HIV Viral Load Suppression in Adults and Children Receiving Antiretroviral Therapy—Results From the IeDEA Collaboration

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Background: Having 90% of patients on antiretroviral therapy (ART) and achieving an undetectable viral load (VL) is 1 of the 90:90:90 by 2020 targets. In this global analysis, we investigated the proportions of adult and paediatric patients with VL suppression in the first 3 years after ART initiation.

Methods: Patients from the IeDEA cohorts who initiated ART between 2010 and 2014 were included. Proportions with VL suppression (<1000 copies/mL) were estimated using (1) strict intention to treat (ITT)–loss to follow-up (LTFU) and dead patients counted as having detectable VL; and (2) modified ITT—LTFU and dead patients were excluded. Logistic regression was used to identify predictors of viral suppression at 1 year after ART initiation using modified ITT.

Results: A total of 35,561 adults from 38 sites/16 countries and 2601 children from 18 sites/6 countries were included. When comparing strict with modified ITT methods, the proportion achieving VL suppression at 3 years from ART initiation changed from 45.1% to 90.2% in adults, and 60.6% to 80.4% in children. In adults, older age, higher CD4 count pre-ART, and homosexual/bisexual HIV exposure were associated with VL suppression. In children, older age and higher CD4 percentage pre-ART showed significant associations with VL suppression.

Conclusions: Large increases in the proportion of VL suppression in adults were observed when we excluded those who were LTFU or had died. The increases were less pronounced in children. Greater emphasis should be made to minimize LTFU and maximize patient retention in HIV-infected patients of all age groups.

Key Words: HIV, suppression, paediatrics, adults, IeDEA

INTRODUCTION

Durable virologic suppression is the primary goal of antiretroviral therapy (ART). Having 90% of patients on ART with undetectable HIV viral load (VL) is the third "90" for global programs as part of the 90:90:90 targets.[1] Increasingly, VL testing is offered as part of ART monitoring to confirm early treatment failure and to indicate second-line treatment switch to reduce the accumulation of HIV drug resistance mutations. The World Health Organization (WHO) now recommends routine VL testing[2] as the preferred method to detect ART failure rather than immunological and clinical monitoring.

The International Epidemiology Databases to Evaluate AIDS (IeDEA) global consortium was established by the U.S. National Institute of Allergy and Infectious Diseases in 2005. There are 7 regional data centers within IeDEA in North America (The North American AIDS Cohort Collaboration on Research and Design, NA-ACCORD), the Caribbean, Central and South America (CCASAnet), the Asia-Pacific (AP), and Africa (East Africa, EA; Central Africa, CA; West Africa, WA; Southern Africa, SnA).[3,4] Currently, IeDEA includes data on more than 1 million people living with HIV/AIDS. According to individual country assessments[5] on HIV indicators for sites within NA-ACCORD and CCASAnet, the percentage of patients on ART in the United States was 67%, whereas the highest was reported for Mexico at 90%. In the African population, in particular EA and SnA, ART coverage increased from 24% in 2010 to 54% in 2015, whereas CA and WA had a lower percentage coverage at 28%. ART usage in AP doubled from 19% in 2010 to 41% in 2015.[6] The proportion of patients with VL suppression across different IeDEA regions in recent years, however, remains unclear. The primary objective of this study was to estimate the proportions of adult and paediatric patients enrolled in IeDEA, who achieved undetectable VL in the first 3 years after initiating ART. The secondary objective was to determine factors associated with VL suppression at 1 year after ART.

METHODS

Study Population and Inclusion Criteria

Adult and paediatric patients enrolled in IeDEA were included if they had initiated ART between 2010 and 2014. Paediatric patients were defined as children and adolescents aged 18 years and younger when starting ART; adults were those aged 18 years and older at ART initiation. ART was defined as 3 or more antiretroviral drugs in a single regimen; those who started treatment with mono- or dual-drug regimens were excluded. Sites within each respective participating region were included if they were confirmed to perform routine annual VL testing. If no specific information was provided regarding VL testing frequency, we performed a calculation by obtaining the average number of VL tests for each patient from the regional cohort enrolment date to the last follow-up date. If the median number of VL tests per patient per site was above 0.8, that site was included in the initial data capture. However, only patients with at least 1 VL test after ART initiation were included in the analyses.

