, in our analysis, we calculated the proportions of PWH with VL <1000 copies/mL, VL ≥1000 copies/mL, no VL testing, and those who died, transferred, and LTFU. Proportions were plotted for each duration of ART (i.e., 1, 2, or 3 years after ART initiation). The proportions of PWH without VL testing were calculated by including in the numerator only those who were in follow-up but did not have a VL measurement. In this ITT analysis, PWH who died, transferred, or were classified as LTFU and those who were presumed to be in care but did not reach a specified time point, were censored at the time of last clinic visit. An inverse variance weighted meta-analysis of the proportions was conducted across regions to account for the differences between the sizes of the cohorts. Second, we determined the proportions of PWH with VL <1000 copies/mL only among those alive, in follow-up, and with VL assessed, for each duration of ART.

Third, we conducted an adjusted analysis to provide estimates of the overall proportions of PWH still alive (including those in follow-up without VL testing, transfers, and LTFU) and virally suppressed at 1, 2, and 3 years after ART initiation. For this analysis, we considered PWH in follow-up with no VL testing, and those transferred (after excluding the estimated deaths among transfers) as having equal proportions of virally suppressed individuals as those in care with VL testing. For plausible ranges, we applied to our data the lower and upper bounds for the proportion of viral suppression using the literature reporting on viral outcomes among PWH in care (supplementary Box 1; appendix pp 1-2). The common estimated plausible ranges of deaths among transfers, and viral suppression among transfers and those without VL testing, were used for all four African regions.

For LTFU, the proportions of PWH who died, and of PWH who were still alive and reconnected to care were extracted from the tracing studies reporting on LTFU outcomes,[16-18] and we applied these proportions to our LTFU population. We then estimated the proportion of PWH who were virally suppressed (including plausible ranges) among those alive and reconnected to care (i.e., unofficial transfers) among LTFU using the data reported from a study assessing viral suppression in a large population of LTFU PWH in Zambia.[18] The same estimated viral suppression proportion (and plausible ranges) were applied to both children/adolescents and adults in all regions. In this way, we estimated the overall proportions of PWH alive and virally suppressed at 1, 2, and 3 years after ART initiation. The steps taken in the adjusted analysis are provided in supplementary box 1, appendix pp 1-2.

Sensitivity analyses varying the common estimate of viral suppression among PWH re-connected to care are provided in the supplementary figures S1 and S2 (appendix pp 19-20).

Multiregional data were managed and analyzed by the Kirby Institute, UNSW Sydney, using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata (StataCorp, STATA 14.0 for Windows, College Station, TX, USA).

Role of the Funding Source

The study funders had no role in design of the study, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the study data and final responsibility for the decision to submit for publication.

Results

A total of 21,594 children/adolescents (55% female) were included from 106 sites in 22 countries across six IeDEA regions: Asia-Pacific (n=1500, 6.9%; 14 sites in 5 countries), CCASAnet (n=245, 1.1%; 9 sites in 5 countries), Central Africa (n=182, 0.8%; 10 sites in 1 country), East Africa (n=6032, 28%; 51 sites in 3 countries), Southern Africa (n=11,455, 53%; 14 sites in 3 countries), and West Africa (n=2180, 10%; 8 sites in 5 countries); 69% of sites were urban or semiurban clinics and 40% were located within regional, provincial, or university hospitals. The median age of children/adolescents at ART initiation was 6.2 (interquartile range [IQR], 1.7-11.8) years (table 1). Overall, 4777 (22%) started ART at age <1.5 years; this varied by region from 627 (10%) in East Africa to 3433 (30%) in Southern Africa. Adolescents (10-17 years at ART start) represented 7050 (33%) of the children/adolescent group, ranging from 383 (26%) in Asia-Pacific to 105 (58%) in Central Africa. Among 11,863 (55%) of children/adolescents with available CD4 count (if age ≥5 years) or CD4 percentage data, 4732 (40%) had severe immunosuppression. Among 13,968 (65%) with measurements, 3533 (25%) were severely underweight (weight-for-age z-score <-3) and 2538 (22%) were severely stunted (height-for-age score <-3). West Africa had the highest proportions of severely underweight (834, 42%) and severely stunted (454, 24%) children/adolescents. 8020 (37%) of children/adolescents were from lower middle-income and 11,981 (55%) were from upper middle-income countries.

Using the ITT approach, the overall proportions of children/adolescents with viral suppression were 36% (7303 of 20,478) at 1 year, 30% (5709 of 19,135) at 2 years, and 24% (4287 of 17,589) at 3 years after ART initiation (figure 1). The proportions presented in figure 1 and the estimated weighted averages are provided in table S1 (appendix pp 3-4). When the analysis was limited to only children/adolescents in 'follow-up with an available VL measurement' (i.e., year 1: n=9902; year 2: n=7649; year 3: n=5641), the proportions with viral suppression increased to 74% at 1 year, 75% at 2 years, and 76% at 3 years. Overall, among 17,589 children/adolescents by the end of year 3, 735 (4.2%)

had died, 3076 (17%) had transferred out, and 5819 (33%) had been classified as LTFU, with percentages varying between regions (figure S3, appendix p 21).

