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Prevalence and Predictors of Persistent Human Immunodeficiency Virus Viremia and Viral Rebound After Universal Test and Treat: A Population-Based Study

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(See the Editorial Commentary by Mastro et al, on pages 1117–9.)

Background. There are limited data on individual human immunodeficiency virus (HIV) viral load (VL) trajectories at the population-level after the introduction of universal test and treat (UTT) in sub-Saharan Africa.

Methods. Human immunodeficiency virus VLs were assessed among HIV-positive participants through 3 population-based surveys in 4 Ugandan fishing communities surveyed between November 2011 and August 2017. The unit of analysis was a visit-pair (2 consecutive person-visits), which were categorized as exhibiting durable VL suppression, new/renewed VL suppression, viral rebound, or persistent viremia. Adjusted relative risks (adjRRs) and 95% confidence intervals (CIs) of persistent viremia were estimated using multivariate Poisson regression.

Results. There were 1346 HIV-positive participants (n = 1883 visit-pairs). The population-level prevalence of durable VL suppression increased from 29.7% to 67.9% during UTT rollout, viral rebound declined from 4.4% to 2.7%, and persistent viremia declined from 20.8% to 13.3%. Younger age (15–29 vs 40–49 years; adjRR = 1.80; 95% CI = 1.19–2.71), male sex (adjRR = 2.09, 95% CI = 1.47–2.95), never being married (vs currently married; adjRR = 1.88, 95% CI = 1.34–2.62), and recent migration to the community (vs long-term resident; adjRR = 1.91, 95% CI = 1.34–2.73) were factors associated with persistent viremia.

Conclusions. Despite increases in durable VL suppression during roll out of UTT in hyperendemic communities, a substantial fraction of the population, whose risk profile tended to be younger, male, and mobile, remained persistently viremic.

Keywords. Africa; cohort studies; HIV prevention; universal test and treat; viral suppression.

UNAIDS targets for human immunodeficiency virus (HIV) epidemic control by 2030 include that 86% of all HIV-positive persons be on antiretroviral therapy (ART) and achieve HIV viral load (VL) suppression [1]. The major policy initiative underpinning this target is universal test and treat (UTT), whereby all HIV-positive persons, irrespective of CD4 count or severity of illness, are immediately prescribed ART [2]. In sub-Saharan Africa, which accounts for more than half of all new HIV diagnoses globally, there has been considerable progress in increasing ART coverage [3]. The PEPFAR Population-Based HIV Impact Assessment (PHIA) Project has shown that ~85% of HIV-positive people were virologically suppressed in 2016 in Malawi, Zambia, and Zimbabwe [4, 5].

Despite the widespread roll out and uptake of ART across sub-Saharan Africa, HIV incidence declines have been modest and rates remain well above elimination thresholds [6]. The PHIA surveys have highlighted variability in ART coverage across subgroups, particularly among men and young people, who have lower HIV VL suppression levels [4]. Such heterogeneities in ART coverage may partially explain the limited population-level effectiveness of UTT on HIV incidence observed in cluster-randomized trials [7–9], especially if those who remain unsuppressed disproportionately drive transmission. Detailed information on which persons remain viremic despite UTT may help target programs accordingly.

Although the PHIA project has provided important insight into HIV programmatic gaps, these and other cross-sectional studies cannot distinguish individuals who subsequently initiate treatment from those who remain persistently unsuppressed or lose VL suppression. Previous studies of longitudinal

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VL measurements have been conducted predominately in non-African settings and in clinical settings [10–14], the latter of which exclude individuals who have never entered into the HIV care system or discontinued care and are most likely to be persistently unsuppressed. In this study, we used population-based data to characterize the longitudinal dynamics of HIV VL suppression after UTT in 4 Lake Victoria fishing communities with adult HIV prevalence ranging from 38% to 43% [15]. We have previously reported on the rapid scale-up of HIV treatment and prevention services in this population between 2011 and 2017 [16], including increases in ART coverage from 16% to 82%. During this period, there was a 48% decline in population-level HIV incidence, but HIV incidence rates still exceeded 1/100 person-years despite widespread coverage of ART and other preventive services. Longitudinal population-based evaluation of HIV VL suppression offers rare opportunity for insight into characteristics of "hard-to-reach" viremic subgroups, such as those who remain persistently viremic, in the setting of UTT.

METHODS

Study Cohort

Data for this study were from the Rakai Community Cohort Study (RCCS), an open population-based cohort of individuals aged 15–49 years in 40 communities, including 4 HIV hyperendemic Lake Victoria fishing communities, located in Rakai and neighboring districts of south-central Uganda [15–17]. The RCCS conducts a household census and interviews consenting individuals to collect self-reported demographic, behavioral, and service uptake data. Free HIV testing and counseling is provided at the time of interview with referral to ART services for all HIV-positive persons and other HIV combination intervention services as appropriate. Human immunodeficiency virus status is determined using a validated 3 rapid HIV test algorithm in the field, and HIV status is confirmed by enzyme immunoassays with participant consent for further testing.

