Global estimates of viral suppression in children and adolescents and adults on antiretroviral therapy adjusted for missing viral load measurements: a multiregional, retrospective cohort study in 31 countries

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*Members of the IeDEA collaboration in participating regions are listed in the appendix (pp 25–37)

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Summary

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

Methods In this retrospective cohort study, seven regional cohorts from the International epidemiology Databases to Evaluate AIDS (IeDEA) consortium contributed data from individuals initiating ART between Jan 1, 2010, and Dec 31, 2019, at 148 sites in 31 countries with annual viral load monitoring. Only people with HIV who started ART after the time a site started routine viral load monitoring were included. Data up to March 31, 2020, were analysed. We estimated the proportions of children and adolescents (aged <18 years at ART initiation) and adults (aged ≥18 years at ART initiation) with viral suppression (viral load <1000 copies per mL) at 1, 2, and 3 years after ART initiation using an intention-to-treat approach and an adjusted approach that accounted for missing viral load measurements.

Findings 21 594 children and adolescents (11 812 [55%] female, 9782 [45%] male) from 106 sites in 22 countries and 255 662 adults (163 831 [64%] female, 91 831 [36%] male) from 143 sites in 30 countries were included. Using the intention-to-treat approach, the proportion of children and adolescents with viral suppression was 7303 (36%) of 20 478 at 1 year, 5709 (30%) of 19 135 at 2 years, and 4287 (24%) of 17 589 at 3 years after ART initiation; the proportion of adults with viral suppression was 106 541 (44%) of 240 600 at 1 year, 79 141 (36%) of 220 925 at 2 years, and 57 970 (29%) of 201 124 at 3 years after ART initiation. After adjusting for missing viral load measurements among those who transferred, were lost to follow-up, or who were in follow-up without viral load testing, the proportion of children and adolescents with viral suppression was 12 048 (64% [plausible range 43–81]) of 18 835 at 1 year, 10 796 (62% [41–77]) of 17 553 at 2 years, and 9177 (59% [38–91]) of 15 667 at 3 years after ART initiation; the proportion of adults with viral suppression was 176 964 (79% [53–80]) of 225 418 at 1 year, 145 552 (72% [48–79]) of 201 238 at 2 years, and 115 260 (65% [43–69]) of 178 458 at 3 years after ART initiation.

Interpretation Although adults with HIV are approaching the global target of 95% viral suppression, progress among children and adolescents is much slower. Substantial efforts are still needed to reach the viral suppression target for children and adolescents.

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Introduction

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

In 2013, WHO recommended routine viral load testing as the preferred way to improve monitoring and earlier identification of treatment failure.[5] 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-term and long-term data on virological outcomes. In 2016, WHO recommended to conduct viral load testing at 6 and 12 months after ART initiation and every 12 months thereafter if the person is stable on ART.[5]

Research in context

Evidence before this study

To support the undetectable equals untransmittable and treatment-as-prevention strategies, accurate estimation of the third 95 of UNAIDS's 95-95-95 targets is crucial. Although routine viral load testing is the standard of care in high-income countries, viral load testing has been slow to expand in low-income and middle-income countries. We searched PubMed on March 18, 2020, for studies published in English after Dec 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 of people who were lost to follow-up from Zambia. The study found that the HIV viraemia, defined by viral load of 1000 copies per mL or more, was present in 18·1% (95% CI 14·0–22·3) of people living with HIV in care, and 71·3% (58·2–84·4) of individuals lost to follow-up. After incorporating tracing outcomes and viral load results among those who were lost to follow-up and traced into the cohort, the study found an overall prevalence of HIV viraemia of 24·7% (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 proportions of people with HIV with viral suppression, both in and out of care, accounting for missing viral load measurements. We found that 4287 (76%) of 5641 children and adolescents and 57 970 (90%) of 64 487 adults, who were in follow-up and had viral load measurements were virally suppressed at 3 years after ART initiation. After adjusting for missing viral load measurements among those who transferred, were lost to follow-up, or were in follow-up but with no viral load testing, 9177 (59% [plausible range 38–91]) of 15 667 children and adolescents and 115 260 (65% [43–69]) of 178 458 adults were virally suppressed at 3 years after ART initiation. The estimated proportions varied widely across regions from 572 (37% [26–53]) of 1529 to 995 (83% [65–86]) of 1194 in children and adolescents and from 339 (21% [11–29]) of 1641 to 1539 (87% [71–88]) of 1761 in adults.

Implications of all the available evidence

Reports on the proportion of people with HIV with viral suppression that do not account for viral loads in the sizeable proportion of people who are lost to follow-up but who are connected to care elsewhere and still receiving ART, or that use viral load estimates that do not account for people with HIV who are in care but who are not tested, are unlikely to reflect the actual proportion of virally suppressed people with HIV who are accessing care. In the era of undetectable equals untransmittable, strategies and increased efforts for better retention in care and more systematic routine viral load testing could be helpful in estimating the actual virally suppressed population. Although adults with HIV are approaching the UNAIDS 95% target, progress among children and adolescents is slower and estimates are still behind the target.