In the adjusted analysis that accounted for the proportions assumed to have suppressed VL among those who were in follow-up but did not have a VL test, and among those who transferred out or were classified as LTFU, the estimated proportions suppressed 1 year after ART initiation ranged from 48% (836 of 1736) in West Africa to 84% (1192 of 1426) in the Asia-Pacific region (table 3; table S2, appendix pp 5-9); estimates ranged from 44% (720 of 1640) in West Africa to 84% (1123 of 1332) in Asia-Pacific at 2 years and 37% (572 of 1529) in West Africa to 83% (995 of 1194) in Asia-Pacific at 3 years after ART initiation (table S2, appendix pp 5-9).

A total of 255,662 adults (64% female) were included from 143 sites in 30 countries across seven IeDEA regions: Asia-Pacific (n=2270, 0.9%; 17 sites in 11 countries), CCASAnet (n=9898, 3.9%; 10 sites in 6 countries), NA-ACCORD (n=10,593, 4.1%; 17 sites in 2 countries), Central Africa (n=2545, 1.0%; 9 sites in 1 country), East Africa (n=61,413, 24%; 68 sites in 2 countries), Southern Africa (n=162,856, 64%; 16 sites in 4 countries), and West Africa (n=6087, 2.4%; 6 sites in 4 countries). Seventy percent of sites were urban or semiurban clinics and 43% were located within regional, provincial, or university hospitals. The median age at ART initiation was 34 (28-43) years (table 2). At ART initiation, 196,914 (77%) had CD4 testing; the median CD4 count at ART initiation was 237 (IQR, 118-377) cells/μL; 83,354 (33%) had a CD4 count <200cells/μL. 55,504 (22%) were from lower middle-income and 17,0311 (66%) were from upper middle-income countries.

Using the ITT approach, the proportion of adults with viral suppression was 44% (106,541 of 240,600) at 1 year, 36% (79,141 of 220,925) at 2 years, and 29% (57,970 of 201,124) at 3 years after ART initiation (figure 1; table S1, appendix pp 3-4). When the analysis was limited to only adults in 'follow-up with available VL measurements' (i.e., year 1: n=119,699; year 2: n=88,463; year 3: n=64,487), the proportions who were virally suppressed increased to 89% at 1 year, 89% at 2 years, and 90% at 3 years. Overall, among 201,124 adults by the end of year 3, 30,130 (5%) had died, and 72,337 (36%) were classified as LTFU, while 30,130 (15%) had transferred out, with percentages varying by regions (figure S4, appendix p 22).

After adjusting the estimates to account for proportions assumed to have viral suppression among those who were in follow-up without a VL test, and among those who transferred or were LTFU, the overall estimated proportions with suppressed VL 1 year after ART initiation ranged from 62% (2994 of 4814) in West Africa to 90% (1851 of 2050) in the Asia-Pacific region (table 4; table S3, appendix pp 10-14). Estimates of suppression ranged from 42% (807 of 1941) in Central Africa to 90% in Asia-Pacific at 2

years after ART initiation. At 3 years after ART initiation, the estimates ranged from 21% in Central Africa (339 of 1641) to 87% (1539 of 1761) in Asia-Pacific (table S3, appendix pp 10-15).

The estimated viral suppression using ITT, adjusted analysis, and estimated proportions among children/adolescents and adults with VL measurements are presented in figure 2 for the overall population and in table S4 and table S5 (appendix pp 15-17) by regions.

Discussion

This study described viral suppression among children/adolescents and adults starting ART between 2010 and 2019 at 148 IeDEA sites in 31 countries. The proportion of people with HIV who were virologically suppressed was low in the unadjusted ITT-like analysis. However, when we adjusted estimates for missing VL among PWH in care but without VL testing, transferred, and LTFU, the proportion virally suppressed increased considerably. The unadjusted analyses, with a denominator that includes a large number of individuals who were LTFU, did not give a plausible approximation of the proportion of people who were virally suppressed, and those results consequently should be interpreted with caution. As countries move towards the third 95 of UNAIDS's targets, a more accurate approximation of the proportion of PWH on ART who are virally suppressed can be achieved by better routine VL testing and maximizing retention or reconnecting PWH to care.

Overall, only 24% of children/adolescents and 29% of adults (unadjusted ITT-like analysis) were virally suppressed after 3 years of ART initiation. Although comparisons with other studies are difficult owing mainly to variations in the populations included in the denominators of the ITT analyses, our estimates of viral suppression are similar to or lower than those reported in other published studies,[19-21] and reports from the Population-based HIV Impact Assessment (PHIA) surveys of multiple African countries and UNAIDS modeling studies.[22,1] A large meta-analysis study conducted after 2010 reported ITT results for children/adolescents aged <18 years living in LMICs reported in which 63% were virally suppressed after 12 months on ART.[19] This study considered all children with missing VL results as having viral failure but did not adequately describe the population included in the analysis. A recent systematic review, including participants from a wide range of settings, showed substantial variation (27% to 89%) in the proportion of children/adolescents achieving viral suppression after 12 months of ART.[20] The proportions of suppressed adults in our ITT-like analysis were lower than the ITT results reported in two meta-analyses, which found that viral suppression in individual studies ranged from 69% to 87% after 12 months of ART.[21,23] However, those studies included PWH only from LMICs or those who started with triple ART regimens, in contrast to our study which included PWH from more diverse populations regardless of the ART regimen used.