This analysis used data from the 4 Lake Victoria fishing communities collected via the RCCS between November 2011 and August 2017 during which time 5 surveys were conducted and UTT was implemented in 2013. Viral load testing on all HIV-positive participants was performed on stored serum/plasma specimens at 3 of the 5 surveys, including the first survey and the final 2 surveys, using the Abbott RealTime assay (Abbott Molecular, Inc., Des Plaines, IL). The first of these 3 surveys at which VL were tested was conducted between December 2011 and June 2012 (median = January 2012) before UTT, the second was conducted between April 2015 and November 2015 (median = May 2015), and the third was conducted between December 2016 and August 2017 (median = January 2017) after UTT was implemented in 2013. Of note, clinics in and surrounding the communities included in this analysis provided free VL monitoring as per Ugandan *Ministry of Health* (MOH) guidelines at 6 and 12 months after ART initiation and then annually. Adherence counseling was standard of care for individuals with detectable VLs. This study was approved by the Research and Ethics Committee of the Uganda Virus Research Institute, the Ugandan Council of Science and Technology, and the Western Institutional Review Board.

Statistical Analysis

Analyses were restricted to the 3 surveys at which VL testing was performed and included HIV-positive participants who contributed 2–3 VL measurements. The primary unit of analysis was a visit-pair, defined as 2 consecutive person-visits (v_i and v_i+_k). Visit-pairs were determined regardless of a missed visit. For instance, an individual observed in the first and third survey but not the second survey contributed 1 visit-pair (eg, v_i and v_{i+2}). Individuals who had VL measurements at baseline and 2 follow-up visits maximally contributed 2 visits-pairs (eg, v_i and v_{i+1} as well as v_{i+1} and v_{i+2}). Visit-pairs were classified into 4 patterns based on the participants' HIV VL suppression status at the index and follow-up visit of each visit-pair: (1) durable VL suppression (D-VLS), (2) new/renewed VL suppression, (3) loss of VL suppression (viral rebound), and (4) persistent viremia. Human immunodeficiency virus VL suppression was defined by a VL <400 copies/mL. The follow-up visit (v_i+_k) of each visit-pair occurred after UTT implementation in 2013.

Temporal changes in the population-level prevalence of cross-sectional HIV VL suppression and each longitudinal VL outcome were assessed at the end of each of the 2 survey intervals using descriptive statistics. The frequency of the 4 longitudinal VL outcomes was also examined by sociodemographic and behavioral characteristics. Sociodemographic variables were ascertained from the index visit (v_i) of each visit-pair. Behavioral variables were ascertained from the follow-up visit (v_i+_1) of each visit-pair. In-migrants were categorized as recent (0–2 years) or nonrecent (>2 years) [18]. Associations between virologic outcomes and self-reported HIV status were also examined at the third and final study visit when self-reported HIV status was first assessed in the RCCS.

We further assessed sociodemographic and behavioral risk factors for persistent viremia over the analysis period. Relative risks (RRs) of persistent viremia were estimated using modified Poisson regression with generalized estimating equations (GEE), an independent correlation matrix, and robust variance estimators to account for multiple visit-pairs from an individual. Visit-pairs characterized by D-VLS or new/renewed suppression were the referent group. Sociodemographic variables in primary multivariate analyses included age group, sex, marital status, education, primary occupation, and in-migration status. Behavioral variables were examined using separate multivariate models that included adjustment for sociodemographic characteristics. Multivariate models also included adjustment for the survey number of the index visit. Missing covariate data were limited (<4% of visit-pairs) and were handled using a complete-case approach in multivariate analyses. We also estimated univariate RRs of a loss in HIV VL suppression relative to D-VLS using the same methods, but we did not assess multivariate associations due to limited events. Subgroup analyses were done stratified by sex.

We re-examined correlates of persistent HIV viremia in separate sensitivity analyses. First, we raised the HIV VL suppression cutoff to VL <1000 copies/mL per WHO guidelines. Second, to account for potential selection bias resulting from loss to follow-up, we used inverse probability of selection weighting (Supplemental Methods). Third, we restricted the analysis to the second survey interval so that both the index and follow-up visits of all visit-pairs occurred after UTT implementation. Fourth, we excluded individuals who were both persistently viremic and on ART (self-report). Finally, a sensitivity analysis was conducted to examine correlates of a viremic outcome restricted to individuals who self-reported ART use.

As an ancillary analysis, we examined longitudinal patterns in HIV VL suppression restricted to participants with HIV VL data at all 3 study visits. In addition, given that the duration follow-up varied among study participants and between survey intervals, we further assessed incidence of new/renewed VL suppression among those who were unsuppressed at the start of each visit-interval as well as loss of VL suppression among those who were initially suppressed. Both incidence and loss of VL suppression were assumed to occur at the midpoint of the visit-interval, and incidence rates were calculated using Poisson regression and reported as a rate per 100 person-years of follow-up. The relative risk of new/renewed suppression and loss of suppression was compared between the first and second survey intervals also using Poisson regression with GEE and reported as incidence rate ratios (IRRs).