To support the undetectable equals untransmittable and treatment-as-prevention strategies, accurate estimation of the third 95 target is crucial. Although routine viral load testing is the standard of care in high-income countries, viral load testing has been slow to expand in low-income and middle-income countries (LMICs).[7] Consequently, in settings that have only recently implemented viral load testing for routine monitoring of people living with HIV who are on ART, data on viral suppression are scarce.[8–12]

The International epidemiology Databases to Evaluate AIDS (IeDEA) is a global research network established in 2006 by the US National Institutes of Health. IeDEA merges and analyses routinely collected data from large and diverse populations of people living with HIV across seven international regions: central Africa; east Africa; southern Africa; west Africa; Asia-Pacific; the Caribbean, Central America, and South America; and North America. In this study, we analysed data from IeDEA treatment sites that provided at least annual routine viral load monitoring to estimate the proportions of children and adolescents and adults with viral suppression at 1, 2, and 3 years after initiating ART.

Methods

Study design and participants

This retrospective cohort study was done in children and adolescents (aged <18 years at ART initiation) and adults (aged ≥18 years at ART initiation) with HIV who initiated ART between Jan 1, 2010, and Dec 31, 2019, at one of 148 IeDEA sites in 31 countries with routine viral load monitoring in seven international IeDEA regions. Routine viral load monitoring was defined as at least one annual viral load test per person as reported by each participating region. Only people with HIV who started ART after the time a site started routine viral load monitoring were included. If no information was provided regarding viral load 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 viral load testing starting from the year when a median of at least one annual viral load test per person was observed. Data from the subsequent calendar years were included irrespective of their median values. We excluded from the analyses people with HIV who were not ART-naive at clinic enrolment, people with HIV 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 31, 2020. The date of database closure differed for each of the participating sites ranging between Sept 18, 2012, and March 31, 2020 (15 [10%] sites before 2017, 32 [22%] sites between 2017 and 2018, 101 [68%] sites between 2019 and 2020).

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See **Online** for appendix

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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.

Procedures

Clinical management, selection of initial ART regimen, laboratory tests, and interventions were performed according to local guidelines.

The main endpoints were the unadjusted and adjusted proportions of children and adolescents and adults with viral suppression (ie, viral load <1000 copies per mL) at 1, 2, and 3 years after ART initiation. For viral load, we selected the single closest value reported during a window of 6 months before and after the specified timepoint, and then classified this measurement as virally suppressed or not virally suppressed. People with HIV were considered active at each timepoint if they had a clinic visit on the specified timepoint or later. Only active people with HIV were included in the numerator to examine the proportions with and without viral load testing at year 1, year 2, and year 3. People with HIV without evidence of contact with the clinic for more than 6 months before site-specific closure dates were classified as lost to follow-up, 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 proportion of CD4 cells less than 25% (age <1 year), less than 20% (age 1 to <3 years), less than 15% (age 3 to 5 years), and less than 15% or less than 200 cells per mm³ (age ≥5 years).[13] We calculated height-for-age z-score using the WHO 2006–07 child growth standards[14] and weight-for-age z-score using the WHO 1977 standards.[15]

Statistical analysis

We conducted separate analyses for the child and adolescent group and for the adult group. We used descriptive statistics to summarise patient characteristics at ART initiation, stratified by IeDEA region. First, we used an intention-to-treat approach to include all people with HIV who started ART with or without viral load outcomes. Quantifying the viral suppression rates among all people with HIV who have started ART, including those with missing viral load measurements owing to loss to follow-up or transfers, is an important indicator in HIV care programmes, especially in the era of treatment-as-prevention (or undetectable equals untransmittable). Therefore, in our analysis, we calculated the proportions of people with HIV with viral loads of less than 1000 copies per mL, the proportions with viral loads of 1000 copies per mL or greater, the proportions with no viral load testing, and the proportion who died, transferred, or were lost to follow-up. Proportions were plotted for each duration of ART (ie, 1, 2, or 3 years after ART initiation). The proportions of people with HIV without viral load testing were calculated by including in the numerator only those who were in follow-up but did not have a viral load measurement. In this intention-to-treat analysis, people with HIV who died, were transferred, or were classified as lost to follow-up, and those who were presumed to be in care but did not reach a specified timepoint, 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 people with HIV with viral loads of less than 1000 copies per mL only among those who were alive, in follow-up, and with viral load assessed, for each duration of ART.

Third, we conducted an adjusted analysis to provide estimates of the overall proportions of people with HIV who were still alive (including those in follow-up without viral load testing, transfers, and those lost to follow-up) and virally suppressed at 1, 2, and 3 years after ART initiation. For this analysis, we considered people with HIV in follow-up with no viral load testing, and those transferred (after excluding the estimated deaths among transfers) as having equal proportions of virally suppressed individuals as those in care with viral load 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 people with HIV in care (appendix pp 1–2). The common estimated plausible ranges of deaths among transfers, and viral suppression among transfers and those without viral load testing, were used for all four African regions.

For those who were lost to follow-up, the proportions of people with HIV who died, and of people with HIV who were still alive and reconnected to care were extracted from the tracing studies reporting on loss to follow-up outcomes,[16–18] and we applied these proportions to our population of people who were lost to follow-up. We then estimated the proportion of people with HIV who were virally suppressed (including plausible ranges) among those alive and reconnected to care (ie, unofficial transfers) among those lost to follow-up using the data reported from a study assessing viral suppression in a large population of people with HIV who were lost to follow-up in Zambia.[18] The same estimated viral suppression proportion (and plausible ranges) were applied to both

the child and adolescent group and the adult group in all regions. In this way, we estimated the overall proportions of people with HIV who were alive and virally suppressed at 1, 2, and 3 years after ART initiation. The steps taken in the adjusted analysis are shown in the appendix (pp 1–2). We did sensitivity analyses varying the common estimate of viral suppression among people with HIV who reconnected to care by plus or minus 25%.