Within 3 years after ART initiation, over half of children/adolescents and adults were LTFU or had transferred out. This partially explains the low proportions of viral suppression observed in our ITT-like analyses. The common risk factors responsible for LTFU such as patient-related factors, site-level factors, tracking systems and lack of access to HIV services were reported in the IeDEA regions.[24] In studies that traced LTFU PWH, a substantial proportion of individuals were found to be alive, connected to care at a different clinic, and still taking ART.[25,26] A recent tracing study of children/adolescents and adults who started ART and were LTFU found that undocumented transfers increased, and mortality decreased over time after the scale-up of ART and decentralization of ART care.[27] Transferred PWH have also been reported to have comparable outcomes to those retained in care, beyond the 3 months following transfer.[28,29] In this study, when we accounted for the estimated percentages of PWH with viral suppression among those who transferred or were classified as LTFU, the overall proportions of PWH with viral suppression increased considerably; however, the proportions with viral suppression at 3 years after ART initiation – after accounting for those LTFU, transferred out, and in care with no VL testing – remained low in regions with large proportions of LTFU (e.g., Central, East and West Africa regions).

In the second analysis, in which we calculated viral suppression among PWH who were alive, in follow-up and had VL testing, proportions remained above 74% in children/adolescents and above 89% in adults. These results were roughly comparable to the previous estimates reported for PWH undergoing routine VL monitoring. Data from the scale-up of Kenya's national HIV program from 2012 to 2016 showed a lower proportion (64%) of children/adolescents virally suppressed after at least 6 months on treatment, but a similar proportion (86%) of adults virally suppressed.[30] Our findings were somewhat higher than an earlier large study of treatment programs in Southern, East, and West Africa, in which 80% of PWH (age ≥16 years) achieved viral suppression by 12 months.[19,31] The earlier studies on HIV viral suppression from settings which performed targeted testing or were still transitioning to routine VL testing may have underestimated viral suppression when missing VL measurements were not taken into account in reporting the suppressed proportions.

Our analysis has several limitations. Despite having a relatively large overall sample size, only one country within Central Africa had annual VL testing across the 2010-2019 period, limiting generalizability to this region. Furthermore, treatment programs included in the IeDEA consortium may not be fully representative of their countries or sub-populations. Data on ethnicity was not available. It is possible that some clinically stable PWH may have been exempted from VL testing within sites offering routine VL testing We also cannot rule out the possibility that mortality was underestimated because of the misclassification of deaths as LTFU. For the adjusted analyses of those LTFU, the common estimate for unascertained mortality we applied to all regions was derived from the three tracing studies conducted in East Africa.[16-18] We did not have access to national-level surveillance

databases to more thoroughly assess rates of reconnection to care across the consortium. In addition, with substantial site-level variations in clinical and program management, choices of treatment regimens/switches, and assays used for VL measurements, reasons for not returning to clinic and outcomes after transferring or becoming LTFU are likely to have varied across settings.[32, 33] These differences may have influenced or biased the results of viral suppression. Heterogeneity in country-specific treatment programs limit generalizability when analyzing large collaborative datasets.

In conclusion**,** in this analysis of children/adolescents and adults receiving care at IeDEA sites, results from the ITT-like analyses showed that low proportions of children/adolescents and adults had attained viral suppression after 3 years on ART. When the estimates were adjusted to account for missing VL measurements, regardless of whether PWH remained in care, the estimated overall proportions with viral suppression increased substantially. Estimates of viral suppression that do not account for the sizeable proportion of LTFU PWH who are connected to care elsewhere and still receiving ART or estimates that do not account for PWH in care who are not tested are unlikely to reflect the actual proportion virally suppressed among those who are accessing care. Although adults with HIV are approaching the 95% target, progress among children/adolescents is slower and estimates are still behind the UNAIDS targets.

Contributors

WMH, AK and MGL conceptualized the concept and designed the study. WMH and AK analyzed the data and wrote up the first draft of the manuscript. MGL, KWK, RM, AE, CY, CC, TJM, AJ, BC, LC, EZ, NF, AHS, AK reviewed and provided contributions into the manuscript writing. WMH and AK had full access to and verified all the data in the study. All authors reviewed and approved the final manuscript.

Declarations of interests

The authors have read the journal's policy and declare the following competing interests: AHS reports grants support to her institution for activities unrelated to this work. ML reports unrestricted grants from Gilead Sciences, Janssen-Cilag, and ViiV HealthCare. CC reports grants support from NIH (U01AI069923) and consultation fees and honoraria from GSK-ViiV, and Merck. KA reports grants support from NIH, with funding payments made to her institution. She reports consultation fees from the All of Us Research Program (NIH) and the Trio Health. Other authors have no conflicts to report.

Data sharing

All study data were stored at the IeDEA Asia-Pacific Regional Data Centre at the Kirby Institute, University of New South Wales, Sydney, Australia. Each site retains ownership of their original data. External users with a formal analysis plan can request access to the data through a formal process detailed at https://www.iedea.org/.

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Figure legends

Figure 1. HIV viral suppression and treatment outcomes for children/adolescents and adults with HIV in the IeDEA global consortium by region at years 1, 2, and 3 following ART initiation (ITT analysis).

The proportions presented in this Figure and the estimated weighted averages are provided in table S1 (appendix pp 3-4).