Definitions

VL suppression was defined as VL <1000 copies/mL at 1, 2, and 3 years from ART initiation to be consistent with the WHO definition for classifying virological failure.[2] Moreover, because of the use of different virological assays across the regions with varying lower limits of detection, the use of this threshold of VL <1000 copies/mL allowed the inclusion of sites with higher undetectable cutoffs. This threshold also removed the concern of unnecessarily excluding patients experiencing transient virological "blips" and then returning to virologic suppression."[7] The annual time points reflect the WHO recommendations for VL testing to monitor for treatment failure.[8] We have chosen to include data up to 3 years after ART initiation to minimize loss to follow-up (LTFU), as patient retention has been shown to decrease to 65% at 3 years.[9] As different sites have different definitions of LTFU, patients in this study were considered to be LTFU according to the LTFU indicator provided in each regional database. If no LTFU information was available, patients who were not seen within 6 months[10] before the database closing date were considered lost at their final visit date defined as the latest of CD4, VL, or clinic visit date.

Statistical Analyses

Simple proportions were calculated by percentages. Two methods were used to estimate proportions of patients with undetectable VL.

Strict Intention to Treat

Patients who were LTFU or dead were counted as having detectable VL after their last visit/death date up until 3 years after ART initiation. Patients who were transferred out were removed from the analyses after their transfer date. The denominator for each 1-, 2-, and 3- year time point included patients who had VL testing at that time point and patients who were LTFU or dead before that time point (counted as having detectable VL). Patients who did not have VL testing or transferred out before each time point were not included in the denominator (Supplemental Digital Content Figs. 1 and 3, http://links.lww.com/QAI/B64).

Modified Intention to Treat

The denominator at each time point included patients who had VL testing at that time point. Patients who did not have VL testing, or those who were LTFU, dead, or

transferred out before each time point were not included in the denominator (Supplemental Digital Content Fig. 2, http://links.lww.com/QAI/B64).

Factors associated with VL suppression at 1 year, as defined by the modified intention-to-treat (ITT) method, were analyzed using logistic regression methods. We chose to analyze VL suppression at 1 year to minimize LTFU cases. In addition, as we included the VL measurement closest to the annual time point, our analyses would not be biased by how often VL was assessed. Covariates included were age at ART initiation, sex, previous AIDS diagnosis, pre-ART CD4 count or percent, HIV mode of exposure, and region. ART combinations were not included in the analyses because of potential collinearity with different regions. For example, we would expect to see most patients from resource-limited regions, such as in Asia and Africa, initiating on a nucleoside reverse transcriptase inhibitors and a non–nucleoside reverse transcriptase inhibitors combination, whereas protease inhibitor–based and integrase inhibitor–based regimens would be most commonly used in developed countries such as those in NA-ACCORD. All variables were entered in the multivariable model; no model selection was attempted. *P*-values <0.05 were considered statistically significant. Sensitivity analyses were performed using the strict ITT definition, as well as using VL failure as the outcome of interest, defined as VL ≥1000 copies/mL.

Each regional data center was responsible for ethics approval, development of data collection systems, extracting data from their regional database or requesting relevant data variables from designated programs within their region, and verifying data quality. The data sets were then centrally aggregated and analyzed at The Kirby Institute, UNSW Sydney (the University of New South Wales), Australia, the regional data center of the IeDEA AP region. All data management and statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC) or Stata software version 14 (Stata Corp., College Station, TX).