Multiregional data were managed and analysed by the Kirby Institute, University of New South Wales Sydney, (Sydney, NSW, Australia) using SAS (version 9.4) and Stata (version 14.0).

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

21 594 children and adolescents (11 812 [55%] female, 9782 [45%] male) were included from 106 sites in 22 countries across six IeDEA regions: Asia-Pacific (14 sites in five countries); the Caribbean, Central America, and South America (nine sites in five countries); central Africa (ten sites in one country); east Africa (51 sites in three countries); southern Africa

	Asia-Pacific (n=1500)	Caribbean, Central America, and South America (n=245)	Central Africa (n=182)	East Africa (n=6032)	Southern Africa (n=11 455)	West Africa (n=2180)	Total (n=21 594)
Sex							
Female	726 (48%)	121 (49%)	102 (56%)	3414 (57%)	6400 (56%)	1049 (48%)	11 812 (55%)
Male	774 (52%)	124 (51%)	80 (44%)	2618 (43%)	5055 (44%)	1131 (52%)	9782 (45%)
Age at ART initiation, 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%)	88 (36%)	51 (28%)	1068 (18%)	1621 (14%)	59 (3%)	2964 (14%)
Median	6·1 (2·1 to 10.0)	10·6 (2·7 to 16·4)	11·7 (4·7 to 15·6)	7·9 (3·4 to 13·1)	5·1 (1·0 to 11·6)	5·3 (2·0 to 9·6)	6·2 (1·7 to 11·8)
Proportion of CD4 cells							
Available data	1060 (71%)	126 (51%)	2 (1%)	762 (13%)	5066 (44%)	1095 (50%)	8111 (38%)
Overall median	15 (7 to 22)	21 (14 to 27)	24 (17 to 31)	19 (11 to 27)	17 (10 to 25)	16 (8 to 23)	16 (9 to 25)
Number aged <5 years; median (IQR)	437; 17 (10 to 25)	44; 26 (12 to 32)	..	191; 22 (14 to 30)	3020; 19 (13 to 28)	542; 17 (11 to 26)	4234; 19 (12 to 28)
CD4 count, cells per µL							
Available data	1170 (78%)	209 (85%)	101 (55%)	2271 (38%)	7680 (67%)	1619 (74%)	13 050 (60%)
Overall median	356 (130 to 725)	424 (249 to 752)	667 (494 to 889)	526 (282 to 909)	414 (210 to 833)	475 (191 to 882)	440 (215 to 842)
Number aged ≥5 years; median (IQR)	681; 256 (71 to 443)	143; 351 (182 to 529)	87; 625 (469 to 829)	1655; 436 (234 to 725)	4211; 291 (142 to 460)	852; 287 (59 to 538)	7629; 316 (146 to 526)
HIV RNA, log_{10} copies per mL							
Available data	456 (30%)	203 (83%)	7 (4%)	380 (6%)	4490 (39%)	559 (26%)	6095 (28%)
Median	5·3 (4·4 to 5·9)	4·6 (3·6 to 5·3)	2·7 (1·3 to 5·5)	4·3 (2·0 to 5·2)	5·3 (4·4 to 5·9)	5·0 (4·0 to 5·8)	5·2 (4·3 to 5·9)
Severe HIV-associated immunodeficiency*	536/1118 (48%)	55/187 (29%)	4/87 (5%)	420/1846 (23%)	3089/7231 (43%)	628/1394 (45%)	4732/11 863 (40%)
Weight-for-age z-score							
Available data	1389 (93%)	208 (85%)	167 (92%)	5875 (97%)	4323 (38%)	2006 (92%)	13 968 (65%)
Median	−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 less than −3	398 (29%)	35 (17%)	34 (20%)	1136 (19%)	1096 (25%)	834 (42%)	3533 (25%)
Height-for-age z-score							
Available data	1287 (86%)	185 (76%)	124 (68%)	5159 (86%)	2972 (26%)	1874 (86%)	11 601 (54%)
Median	−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 less than −3	289 (22%)	28 (15%)	25 (20%)	874 (17%)	868 (29%)	454 (24%)	2538 (22%)

(Table 1 continues on next page)