Figure 2. HIV viral suppression proportions using ITT, children/adolescents and adults with viral load measurements and adjusted analyses in the IeDEA global consortium at years 1, 2, and 3 following ART initiation

Table 1. Characteristics of children and adolescents at ART initiation, by IeDEA region

	Asia-Pacific n = 1500 (6.9%)	Caribbean, Central & South America n = 245 (1.1%)	Central Africa n = 182 (0.8)	East Africa n = 6032 (28%)	Southern Africa n = 11,455 (53%)	West Africa n = 2180 (10%)	Total n = 21,594 (100%)
Sex, female	726 (48)	102 (56)	121 (49)	3414 (57)	6400 (56)	1049 (48)	11812 (55)
Age (years)							
<1.5	290 (19)	42 (17)	20 (11)	627 (10)	3433 (30)	365 (17)	4777 (22)
1.5 to <5	364 (24)	42 (17)	28 (15)	1419 (24)	2191 (19)	686 (31)	4730 (22)
5 to <10	463 (31)	38 (16)	29 (16)	1634 (27)	2258 (20)	615 (28)	5037 (23)
10 to <15	306 (20)	35 (14)	54 (30)	1284 (21)	1952 (17)	455 (21)	4086 (19)
15 to 17	77 (5.1)	88 (36)	51 (28)	1068 (18)	1621 (14)	59 (2.7)	2964 (14)
Median (IQR), years	6.1 (2.1-10.0)	10.6 (2.7-16.4)	11.7 (4.7-15.6)	7.9 (3.4-13.1)	5.1 (1.0-11.6)	5.3 (2.0-9.6)	6.2 (1.7-11.8)
CD4 percentage							
Available data, n (%)	1060 (71)	126 (51)	2 (1.1)	762 (13)	5066 (44)	1095 (50)	8111 (38)
Median (IQR)	15 (7-22)	21 (14-27)	24 (17-31)	19 (11-27)	17 (10-25)	16 (8-23)	16 (9-25)
n (<5 years), median (IQR)	437 17 (10-25)	44 26 (12-32)	-	191 22 (14-30)	3020 19 (13-28)	542 17 (11-26)	4234 19 (12-28)
CD4 count, cells/µL							
Available data, n (%)	1170 (78)	209 (85)	101 (55)	2271 (38)	7680 (67)	1619 (74)	13,050 (60)
Median (IQR)	356 (130-725)	424 (249-752)	667 (494-889)	526 (282-909)	414 (210-833)	475 (191-882)	440 (215-842)
n (≥5 years), median (IQR)	681 256 (71-443)	143 351 (182-529)	87 625 (469-829)	1655 436 (234-725)	4211 291 (142-460)	852 287 (59-538)	7629 316 (146-526)
HIV RNA, log_{10} copies/mL							
Available data, n (%)	456 (30)	203 (83)	7 (3.8)	380 (6.3)	4490 (39)	559 (26)	6095 (28)
Median (IQR)	5.3 (4.4-5.9)	4.6 (3.6-5.3)	2.7 (1.3-5.5)	4.3 (2.0-5.2)	5.3 (4.4-5.9)	5.0 (4.0-5.8)	5.2 (4.3-5.9)

Severe HIV-associated immunodeficiency*	536 (48)	55 (29)	4 (8.3)	420 (23)	3089 (43)	628 (45)	4732 (40)
Weight-for-age z-score							
Available data, n (%)	1389 (93)	208 (85)	167 (92)	5875 (97)	4323 (38)	2006 (92)	13,968 (65)
Median (IQR)	-2.0 (-3.2 to -0.9)	-1.1 (-2.4 to -0.2)	-1.2 (-2.5 to -0.2)	-1.4 (-2.6 to -0.3)	-1.8 (-3.0 to -0.7)	-2.5 (-4.2 to -1.2)	-1.7 (-3.0 to -0.6)
z-score < -3	398 (29)	35 (17)	34 (20)	1136 (19)	1096 (25)	834 (42)	3533 (25)
Height-for-age z-score							
Available data, n (%)	1287 (86)	185 (76)	124 (68)	5159 (86)	2972 (26)	1874 (86)	11,601 (54)
Median (IQR)	-2.0 (-2.9 to -1.0)	-1.5 (-2.6 to -0.7)	-1.5 (-2.5 to -0.6)	-1.5 (-2.5 to -0.4)	-2.2 (-3.2 to -1.2)	-1.9 (-3.0 to -0.8)	-1.8 (-2.8 to -0.7)
z-score < -3	289 (22)	28 (15)	25 (20)	874 (17)	868 (20)	454 (24)	2538 (22)
Calendar year of ART initiation							
2010-2012	452 (30)	97 (40)	0 (0)	0 (0)	5583 (49)	540 (25)	6672 (31)
2013-2015	495 (33)	91 (37)	0 (0)	3440 (57)	3440 (57)	958 (44)	8587 (40)
2016-2019	553 (37)	57 (23)	182 (100)	2592 (43)	2592 (43)	682 (31)	6335 (29)
World Bank country income group							
High income	0 (0)	6 (2.5)	0 (0)	0 (0)	0 (0)	0 (0)	6 (0.03)
Upper middle income	574 (38)	188 (77)	0 (0)	0 (0)	11,219 (98)	0 (0)	11,981 (55)
Lower middle income	926 (62)	51 (21)	0 (0)	5396 (89)	236 (2.1)	1411 (65)	8020 (37)
Low income	0 (0)	0 (0)	182 (100)	636 (11)	0 (0)	769 (35)	1587 (7.4)
Initial ART regimen							
NNRTI-based	1176 (78)	164 (67)	147 (81)	5201 (86)	6903 (60)	1576 (72)	15,167 (70)
PI-based	274 (18)	69 (28)	34 (19)	818 (14)	4513 (39)	569 (26)	6277 (29)
INSTI-based	26 (1.7)	9 (3.7)	1 (0.6)	9 (0.2)	4 (<0.1)	0 (0)	49 (<0.1)
Others	24 (1.6)	3 (1.2)	0 (0)	4 (0.1)	35 (0.3)	35 (1.6)	101 (0.5)

Values are number (column percentage) unless otherwise indicated. Children/adolescents, <18 years at ART initiation; ART, consists of the combination of at least three antiretrovirals.