RESULTS

Adults

There were a total of 38 sites from 16 countries: 12 sites/8 countries from AP, 6 sites/5 countries from CCA-SAnet, 14 sites/2 countries from NA-ACCORD, and 6 sites from South Africa (SA), a country within the IeDEA SnA regional cohort that met the eligibility criteria for adult analyses. Median VL testing frequency for each site ranged from 0.9 to 4.2 per patient per year. A total of 35,561 patients were included in the analyses: 2121 (6.0%) from AP; 3404 (9.6%) from CCASAnet; 14,579 (41.0%) from NA-ACCORD; and 15,457 (43.5%) from SA (Table 1 and Supplemental Digital Content Table 5, http://links.lww.com/QAI/B64). Sixty-one percent were men. At ART initiation, the median age was 37 years [interquartile range (IQR 30–46 years)] and the median CD4 cell count was 218 cells/μL (IQR: 105-344 cells/μL).

Using the strict ITT method, the overall proportion of adults with VL suppression at 1 year from ART initiation was

**TABLE 1.** Patient Characteristics

	Total Adults: 35,561	Total Children: 2601
	Number* (%)	**Number* (%)**
Median age at ART initiation (yrs)	37 (IQR 30–46)	4.65 (IQR 1.02–9.75)
Sex		
Male	21,623 (60.8)	1299 (49.9)
Female	13,935 (39.2)	1302 (50.1)
Unknown	3 (0.0)	0 (0.0)
Previous AIDS-defining illness		
No	15,508 (43.6)	164 (6.3)
Yes	2695 (7.6)	52 (2.0)
Unknown	17,358 (48.8)	2385 (91.7)
Median pre-ART CD4 count	218 cells/μL (IQR 105–344)	15.89% (IQR 8.70–23.24)
HIV mode of exposure		
Homosexual/bisexual	8537 (24.0)	0 (0.0)
Heterosexual	14,216 (40.0)	0 (0.0)
IDU	1639 (4.6)	0 (0.0)
Perinatal	0 (0.0)	2119 (81.5)
Other†	645 (1.8)	190 (7.3)
Unknown	10,524 (29.6)	292 (11.2)
Region		
Asia-Pacific	2121 (6.0)	291 (11.2)
Caribbean, Central and South America	3404 (9.6)	75 (2.9)
North America	14,579 (41.0)	0 (0.0)
South Africa	15,457 (43.5)	2235 (85.9)

*Unless otherwise specified.
†For children, "Other" includes sexual behaviour (184), sexual abuse (2), blood transfusion (2), and breastfeeding (2).
IDU, injecting drug users.

83.0%; 70.0% at 2 years; and 45.1% at 3 years. Figure 1A shows the proportions of adults with VL suppression decreasing after 2 years for NA-ACCORD and SA, with AP maintaining the highest VL suppression over the full 3 years. Using the modified ITT method where patients who were LTFU or dead were excluded, of the 35,561 adults patients, 26,153 (73.5%) had VL testing at 1 year; 13,602 (38.2%) at 2 years; and 4629 (13.0%) at 3 years. Overall, VL suppression increased to 88.5%, 89.5%, and 90.2% for years 1–3, with all regions showing high proportions above 85% for all years (Fig. 1B).