	Asia-Pacific (n=1500)	Caribbean, Central America, and South America (n=245)	Central Africa (n=182)	East Africa (n=6032)	Southern Africa (n=11 455)	West Africa (n=2180)	Total (n=21 594)
(Continued from previous page)							
Calendar year of ART initiation							
2010–12	452 (30%)	97 (40%)	0	0	5583 (49%)	540 (25%)	6672 (31%)
2013–15	495 (33%)	91 (37%)	0	3440 (57%)	3603 (31%)	958 (44%)	8587 (40%)
2016–19	553 (37%)	57 (23%)	182 (100%)	2592 (43%)	2269 (20%)	682 (31%)	6335 (29%)
World Bank country income group							
High income	0	6 (2%)	0	0	0	0	6 (<1%)
Upper-middle income	574 (38%)	188 (77%)	0	0	11 219 (98%)	0	11 981 (55%)
Lower-middle income	926 (62%)	51 (21%)	0	5396 (89%)	236 (2%)	1411 (65%)	8020 (37%)
Low income	0	0	182 (100%)	636 (11%)	0	769 (35%)	1587 (7%)
Initial ART regimen							
NNRTI-based	1176 (78%)	164 (67%)	147 (81%)	5201 (86%)	6903 (60%)	1576 (72%)	15 167 (70%)
Protease inhibitor-based	274 (18%)	69 (28%)	34 (19%)	818 (14%)	4513 (39%)	569 (26%)	6277 (29%)
INSTI-based	26 (2%)	9 (4%)	1 (1%)	9 (<1%)	4 (<1%)	0	49 (<1%)
Others†	24 (2%)	3 (1%)	0	4 (<1%)	35 (<1%)	35 (2%)	101 (1%)

Data are n (%), median (IQR), n; median (IQR), or n/N (%). ART consists of the combination of at least three antiretrovirals. ART=antiretroviral therapy. IeDEA=International epidemiology Databases to Evaluate AIDS. INSTI=integrase strand transfer inhibitors. NNRTI=non-nucleoside reverse transcriptase inhibitors. *Severe HIV-associated immunodeficiency was defined according to WHO criteria as proportion of CD4 cells <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); denominators are the total number of individuals with available CD4 data. †Others category in initial ART regimen included dual therapy, entry inhibitors, and other atypical ART regimen.

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

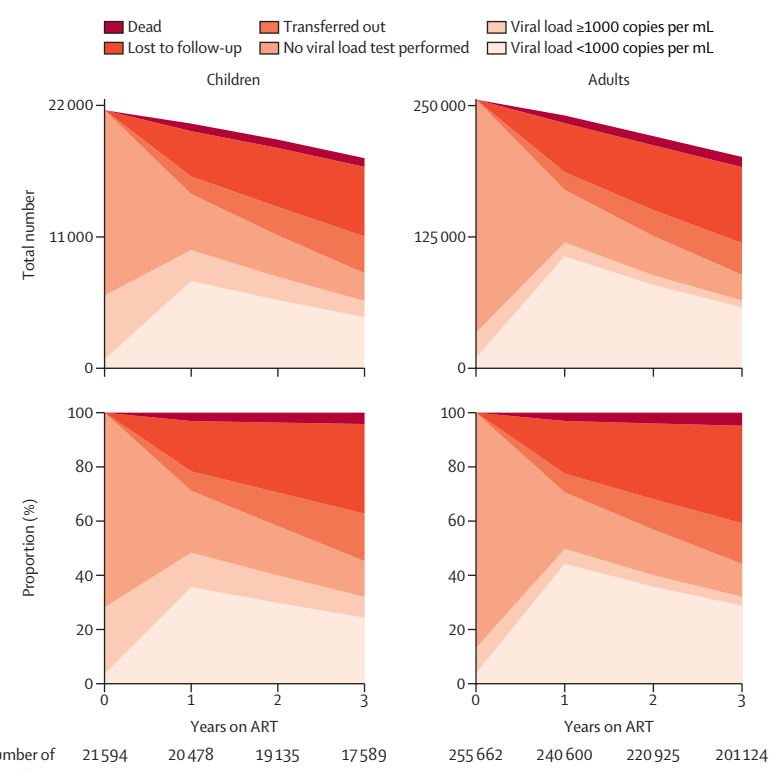

Figure 1: **HIV viral suppression and treatment outcomes for children and adolescents and adults with HIV in the International epidemiology Databases to Evaluate AIDS global consortium at years 1, 2, and 3 following antiretroviral initiation (intention-to-treat analysis)**
The proportions in this figure and the estimated weighted averages are shown in the appendix (pp 3–4).

(14 sites in three countries); and west Africa (eight sites in five countries; table 1). 73 (69%) of 106 sites were urban or semiurban clinics and 42 (40%) were located within regional, provincial, or university hospitals. The median age of children and adolescents at ART initiation was 6·2 years (IQR 1·7–11·8). Overall, 4777 (22%) in the child and adolescent group started ART younger than 1·5 years, and the proportion of children younger than 1·5 years at ART initiation varied by region (table 1). Adolescents (aged 10–17 years at ART start) represented 7050 (33%) of the child and adolescent group, ranging from 383 (26%) in Asia-Pacific to 105 (58%) in central Africa. Among 11 863 (55%) children and adolescents with available CD4 cell count (n=7629 for those aged ≥5 years) or CD4 proportion data (n=4234 for those younger than 5 years), 4732 (40%) had severe immunosuppression. The proportion of children and adolescents who were severely underweight or severely stunted varied between regions, as did the proportions of children and adolescents who were from lower-middle income and upper-middle income countries (table 1).