*Severe HIV-associated immunodeficiency was defined according to WHO criteria as CD4% <25% (age <1 year), <20% (age 1 to <3 years), <15% (age 3 to 5 years), and <15% or <200 cells/mm^3 (age ≥5 years).

Abbreviations: IQR, Interquartile range; ART, antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; INSTI, integrase strand transfer inhibitors. "Others" category in initial ART regimen included dual therapy, entry inhibitors and other atypical ART regimen. One decimal point for figures was given only when the percentage is less than 10.

Table 2. Characteristics of adults at ART initiation, by IeDEA region

	Asia-Pacific n = 2270 (8.9%)	**Caribbean, Central & South America n = 9898 (3.9%)**	**Central Africa n = 2545 (1.0%)**	**East Africa n = 61,413 (24%)**	**Southern Africa n = 162,856 (64%)**	**West Africa n = 6087 (2.4%)**	**North America n = 10,593 (4.1%)**	**Total n = 255,662 (100%)**
Sex, female	855 (38)	1977 (20)	1487 (58)	39,724 (65)	113,396 (70)	4162 (68)	2230 (21)	163,831 (64)
Age (years)								
<24	265 (12)	1414 (14)	297 (12)	7199 (12)	16,808 (10)	230 (3.8)	594 (5.6)	26,807 (10)
24 to 50	1723 (76)	7519 (76)	2030 (80)	46,889 (76)	129,853 (80)	4809 (79)	6687 (63)	199,510 (78)
>50	282 (12)	965 (10)	218 (8.6)	7325 (12)	16195 (10)	1048 (17)	3312 (31)	29,345 (12)
Median (IQR))	35 (29-44)	33 (27-41)	34 (28-41)	34 (28-43)	34 (28-42)	39 (33-47)	43 (33-52)	34 (28-43)
CD4 count, cells/μL								
<200	628 (28)	3565 (36)	275 (11)	9940 (16)	64,040 (39)	2121 (34)	2786 (26)	83,354 (33)
200-349	312 (13)	2276 (23)	308 (12)	7327 (12)	43,695 (27)	1477 (24)	2133 (20)	57,527 (22)
350-499	157 (6.9)	1396 (14)	312 (12)	7052 (12)	18,366 (11)	641 (11)	2001 (19)	29,923 (12)
≥500	152 (6.7)	1211 (12)	748 (29)	6035 (10)	14,761 (9.1)	649 (11)	2554 (24)	26,110 (10)
Missing	1021 (45)	1450 (15)	902 (36)	31,059 (51)	21,994 (14)	1199 (20)	1119 (11)	58,748 (23)

Median (IQR)	196 (43-348)	243 (94-388)	463 (263-678)	309 (148-464)	219 (113-341)	231 (104-360)	336 (162-520)	237 (118-377)
HIV RNA, log_{10} copies/mL								
Available data, n (%)	987 (4.3)	7813 (79)	117 (4.6)	2208 (3.6)	12,432 (7.6)	964 (16)	9217 (87)	33,738 (13)
Median (IQR)	4.9 (4.3-5.5)	4.9 (4.2-5.4)	2.3 (1.3-4.1)	2.7 (0-4.5)	3.9 (2.6-4.9)	4.0 (0-5.4)	4.3 (2.7-5.0)	4.4 (2.6-5.2)
Calendar year of ART initiation								
2010-2012	861 (38)	2517 (25)	0 (0)	0 (0)	56,309 (35)	1802 (30)	6731 (64)	68,220 (27)
2013-2015	777 (34)	4021 (41)	0 (0)	29180 (48)	57,232 (35)	2256 (37)	3373 (32)	96,839 (38)
2016-2019	632 (28)	3360 (34)	2545 (100)	32233 (52)	49,315 (30)	2029 (33)	489 (4.6)	90,603 (35)
World Bank country income group								
High income	170 (7.5)	1828 (18)	0 (0)	0 (0)	0 (0)	0 (0)	10593 (100)	12,591 (5.6)
Upper middle income	975 (43)	7721 (78)	0 (0)	0 (0)	161,615 (99)	0 (0)	0 (0)	17,0311 (66)
Lower middle income	1125 (50)	349 (3.5)	0 (0)	49,652 (81)	0 (0)	3137 (52)	0 (0)	55,504 (22)
Low income	0 (0)	0 (0)	2545 (100)	11,691 (19)	1241 (0.8)	2950 (48)	0 (0)	17186 (7.6)
Initial ART regimen								
NNRTI-based	2099 (92)	7499 (76)	2507 (99)	60,206 (98)	160,949 (99)	5389 (89)	1117 (11)	239,766 (94)
PI-based	158 (6.9)	1557 (16)	14 (0.6)	533 (0.9)	1557 (1.0)	608 (10)	6148 (56)	10,575 (4.1)
INSTI-based	3 (0.1)	746 (7.5)	19 (0.7)	657 (1.1)	22 (<0.1)	21 (0.3)	2290 (22)	3758 (1.5)
Others	10 (0.4)	96 (1.0)	5 (0.2)	17 (<0.1)	244 (0.1)	69 (1.1)	1038 (9.8)	1563 (0.6)

Values are number (column percentage) unless otherwise indicated. Adults, ≥18 years at ART initiation; ART, consists of the combination of at least three antiretrovirals.