Table 2 shows factors associated with VL suppression at 1 year using the modified ITT method. The multivariate results show that after adjustment for all variables, sex was the only factor showing no association with VL suppression (*P* = 0.358). The odds for VL suppression increased with age 25–49 years [odds ratio (OR) = 1.42, 95% confidence interval (CI): 1.24 to 1.63], and age 50 years and older (OR = 2.20, 95% CI: 1.86 to 2.60), all *P* < 0.001, compared with age 24 years and younger. Pre-ART CD4 count also showed an increasing trend: 200–349 cells/μL (OR = 1.60, 95% CI: 1.44 to 1.78), 350–499 cells/μL (OR = 1.73, 95% CI: 1.48 to 2.02), and ≥500 cells/μL (OR = 1.91, 95% CI: 1.62 to 2.26), all *P* < 0.001, compared with CD4 <200 cells/μL. Patients
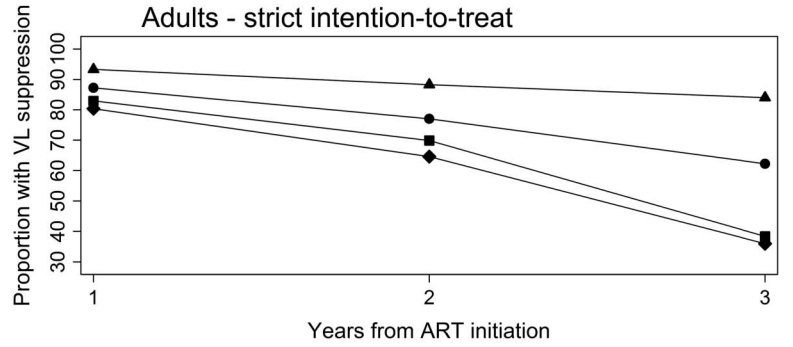
FIGURE 1. Proportion of adults with viral load (VL) suppression using (A) strict intention-to-treat and (B) modified intention-to-treat methods. CCASAnet, Caribbean, Central, and South America; VL, viral load.

with homosexual/bisexual mode of HIV exposure were more likely to have VL suppression (OR = 1.66, 95% CI: 1.46 to 1.89, $P < 0.001$), whereas injecting drug users had reduced odds compared with heterosexual mode of exposure (OR = 0.69, 95% CI: 0.58 to 0.83, $P < 0.001$). Having a previous AIDS-defining illness also negatively affected VL response (OR = 0.82, 95% CI: 0.71 to 0.95, $P = 0.008$). Comparison of different regions showed that when compared with NA-ACCORD, AP (OR = 2.78, 95% CI: 2.2 to 3.52, $P < 0.001$) and CCASAnet (OR = 1.70, 95% CI: 1.45 to 2.00, $P < 0.001$) had higher proportions of VL suppression. When AP was the reference group, patients in CCASAnet (OR = 0.61, 95% CI: 0.47 to 0.79, $P < 0.001$); NA-ACCORD (OR = 0.36, 95% CI: 0.28 to 0.45, $P < 0.001$); and SA (OR = 0.37, 95% CI: 0.29 to 0.48, $P < 0.001$), had smaller proportions of patients with VL suppression. Additional tests for multi-

collinearity showed that there was no collinearity among the variables included.

Paediatrics

The paediatric analysis included 18 clinical centers from 3 IeDEA regions with 2601 children overall: 291 (11.2%) from 10 AP sites/3 countries, 75 (2.9%) from 4 CCASAnet sites/2 countries, and 2235 (85.9%) from 4 sites in SA (Table 1 and Supplemental Digital Content Table 6, http://links.lww.com/QAI/B64). Median VL testing frequency for each site ranged from 1.5 to 2.7 per patient per year. At ART initiation, the median age was 4.7 years (IQR 1.0–9.8). For 1677 children with available data, the median CD4 percentage was 15.9 (IQR 8.70–23.24) with 477 (18.3%) children having CD4 percentage <10%. A small

TABLE 2. Factors Associated With Viral Load Suppression at 1 Year From ART Initiation, Adult Analysis Using Modified Intention-to-Treat Method (N = 26,153)