Using the intention-to-treat approach, the proportion of children and adolescents with viral suppression was 7303 (36%) of 20 478 at 1 year, 5709 (30%) of 19 135 at 2 years, and 4287 (24%) of 17 589 at 3 years after ART initiation (figure 1; appendix pp 3–4). When the analysis was limited to only children and adolescents who were in follow-up with an available viral load measurement, the proportions with viral suppression increased to 7303 (74%) of 9902 at 1 year, 5709 (75%) of 7649 at 2 years,

	Year 1			Year 2			Year 3		
	Estimated number with viral load <1000 copies per mL (plausible range)	Total non-deaths	Proportion with viral load <1000 copies per mL (plausible range)	Estimated number with viral load <1000 copies per mL (plausible range)	Total non-deaths	Proportion with viral load <1000 copies per mL (plausible range)	Estimated number with viral load <1000 copies per mL (plausible range)	Total non-deaths	Proportion with viral load <1000 copies per mL (plausible range)
Asia-Pacific	1192 (961–1259)	1426	84% (68–89)	1123 (887–1165)	1332	84% (67–87)	995 (778–1026)	1194	83% (65–86)
Caribbean, Central America, and South America	174 (125–201)	238	73% (53–84)	151 (110–180)	226	67% (49–80)	129 (91–150)	210	61% (43–71)
Central Africa	94 (55–109)	156	60% (35–70)	65 (36–74)	142	46% (25–52)	NA	NA	NA
East Africa	3293 (2115–4115)	5085	65% (42–81)	2598 (1671–3279)	4312	60% (39–76)	1980 (1238–2454)	3478	57% (36–71)
Southern Africa	6459 (4311–8375)	10194	63% (42–82)	6139 (3960–7740)	9901	62% (40–78)	5501 (3481–6855)	9256	59% (38–74)
West Africa	836 (586–1169)	1736	48% (34–67)	720 (492–999)	1640	44% (30–61)	572 (390–815)	1529	37% (26–53)
Overall	12048 (8153–15228)	18835	64% (43–81)	10796 (7156–13437)	17553	62% (41–77)	9177 (597–14300)	15667	59% (38–91)

ART consists of the combination of at least three antiretrovirals. Plausible ranges were generated by applying data for lower and upper bounds for the proportion of viral suppression using the literature reporting on viral outcomes among people with HIV in care (appendix pp 1–2). IeDEA=International epidemiology Databases to Evaluate AIDS. NA=not available.

Table 2: **Estimated total numbers and proportions of children and adolescents still alive with HIV viral load less than 1000 copies per mL by years on ART, stratified by IeDEA region (adjusted analysis)**

and 4287 (76%) of 5641 at 3 years. Overall, among 17589 children and adolescents by the end of year 3, 735 (4%) had died, 3076 (17%) had transferred out, and 5819 (33%) had been classified as lost to follow-up, with proportions varying between regions (appendix p 21).

The results of the adjusted analysis that accounted for the proportions of children and adolescents assumed to have a suppressed viral load among those who were in follow-up but did not have a viral load test, and among those who transferred out or were classified as lost to follow-up, are shown in table 2 and the appendix (pp 5–9).

255662 adults (163831 [64%] female, 91831 [36%] male) were included from 143 sites in 30 countries across seven IeDEA regions: Asia-Pacific (17 sites in 11 countries); the Caribbean, Central America, and South America (ten sites in six countries); North America (17 sites in two countries); central Africa (nine sites in one country); east Africa (68 sites in two countries); southern Africa (16 sites in four countries); and west Africa (six sites in four countries; table 3). 100 (70%) of 143 sites were urban or semiurban clinics and 61 (43%) were located within regional, provincial, or university hospitals. The median age of adults at ART initiation was 34 years (IQR 28–43; table 3). Baseline characteristics at ART initiation, including CD4 cell count and country income group, are shown in table 3.

Using the intention-to-treat approach, the proportion of adults with viral suppression was 106541 (44%) of 240600 at 1 year, 79141 (36%) of 220925 at 2 years, and 57970 (29%) of 201124 at 3 years after ART initiation (figure 1; appendix pp 3–4). When the analysis was limited to only adults who were in follow-up with available viral load, the proportions who were virally suppressed increased to 106541 (89%) of 119699 at 1 year, 79141 (89%) of 88463 at 2 years, and 57970 (90%) of 64487 at 3 years. Overall, among 201124 adults by the end of year 3, 30130 (5%) had died, 30130 (15%) had transferred out, and 72337 (36%) were classified as lost to follow-up, with proportions varying between regions (appendix p 22).

The results of the adjusted analysis accounting for the proportions of adults assumed to have viral suppression among those who were in follow-up without a viral load test, and among those who transferred or were lost to follow-up, are shown in table 4 and the appendix (pp 10–15).

The estimated viral suppression in the intention-to-treat analysis, adjusted analysis, and estimated proportions among the child and adolescent group and the adult group with viral load measurements are shown in figure 2 for the overall population and in appendix pp 15–17 by region. The results of the sensitivity analyses varying the common estimate of viral suppression among people with HIV who reconnected to care are shown in the appendix (pp 19–20).