Abbreviations: IQR, Interquartile range; ART, antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; INSTI, integrase strand transfer inhibitors. "Others" category in initial ART regimen included dual therapy, entry inhibitors and other atypical ART regimen. One decimal point for figures were given only when the percentage is less than 10.

Table 3. Estimated total numbers and proportions of children/adolescents still alive with HIV viral load <1000 copies/mL by years on ART, stratified by IeDEA region (adjusted analysis)

	Year 1		Year 2		Year 3	
	Total estimated VL <1000 copies/ml (plausible ranges)	Proportions (plausible ranges)	Total estimated VL <1000 copies/ml (plausible ranges)	Proportions (plausible ranges)	Total estimated VL <1000 copies/ml (plausible ranges)	Proportions (plausible ranges
Asia-Pacific	1192 (961-1259)	84% (68%-89%)	1123 (887-1165)	84% (67%-87%)	995 (778-1026)	83% (65%-86%)
Total non-deaths	1426		1332		1194	
CCASAnet	174 (125-201)	73% (53%-84%)	151 (110-180)	67% (49%-80%)	129 (91-150)	61% (43%-71%)
Total non-deaths	238		226		210	
Central Africa	94 (55-109)	60% (35%-70%)	65 (36-74)	46% (25%-52%)	N/A	N/A
Total non-deaths	156		142		N/A	
East Africa	3293 (2115-4115)	65% (42%-81%)	2598 (1671-3279)	60% (39%-76%)	1980 (1238-2454)	57% (36%-71%)
Total non-deaths	5085		4312		3478	
Southern Africa	6459 (4311-8375)	63% (42%-82%)	6139 (3960-7740)	62% (40%-78%)	5501 (3481-6855)	59% (38%-74%)
Total non-deaths	10,194		9901		9256	
West Africa	836 (586-1169)	48% (34%-67%)	720 (492-999)	44% (30%-61%)	572 (390-815)	37% (26%-53%)
Total non-deaths	1736		1640		1529	
Overall	12,048 (8153-15,228)	64% (43%-81%)	10,796 (7156-13,437)	62% (41-77%)	9177 (5978-14,300)	59% (38%-91%)
Total non-deaths	18,835		17,553		15,667	

ART consists of the combination of at least three antiretrovirals. Plausible ranges were generated by applying data the lower and upper bounds for the proportion of viral suppression using the literature reporting on viral outcomes among PWH in care (Supplementary Box 1; appendix pp 1-2).

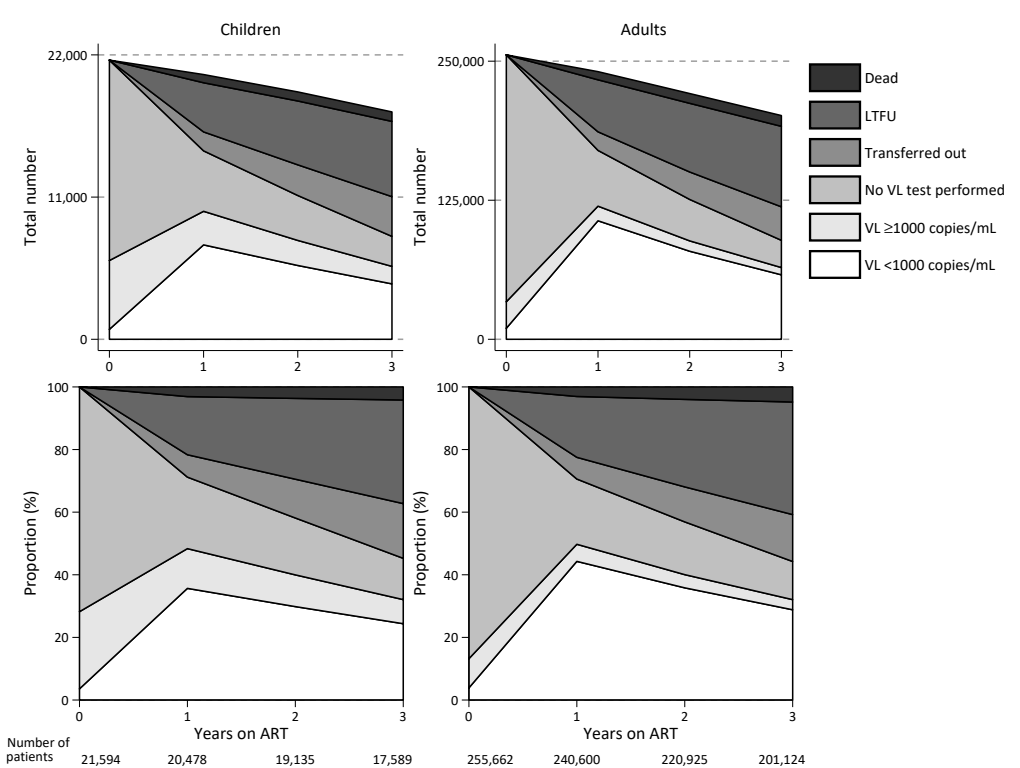
Abbreviations: VL, viral load; CCASAnet, Caribbean/Central and South America.