	Total Patients	VL <1000 Copies/mL	Univariate			Multivariate		
			OR	95% CI	P	OR	95% CI	P
Age at ART initiation (yrs)					<0.001			**<0.001**
18–24	2065	1773	Ref			Ref		
25–49	19,275	16,974	1.21	1.07 to 1.39	0.004	**1.42**	**1.24 to 1.63**	**<0.001**
≥50	4813	4393	1.72	1.47 to 2.02	<0.001	**2.20**	**1.86 to 2.60**	**<0.001**
Sex								
Male	16,323	14,565	Ref			Ref		
Female	9828	8573	0.82	0.76 to 0.89	<0.001	1.04	0.95 to 1.14	0.358
Unknown	2	2						
Previous AIDS-defining illness					0.027			**0.008**
No	11,027	9705	Ref			Ref		
Yes	2000	1725	0.85	0.74 to 0.98	0.027	**0.82**	**0.71 to 0.95**	**0.008**
Unknown	13,126	11,710	1.13	1.04 to 1.22	0.003	**0.83**	**0.69 to 0.99**	**0.036**
Pre-ART CD4 count (cells/μL)					<0.001			**<0.001**
<200	10,000	8590	Ref			Ref		
200–349	6241	5661	1.60	1.45 to 1.77	<0.001	**1.60**	**1.44 to 1.78**	**<0.001**
350–499	2631	2393	1.65	1.43 to 1.91	<0.001	**1.73**	**1.48 to 2.02**	**<0.001**
≥500	2363	2160	1.75	1.50 to 2.04	<0.001	**1.91**	**1.62 to 2.26**	**<0.001**
Missing	4918	4336	1.22	1.10 to 1.36	<0.001	**1.29**	**1.16 to 1.44**	**<0.001**
HIV mode of exposure					<0.001			**<0.001**
Homosexual/bisexual	6676	6139	1.73	1.56 to 1.92	<0.001	**1.66**	**1.46 to 1.89**	**<0.001**
Heterosexual	10,403	9036	Ref			Ref		
IDU	1229	1017	0.73	0.62 to 0.85	<0.001	**0.69**	**0.58 to 0.83**	**<0.001**
Other	504	449	1.24	0.93 to 1.64	0.148	1.10	0.82 to 1.48	0.534
Unknown	7341	6499	1.17	1.07 to 1.28	0.001	**1.23**	**1.12 to 1.36**	**<0.001**
Region					<0.001			**<0.001**
Asia-Pacific	1806	1719	0.38	0.31 to 0.48	<0.001	**2.78**	**2.20 to 3.52**	**<0.001**
Caribbean, Central and South America	2777	2546	0.68	0.59 to 0.79	<0.001	**1.70**	**1.45 to 2.00**	**<0.001**
North America	10,970	9685	Ref			Ref		
South Africa	10,600	9190	1.16	1.07 to 1.25	<0.001	1.03	0.85 to 1.25	0.767

Values in bold represent significant covariates in the adjusted model.
IDU, injecting drug use.

proportion (0.2) had experienced WHO clinical stage 4 events before ART initiation. These baseline patient characteristics differed between regions. Median CD4 percentage and age were 12% and 8 years in AP, 23% and 11 years in CCASAnet, and 16% and 4 years in SA.

Using strict ITT methods as shown in Figure 2A, a decrease in the proportion of children with VL <1000 copies/mL over time was seen for CCASAnet (80.3% at year 1, 68.3% at year 2 and 50.0% at year 3) and SA regions (73.3%–67.5% and 56.7%). Using the modified ITT approach, CCASAnet still showed a decline in the proportion of children with viral suppression from 81.7% to 73.7%, and 69.2% for years 1–3. Overall, during the follow-up period, 69.2%–83.0% of children maintained VL <1000 copies/mL (Fig. 2B).