Discussion

This study described viral suppression among children and adolescents as well as adults starting ART between 2010 and 2019 at 148 IeDEA sites in 31 countries. The proportion of people with HIV who were virally suppressed was low in the unadjusted intention-to-treat analysis. However, when we adjusted estimates for missing viral load among people with HIV who were in care but without viral load testing, who had transferred, or who were lost to follow-up, the proportion who were virally suppressed increased considerably. The unadjusted analyses, with a denominator that included a large number of individuals who were lost to follow-up, 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 people with HIV on ART who are virally suppressed can be achieved by better

	Asia-Pacific (n=2270)	Caribbean, Central America, and South America (n=9898)	Central Africa (n=2545)	East Africa (n=61 413)	Southern Africa (n=162 856)	West Africa (n=6087)	North America (n=10 593)	Total (n=255 662)
Sex								
Female	855 (38%)	1977 (20%)	1487 (58%)	39 724 (65%)	113 396 (70%)	4162 (68%)	2230 (21%)	163 831 (64%)
Male	1415 (62%)	7921 (80%)	1058 (42%)	21 689 (35%)	49 460 (30%)	1925 (32%)	8363 (79%)	91 831 (36%)
Age, years								
<24	265 (12%)	1414 (14%)	297 (12%)	7199 (12%)	16 808 (10%)	230 (4%)	594 (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 (9%)	7325 (12%)	16 195 (10%)	1048 (17%)	3312 (31%)	29 345 (11%)
Median	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 per μL								
<200	628 (28%)	3565 (36%)	275 (11%)	9940 (16%)	64 040 (39%)	2121 (35%)	2786 (26%)	83 354 (33%)
200–349	312 (14%)	2276 (23%)	308 (12%)	7327 (12%)	43 695 (27%)	1477 (24%)	2133 (20%)	57 527 (23%)
350–499	157 (7%)	1396 (14%)	312 (12%)	7052 (11%)	18 366 (11%)	641 (11%)	2001 (19%)	29 923 (12%)
≥500	152 (7%)	1211 (12%)	748 (29%)	6035 (10%)	14761 (9%)	649 (11%)	2554 (24%)	26 110 (10%)
Missing data	1021 (45%)	1450 (15%)	902 (35%)	31 059 (51%)	21 994 (14%)	1199 (20%)	1119 (11%)	58 748 (23%)
Median	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 per mL								
Available data	987 (43%)	7813 (79%)	117 (5%)	2208 (4%)	12 432 (8%)	964 (16%)	9217 (87%)	33 738 (13%)
Median	4·9 (4·3–5·5)	4·9 (4·2–5·4)	2·3 (1·3–4·1)	2·7 (0·0–4·5)	3·9 (2·6–4·9)	4·0 (0·0–5·4)	4·3 (2·7–5·0)	4·4 (2·6–5·2)
Calendar year of ART initiation								
2010–12	861 (38%)	2517 (25%)	0	0	56 309 (35%)	1802 (30%)	6731 (64%)	68 220 (27%)
2013–15	777 (34%)	4021 (41%)	0	29 180 (48%)	57 232 (35%)	2256 (37%)	3373 (32%)	96 839 (38%)
2016–19	632 (28%)	3360 (34%)	2545 (100%)	32 233 (52%)	49 315 (30%)	2029 (33%)	489 (5%)	90 603 (35%)
World Bank country income group								
High income	170 (7%)	1828 (18%)	0	0	0	0	10 593 (100%)	12591 (5%)
Upper-middle income	975 (43%)	7721 (78%)	0	0	161 615 (99%)	0	0	170 311 (67%)
Lower-middle income	1125 (50%)	349 (4%)	0	49 722 (81%)	0	3137 (52%)	0	55 574 (22%)
Low income	0	0	2545 (100%)	11 691 (19%)	1241 (1%)	2950 (48%)	0	17 186 (7%)
Initial ART regimen								
NNRTI-based	2099 (92%)	7499 (76%)	2507 (99%)	60 206 (98%)	160 949 (99%)	5389 (89%)	1117 (11%)	239 766 (94%)
Protease inhibitor-based	158 (7%)	1557 (16%)	14 (1%)	533 (1%)	1557 (1%)	608 (10%)	6148 (58%)	10 575 (4%)
INSTI-based	3 (<1%)	746 (8%)	19 (1%)	657 (1%)	22 (<1%)	21 (<1%)	2290 (22%)	3758 (1%)
Others*	10 (<1%)	96 (1%)	5 (<1%)	17 (<1%)	244 (<1%)	69 (1%)	1038 (10%)	1563 (1%)

Data are n (%) or median (IQR). ART consists of the combination of at least three antiretrovirals. ART=antiretroviral therapy. IeDEA=International epidemiology Databases to Evaluate AIDS. INSTI=integrase strand transfer inhibitors. NNRTI=non-nucleoside reverse transcriptase inhibitors. *Others category in initial ART regimen included dual therapy, entry inhibitors, and other atypical ART regimen.

Table 3: **Characteristics of adults at ART initiation, by IeDEA region**

routine viral load testing and maximising retention or reconnecting people with HIV to care.

Overall, only 24% of children and adolescents and 29% of adults (unadjusted intention-to-treat 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 intention-to-treat analyses, our estimates of viral suppression are similar to or lower than those reported in other studies[19–21] and reports from the Population-based HIV Impact Assessment surveys of multiple African countries and UNAIDS modelling studies.[22,1] A large meta-analysis conducted after 2010 reported intention-to-treat results for children and adolescents younger than 18 years living in LMICs and showed that 63% were virally suppressed after 12 months on ART.[19] This study considered all children with missing viral load results as having viral failure, but did not adequately describe the population included in the analysis. A 2016 systematic review, including participants from a wide range of settings, showed substantial variation (27–89%) in the proportion of children and adolescents with viral suppression after 12 months of ART.[20] The proportions of virally suppressed