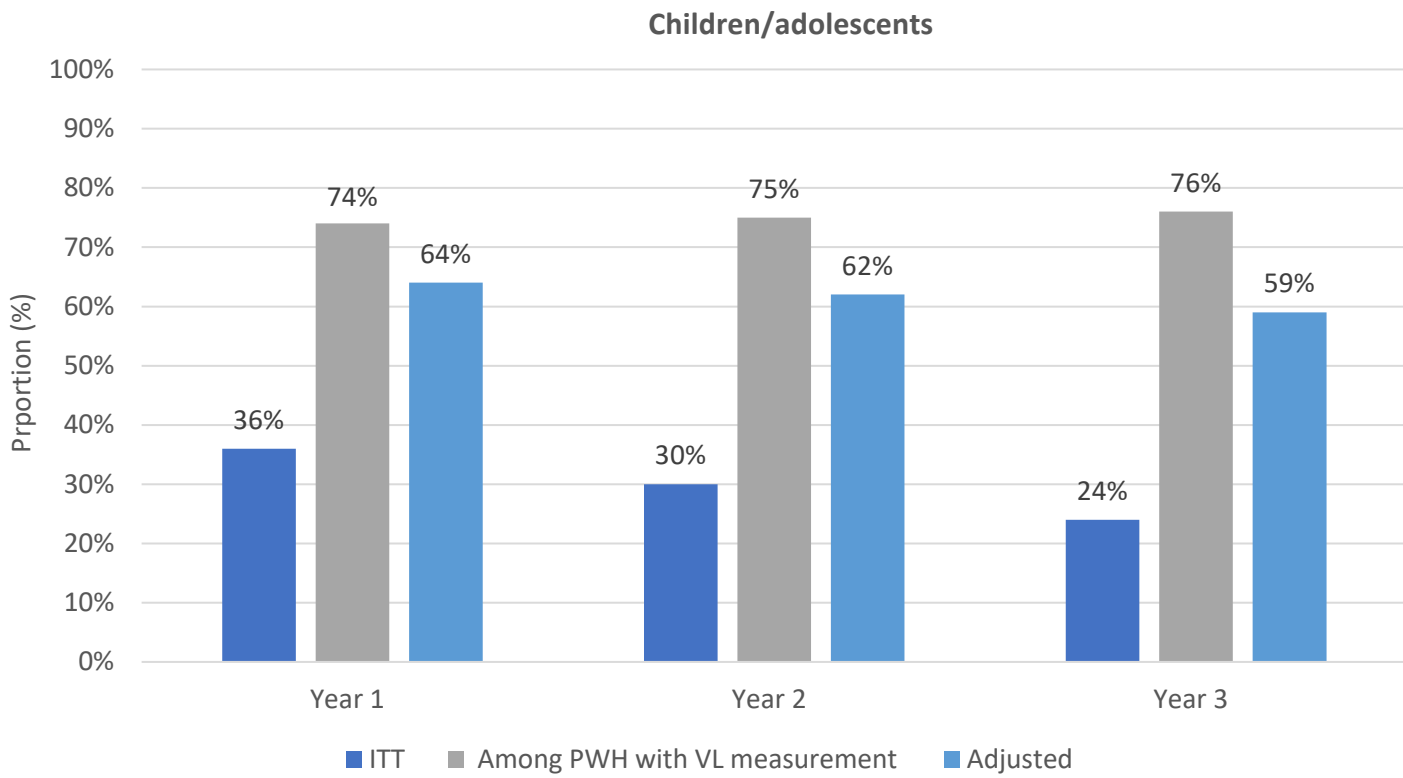
Table 4. Estimated total numbers and proportions of adults still alive with HIV viral load <1000 copies/mL by years on ART, stratified by IeDEA region (adjusted analysis)