The adjusted statistical analysis (Table 3) identified the following baseline characteristics to be associated with VL suppression at 1 year after ART initiation: age 1.5–4 years (OR = 2.33, 95% CI: 1.73 to 3.14, P < 0.001)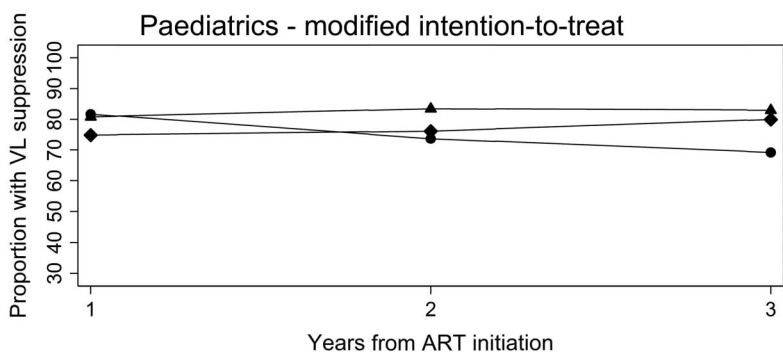; 5–9 years (OR = 2.79, 95% CI: 2.06 to 3.78, P < 0.001); 10–14 years (OR = 2.32, 95% CI: 1.70 to 3.16, P < 0.001); and 15–17 years (OR = 2.34, 95% CI: 1.28 to 4.27, P = 0.006) compared with children younger than 1.5 years (the reference group); and pre-ART CD4 percentage 15%–24% (OR = 2.38, 95% CI: 1.67 to 3.41, P < 0.001) and ≥25% (OR = 1.81, 95% CI: 1.24 to 2.64, P = 0.002) versus CD4 <10%. Other factors, including sex, WHO clinical stage 4, mode of exposure, and region were not significantly associated with VL suppression. No collinearity was detected among the variables.

The strict ITT sensitivity analyses (Supplemental Digital Content Tables 1 and 2, http://links.lww.com/QAI/B64) showed similar results to the main analyses. In VL failure analyses (Supplemental Digital Content Tables 3 and 4, http://links.lww.com/QAI/B64), the ORs of the covariates were simply the reciprocal of the ORs reported in the main analyses, with the same P-values. This indicates that the use of logistic regression was appropriate for both VL suppression and VL failure outcomes in adults and children.

Paediatrics - strict intention-to-treat

Total patients			
Asia-Pacific	229	194	137
CCASAnet	61	41	18
South Africa	1714	1070	556

A

Paediatrics - modified intention-to-treat

Total patients			
Asia-Pacific	229	187	129
CCASAnet	60	38	13
South Africa	1679	948	394

FIGURE 2. Proportion of paediatric patients with viral load (VL) suppression using (A) strict intention-to-treat and (B) modified intention-to-treat methods. CCASAnet, Caribbean, Central, and South America; VL, viral load.

B

—▲— Asia-Pacific   —●— CCASAnet
—◆— South Africa

DISCUSSION

Our study included data from 4 IeDEA regions covering 35,561 patients from 38 adult sites and 2601 patients from 24 paediatric sites who initiated ART between 2010 and 2014. Using the modified ITT approach that excludes LTFU and those who died, the proportions of patients with VL suppression was 90% for adults and 80% for children at 3 years. However, when the strict ITT approach was used, including LTFU and deceased patients and categorizing them as having detectable VL, these estimates decreased to 45% in adults and 61% in children. In adults, older age, higher pre-ART CD4 count, homosexual/bisexual and other modes of HIV exposure were associated with a better chance of achieving VL suppression at 1 year from ART initiation. Children older than 1.5 years and CD4 ≥15% were associated with a higher chance of achieving VL suppression.

Adults from the AP region performed significantly better than other regions. In children, VL suppression at 1 year did not differ significantly between regions.

Patients included in this study were those from sites that offered routine annual VL testing. Many resource-limited countries throughout the world currently do not offer routine VL tests for the detection of HIV treatment failure. For example, all sites within the WA, CA, and EA IeDEA regions and countries within the SnA IeDEA region outside SA did not have annual VL testing for the 2010–2014 time period. Some countries in the AP region, including Cambodia and Vietnam, also did not perform routine VL testing. The WHO[2] guidelines have recently recommended that VL testing be the preferred method of detecting treatment failure, and many countries have adopted this recommendation and are scaling-up their VL monitoring capacity.[11,12] Studies have