	Year 1			Year 2			Year 3		
	Estimated number with viral load <1000 copies per mL (plausible range)	Total non-deaths	Proportion with viral load <1000 copies per mL (plausible range)	Estimated number with viral load <1000 copies per mL (plausible range)	Total non-deaths	Proportion with viral load <1000 copies (plausible range)	Estimated number with viral load <1000 copies per mL (plausible range)	Total non-deaths	Proportion with viral load <1000 copies per mL (plausible range)
Asia-Pacific	1851 (1568–1898)	2050	90% (77–93)	1691 (1385–1705)	1886	90% (73–90)	1539 (124–1557)	1761	87% (71–88)
Caribbean, Central America, and South America	7611 (4356–7784)	9067	84% (48–86)	6327 (3641–6563)	8111	78% (45–81)	5161 (297–5426)	7255	71% (41–75)
North America	7603 (6257–7790)	9516	80% (66–82)	6119 (4960–6294)	8232	74% (60–76)	4991 (397–5161)	7219	69% (55–71)
Central Africa	1373 (871–1520)	2231	62% (39–68)	807 (504–955)	1941	42% (26–49)	339 (188–470)	1641	21% (11–29)
East Africa	37 824 (25 039–41 583)	50 525	75% (50–82)	30 354 (20 158–32 589)	41 749	68% (44–75)	19 505 (12 544–21 759)	32 799	59% (38–66)
Southern Africa	117 708 (79 580–116 654)	147 215	78% (52–86)	97 793 (65 164–108 645)	134 739	73% (48–81)	81 832 (53 831–86 679)	123 456	66% (44–70)
West Africa	2994 (1933–3327)	4814	62% (40–69)	2461 (1576–2794)	4580	54% (34–61)	1893 (1182–2208)	4327	44% (27–51)
Overall	176 964 (119 604–180 556)	225 418	79% (53–80)	145 552 (97 388–159 545)	201 238	72% (48–79)	115 260 (75 933–123 260)	178 458	65% (43–69)

ART consists of the combination of at least three antiretrovirals. Plausible ranges were generated by applying data for lower and upper bounds for the proportion of viral suppression using the literature reporting on viral outcomes among people with HIV in care (appendix pp 1–2). ART=antiretroviral therapy. IeDEA=International epidemiology Databases to Evaluate AIDS.

Table 4: **Estimated total numbers and proportions of adults still alive with HIV viral load less than 1000 copies per mL by years on ART, stratified by IeDEA region (adjusted analysis)**

adults in our intention-to-treat analysis were lower than the intention-to-treat 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 people with HIV only from LMICs or those who started with triple ART regimens, in contrast with our study, which included people with HIV from more diverse populations, regardless of the ART regimen used.

3 years after ART initiation, more than half of children and adolescents and adults were lost to follow-up or had transferred out. This partially explains the low proportions of viral suppression observed in our intention-to-treat analyses. The common risk factors responsible for loss to follow-up, such as patient-related factors, site-level factors, tracking systems, and poor access to HIV services, were reported in the IeDEA regions.[24] In studies that traced people with HIV who were lost to follow-up, a substantial proportion of individuals were found to be alive, connected to care at a different clinic, and still taking ART.[25,26] A 2017 tracing study of children and adolescents and adults who started ART and were lost to follow-up found that undocumented transfers increased and mortality decreased over time after the scale-up of ART and decentralisation of ART care.[27] People with HIV who transferred have also been reported to have similar outcomes to those who were retained in care, beyond the 3 months following transfer.[28,29] In this study, when we accounted for the estimated proportions of people with HIV with viral suppression among those who transferred or were classified as lost to follow-up, the overall proportions of people with HIV with viral suppression increased considerably; however, the proportions with viral suppression at 3 years after ART initiation—after

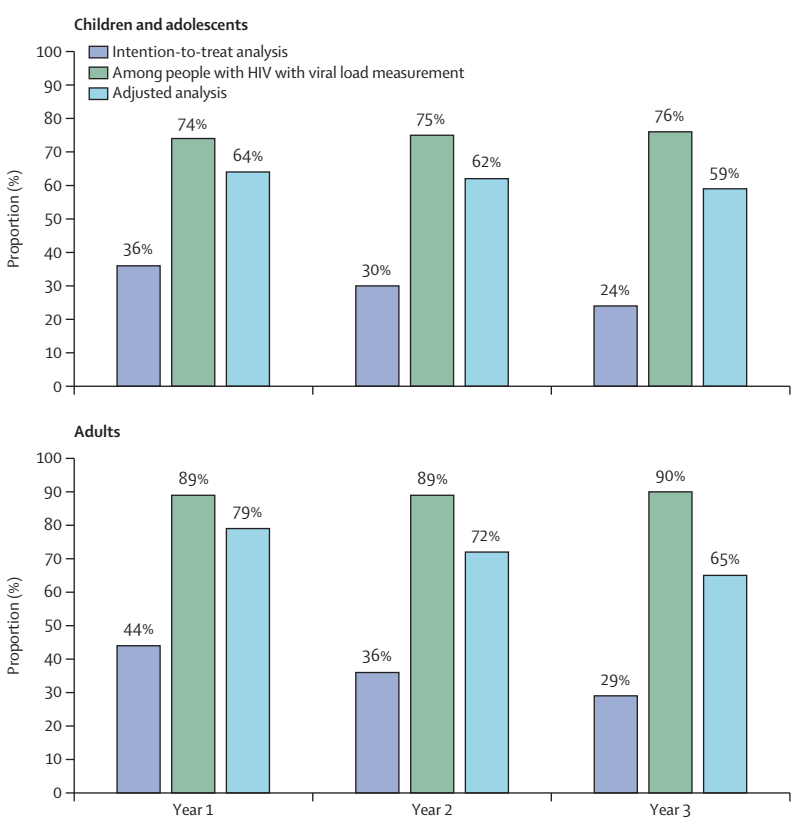

Figure 2: **Proportions of children and adolescents and adults with HIV viral suppression in the intention-to-treat population, among individuals with viral load measurements, and in the adjusted analyses in the International epidemiology Databases to Evaluate AIDS global consortium at years 1, 2, and 3 following antiretroviral therapy initiation**