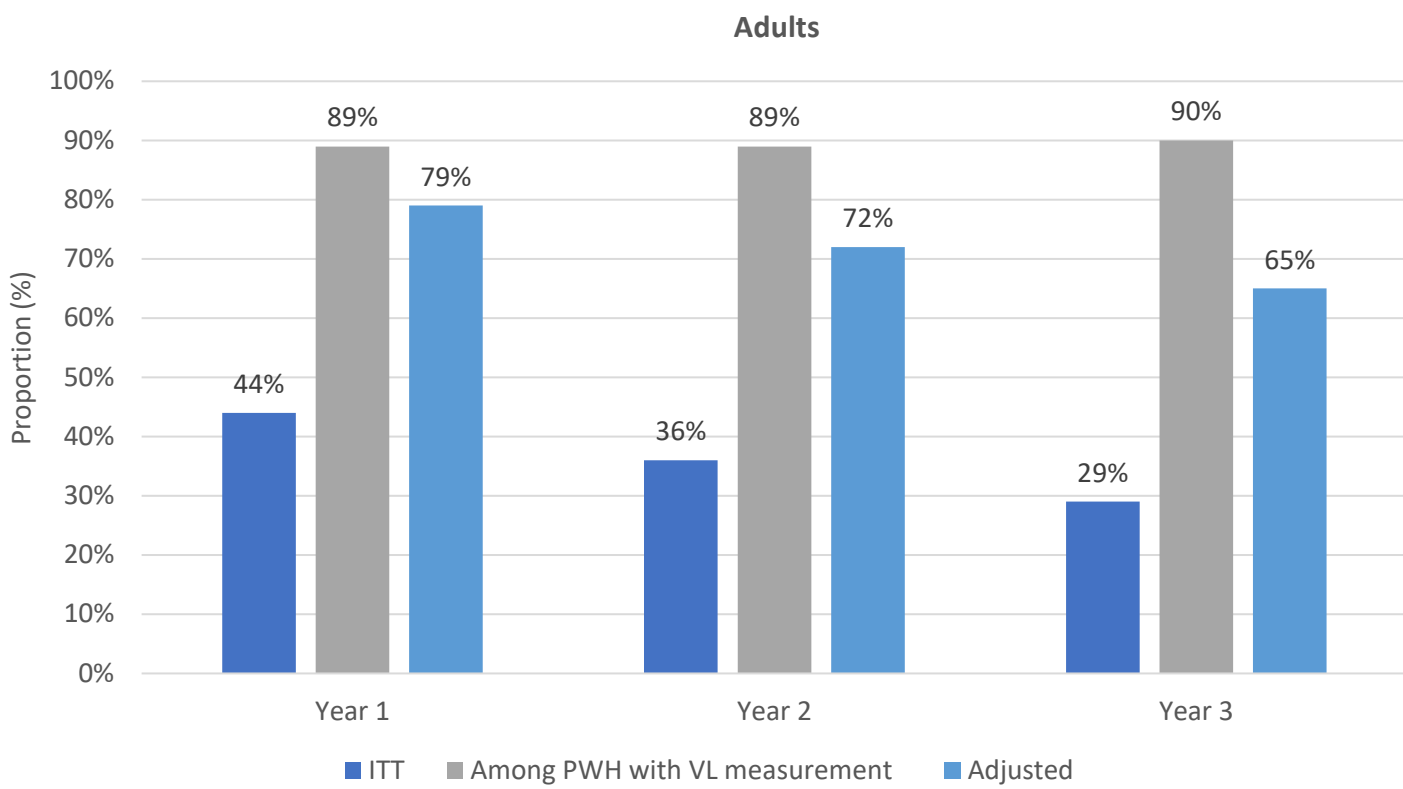
	Year 1		Year 2		Year 3	
	Total estimated VL <1000 copies/ml (plausible ranges)	Proportions (plausible ranges)	Total estimated VL <1000 copies/ml (plausible ranges)	Proportions (plausible ranges)	Total estimated VL <1000 copies/ml (plausible ranges)	Proportions (plausible ranges
Asia-Pacific	1851 (1568-1898)	90% (77%-93%)	1691 (1385-1705)	90% (73%-90%)	1539 (1246-1557)	87% (71%-88%)
Total non-deaths	2050		1886		1761	
CCASAnet	7611 (4356-7784)	84% (48%-86%)	6327 (3641-6563)	78% (45%-81%)	5161 (2970-5426)	71% (41%-75%)
Total non-deaths	9067		8111		7255	
NA-ACCORD	7603 (6257-7790)	80% (66%-82%)	6119 (4960-6294)	74% (60%-76%)	4991 (3972-5161)	69% (55%-71%)
Total non-deaths	9516		8232		7219	
Central Africa	1373 (871-1520)	62% (39%-68%)	807 (504-955)	42% (26%-49%)	339 (188-470)	21% (11%-29%)
Total non-deaths	2231		1941		1641	
East Africa	37,824 (25,039-41,583)	75% (50%-82%)	30,354 (20,158-32,589)	68% (44%-75%)	19,505 (12,544-21,759)	59% (38%-66%)
Total non-deaths	50,525		41,749		32,799	
Southern Africa	117,708 (79,580-116,654)	78% (52%-86%)	97,793 (65,164-108,645)	73% (48%-81%)	81,832 (53,831-86,679)	66% (44%-70%)
Total non-deaths	147,215		134,739		123,456	
West Africa	2994 (1933-3327)	62% (40%-69%)	2461 (1576-2794)	54% (34%-61%)	1893 (1182-2208)	44% (27%-51%)
Total non-deaths	4814		4580		4327	
Overall	176,964 (119,604-180,556)	79% (53%-80%)	145,552 (97,388-159,545)	72% (48%-79%)	115,260 (75,933-123,260)	65% (43%-69%)
Total non-deaths	225,418		201,238		178,458	

ART consists of the combination of at least three antiretrovirals. Plausible ranges were generated by applying data the lower and upper bounds for the proportion of viral suppression using the literature reporting on viral outcomes among PWH in care (Supplementary Box 1; appendix pp 1-2).

Abbreviations: VL, viral load; CCASAnet, Caribbean/Central and South America; NA-ACCORD, North America.


Children
Adults
Dead
LTFU
Transferred out
No VL test performed
VL ≥1000 copies/mL
VL <1000 copies/mL
Total number
22,000
11,000
0
250,000
125,000
Proportion (%)
100
80
60
40
20
Years on ART
0
1
2
3
Number of patients
21,594
20,478
19,135
17,589
255,662
240,600
220,925
201,124


Children/adolescents
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Prportion (%)
74%
64%
36%
75%
62%
30%
76%
59%
24%
Year 1
Year 2
Year 3
ITT
Among PWH with VL measurement
Adjusted


Adults
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Proportion (%)
89%
79%
44%
89%
72%
36%
90%
65%
29%
Year 1
Year 2
Year 3
ITT
Among PWH with VL measurement
Adjusted