TABLE 3. Factors Associated With Viral Suppression at 1 Year From ART Initiation, Paediatric Analysis Using Modified Intention to Treat Method (N = 1968)

	Total Patients	VL <1000 Copies/mL	Univariate			Multivariate		
			OR	95% CI	P	OR	95% CI	P
Age at ART initiation (yrs)					<0.001			**<0.001**
<1.5	569	364	Ref			Ref		
1.5–4	441	355	2.32	1.74 to 3.11	<0.001	**2.33**	**1.73 to 3.14**	**<0.001**
5–9	492	405	2.62	1.97 to 3.50	<0.001	**2.79**	**2.06 to 3.78**	**<0.001**
10–14	395	311	2.09	1.55 to 2.80	<0.001	**2.32**	**1.70 to 3.16**	**<0.001**
15–17	71	56	2.10	1.16 to 3.81	0.014	**2.34**	**1.28 to 4.27**	**0.006**
Sex								
Male	977	731	Ref			Ref		
Female	991	760	1.11	0.90 to 1.36	0.333	1.11	0.89 to 1.37	0.350
Previous AIDS-defining illness					0.199			0.613
No	127	111	Ref			Ref		
Yes	38	30	0.54	0.21 to 1.38	0.199	0.78	0.30 to 2.03	0.613
Unknown	1803	1350	0.43	0.25 to 0.73	0.002	0.53	0.31 to 0.92	0.024
Pre-ART CD4 (%)					0.021			**<0.001**
<10	396	291	Ref			Ref		
10–14	228	175	1.19	0.81 to 1.74	0.366	1.43	0.97 to 2.11	0.074
15–24	419	356	2.04	1.44 to 2.89	<0.001	**2.38**	**1.67 to 3.41**	**<0.001**
≥25	293	226	1.22	0.86 to 1.73	0.274	**1.81**	**1.24 to 2.64**	**0.002**
Missing	632	443	0.85	0.64 to 1.12	0.242	1.11	0.83 to 1.49	0.491
HIV mode of exposure					0.238			0.164
Perinatal	1592	1197	0.76	0.49 to 1.19	0.238	0.72	0.46 to 1.14	0.164
Sexual behaviour	129	103	Ref			Ref		
Other/Unknown	247	191	0.86	0.51 to 1.45	0.575	0.86	0.50 to 1.48	0.591
Region					0.083			0.384
Asia-Pacific	229	185	Ref			Ref		
Caribbean, Central and South America	60	49	1.06	0.51 to 2.20	0.877	1.02	0.47 to 2.21	0.959
South Africa	1679	1257	0.71	0.50 to 1.00	0.051	0.80	0.56 to 1.14	0.217

Values in bold represent significant covariates in the adjusted model.

shown that the WHO's immunologic and clinical failure criteria have performed poorly in predicting virological treatment failure leading to unnecessary switch to second-line ART during periods of VL suppression, or delayed switch because of the misclassification of treatment failure.[13–15] Using CD4 monitoring in the presence of HIV drug resistance, mutations during periods of viraemia may also lead to delayed ART switches compared with VL monitoring alone.[16] Delayed second-line ART switch can lead to the accumulation of drug-resistant mutations,[17,18] which can compromise treatment options for second-line therapy, particularly in resource-limited countries. In addition, low positive predictive value of current immunological criteria may result in increased costs because of unnecessary switches to second-line therapy in people with adequate VL suppression.[14] Unfortunately, some countries that do not yet offer VL monitoring continue to refer to CD4 measurements and clinical monitoring in the assessment of HIV treatment outcomes.