accounting for those lost to follow-up, transferred out, and in care with no viral load testing—remained low in regions with large proportions of loss to follow-up (eg, the central, east, and west Africa regions).

In the second analysis, in which we calculated viral suppression among people with HIV who were alive, in follow-up, and had viral load testing, proportions were greater than 74% in children and adolescents and greater than 89% in adults. These results were similar to previous estimates reported for people with HIV with routine viral load monitoring. Data from the scale-up of Kenya's national HIV programme from 2012 to 2016 showed a smaller proportion (64%) of children and adolescents who were virally suppressed after at least 6 months on treatment, but a similar proportion (86%) of adults who were virally suppressed.[30] Our findings showed somewhat greater proportions of viral suppression than those from an earlier large study of treatment programmes in southern, east, and west Africa, in which 80% of people with HIV (aged ≥16 years) had viral suppression by 12 months.[19,31] The earlier studies on HIV viral suppression from settings that did targeted testing or were still transitioning to routine viral load testing might have underestimated viral suppression when missing viral load measurements were not taken into account in reporting the virally suppressed proportions.

Our analysis has several limitations. Despite having a relatively large overall sample size, only one country within central Africa had annual viral load testing across the 2010–19 period, limiting generalisability in this region. Furthermore, treatment programmes included in the IeDEA consortium might not be fully representative of their countries or subpopulations. Data on ethnicity were not available. It is possible that some clinically stable people with HIV might have been exempted from viral load testing within sites offering routine testing. We also cannot rule out the possibility that mortality was underestimated because of the misclassification of deaths as loss to follow-up. For the adjusted analyses of those who were lost to follow-up, 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 programme management, choices of treatment regimens, treatment switches, and assays used for viral load measurements, reasons for not returning to clinic, and outcomes after transferring or becoming lost to follow-up are likely to have varied across settings.[32,33] These differences might have influenced or biased the results of viral suppression. Heterogeneity in country-specific treatment programmes limit generalisability when analysing large, collaborative datasets.

In conclusion, in this analysis of children and adolescents and adults receiving care at IeDEA sites, results from the intention-to-treat analyses showed that low proportions of children and adolescents and adults had viral suppression after 3 years on ART. When the estimates were adjusted to account for missing viral load measurements, regardless of whether people with HIV 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 people with HIV who are lost to follow-up who are connected to care elsewhere and still receiving ART, or estimates that do not account for people with HIV in care who are not tested, are unlikely to reflect the actual proportion who are virally suppressed among those who are accessing care. Although adults with HIV are approaching the 95% target, progress among children and adolescents is slower and estimates are still behind the UNAIDS targets.

Contributors

WMH, AK, and MGL conceptualised and designed the study. WMH and AK analysed the data and wrote the first draft of the manuscript. MGL, KW-K, RM, AE, CY, CPC, TJM, AJ, BC, LEC, EZ, NF, AHS, and AK reviewed and contributed to 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. All authors had full access to the study data and final responsibility for the decision to submit for publication.

Declaration of interests

AHS reports grant support to her institution for activities unrelated to this work. MGL reports unrestricted grants from Gilead Sciences, Janssen–Cilag, and ViiV Healthcare. CPC reports grant support from National Institutes of Health (NIH; U01AI069923) and consultation fees and honoraria from GSK–ViiV, and Merck. KNA reports grant support from NIH, with funding payments made to her institution; and consultation fees from the All of Us Research Program (NIH) and Trio Health. All other authors report no competing interests.

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, NSW, 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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U01AI069434, U01AI103390, U01AI103397, U01AI103401, U01AI103408, U01DA036935, U01HD032632, U10EY008057, U10EY008052, U10EY008067, U24AA020794, U54MD007587, UL1RR024131, UL1TR000004, UL1TR000083, UL1TR000454, UM1AI035043, Z01CP010214, and Z01CP010176 (The North American AIDS Cohort Collaboration on Research and Design [NA-ACCORD]); contracts CDC-200-2006-18797 and CDC-200-2015-63931 from the US Centers for Disease Control and Prevention; contract 90047713 from the US Agency for Healthcare Research and Quality; contract 90051652 from the US Health Resources and Services Administration; grants CBR-86906, CBR-94036, HCP-97105, and TGF-96118 from the Canadian Institutes of Health Research; Ontario Ministry of Health and Long Term Care; and the Government of Alberta, Canada. Additional support was provided to NA-ACCORD by the Intramural Research Program of the National Cancer Institute. Informatics resources were supported by the Harmonist project, R24AI124872. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above. Complete investigator lists and regional acknowledgments are in the appendix.

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