The overall high proportions of VL suppression under the modified ITT analyses indicate that patients who are followed-up and retained in care have a good response to treatment. This is in contrast to the decrease in the proportion of adults and children achieving VL suppression when LTFU and dead patients were included as being detectable under strict ITT methods. The decrease in the proportion of patients with VL suppression was less pronounced in children. When compared with adults, children had higher rates of suppression when we considered LTFU and death as detectable. This might be explained by a lower rate of LTFU in children (6%) compared with adults (12%) in this study. The decrease in VL suppression when patients who were LTFU or dead were assumed to have detectable viraemia has also been reported in another study,[19] which suggests the importance of retention in HIV care. Mortality rates were often found to be higher in children and adults who were LTFU or transferred out compared with patients who were retained in care.[20,21] An Australian study, however, showed no association between LTFU and mortality, possibly because of unreported reengagement into care.[22]

The multivariate analyses in this study indicate that the adult AP cohort has performed significantly better than NA-ACCORD as well as other cohorts, although proportions of VL suppression were above 85% for all regions. These results most likely reflect the patient recruitment process within AP. Sites in AP are urban referral centres and patients were recruited based on the likelihood of remaining in care.[23]

These results therefore do not represent the general HIV-infected population in Asia, and should be interpreted with caution. In contrast, for children the chance of VL suppression did not differ across regions which may indicate less between-region heterogeneity and less variations in both patient-level and site-specific factors. High clinical resources and access to paediatric antiretroviral formulations were reported in a survey of paediatric HIV programmatic and clinical management practices in Asia and sub-Saharan Africa.[24]

The association between older age and higher pre-ART CD4 count with VL suppression, and the increased risk of VL failure in patients with injecting drug users mode of exposure and those who had a previous AIDS-defining illness in adults are consistent with other published literature.[19,25–27] Although homosexual mode of exposure is often associated with lower adherence levels leading to poorer treatment outcomes,[28] the positive effect of this transmission group could possibly be explained by better ART adherence levels reported in some patients.[29–31] We found that children who initiated ART when CD4 >10% and those who started at 1.5 years of age were more likely to achieve VL suppression. This may reflect the impact of early access to ART and higher baseline level of RNA in infants and young children. An early study conducted in America found that infants whose disease progressed rapidly have high numbers of HIV-1 RNA copies during the first 24 months of life.[32] The association between high baseline VL (>1 million copies/mL) and VL failure has been also reported by a more recent study conducted in children in SA.[33] In addition, adherence issues related to taste and formulation, dosing and/or high pharmacokinetic variability of drugs might adversely affect virological response and contribute to poorer responses in younger children.[34]

Our study has several limitations including the classification of LTFU and dead patients as having detectable VL. Classifying dead patients as virological failure is debatable in terms of 90:90:90 and treatment as prevention. However, we have used this definition to be consistent with that used in clinical trials where LTFU and dead patients would generally be classified as "failed." It is also consistent with a strict ITT approach which includes all patients. Known transferred cases were excluded from the calculations, but there may be instances where patients have self-transferred without the knowledge of the treating physician. Patients in follow-up without VL testing were also not included in our analyses. This could be considered a potential bias as targeted VL testing to confirm treatment failure often occurs in resource-limited settings. However, as our study only included sites with annual VL testing, we assume that the bias caused by targeted VL testing would be minimized. Last, the lack of data completeness and heterogeneity of treatment approaches and settings are another concern when analyzing large collaborative data set. There may be discrepancies between the actual last follow-up date and the final visit date calculated using our definition which could lead to misclassifications of LTFU patients. Furthermore, 86% of children in this study are from SA, therefore the generalizability of our paediatric findings is limited. Data on ART adherence and factors related to ART adherence such as disclosure and orphan status in children were not available in our data set and therefore were not included in the multivariate analyses. As adherence level is a known predictor of virological outcomes[35] and disclosure in children is associated with ART adherence,[36] our analysis results should be interpreted with this in mind.

CONCLUSIONS

This multiregional collaborative study showed that a high level of VL suppression can be achieved among children and adults receiving ART in resource-limited settings. Our findings highlight that even for those retained in care, achieving 90:90:90 for children may be more challenging. Sustainable approaches are needed to ensure optimal clinical outcomes and to minimize LTFU and increase patient retention.

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