RESULTS

Study Population

There were 3034 HIV-positive individuals observed across the 3 surveys. We excluded 579 participants whose baseline visit was the third survey because they were not yet eligible for follow-up. An additional 3 participants were excluded because of missing data on HIV VL at baseline. Of the remaining 2452 participants, 1346 (54.9%) participants had HIV VL data at baseline and ≥1 follow-up visit, contributing 1883 visit-pairs to the analysis. There was a subset of 537 participants who had HIV VL data at baseline and 2 follow-up visits; this group contributed 2 visit-pairs to the analysis (n = 1074 visit-pairs). The 45.1% (n = 1106) of participants lost to follow-up were more likely to not work in agriculture and be younger, male, and a recent in-migrant at their baseline visit. Those lost to follow-up were also less likely to report having a prior HIV test, self-report ART use, and have HIV VL suppression at baseline (Table 1, Supplementary Table S1). Baseline characteristics of the analytic study population are shown in Table 1 and by sex in Supplementary Table S2.

Population-Level Prevalence and Incidence of Human Immunodeficiency Virus Viral Load Outcomes

Overall, D-VLS was observed in 949 (50.4%) visit-pairs, new/renewed VL suppression was observed in 571 (30.3%) visit-pairs, a loss of VL suppression (viral rebound) was observed in 54 (2.9%) visit-pairs, and persistent viremia was observed in 309 (16.4%) visit-pairs (Table 2; see Supplementary Tables S3 and S4 for sex-stratified results). The geometric mean VL among those with loss of suppression and persistent viremia was 6443 (interquartile range [IQR] = 1804–21 184) and 15 445 copies/mL (IQR = 4537–50 892), respectively (Wilcoxon rank-sum test, $P < .001$).

The population-level prevalence of D-VLS increased from 29.7% (216 of 727) over the first survey interval to 67.9% (698 of 1028) over the second survey interval (Table 3). Conversely, the population-level prevalence of persistent viremia declined from 20.8% (151 of 727) to 13.3% (137 of 1028). Supplementary Table 5 shows the incidence rate of new/renewed VL suppression and loss of suppression during the 2 survey intervals. Between the first and second intervals, the rate of new/renewed suppression increased by 48% (IRR = 1.48, 95% CI = 1.25–1.75), while the rate of loss of suppression declined by more than half (IRR = 0.45, 95% CI = 0.26–0.78). Trends over time were similar between men and women.

Figure 1 shows longitudinal patterns in VL suppression and viremia among 537 participants observed at all 3 surveys (see Supplementary Figure S1 for sex-stratified results). The majority of participants (76.9%, n = 413) achieved D-VLS by the third visit. Only 7.8% (n = 42) of participants were viremic at all 3 study visits, and 5.0% (n = 27) of participants exhibited intermittent viremia or loss of suppression.

Among visit-pairs where participants did not self-report ART use (n = 274 of 1883), 79% (n = 215) were viremic, and, of these pairs, 90.7% (n = 195) were persistently viremic. Of note, 36.9% (n = 114) of all visit-pairs characterized by persistent viremia occurred among participants who reported ART use (n = 101 individuals). Recent in-migration was more common among those reporting ART use with persistent viremia compared with those not reporting ART use with persistent viremia (Supplementary Table S6). The geometric mean VL among visit-pairs with persistent viremia did not differ significantly by self-reported ART status (13 087 in ART vs 17 007 copies per/mL in non ART users; Wilcoxon rank-sum test, $P = .127$).

In the final survey, participants were asked to self-report their HIV status. Overall, 96.3% (1113 of 1156) of the analytic cohort correctly self-identified as HIV-positive by either reporting their HIV status directly (n = 1103) or by disclosing that they were using ART (n = 10). Although acknowledgment of HIV seropositivity during survey interview was high overall, it was significantly lower among those with persistent viremia (81.0%, 128 of 158), compared with those with D-VLS (99.5%, 729 of 733), new/renewed

Table 1. Baseline Characteristics of the Study Population Included in the Analytic Cohort (≥1 Follow-Up Visit) and Those Lost to Follow-Up After Baseline

	No. of Participants (%)			
Characteristic	Overall (N = 2452)	Included (N = 1346)	Loss to Follow-Up[a] (N = 1106)	P
Survey Visit (Midpoint Date)				.072
(1) January 2012	1596 (65.1)	855 (63.5)	741 (67.0)	
(2) May 2015	856 (34.9)	491 (36.5)	365 (33.0)	
Community				.259
1	1297 (52.9)	719 (53.4)	578 (52.3)	
2	259 (10.6)	149 (11.1)	110 (10.0)	
3	614 (25.0)	338 (25.1)	276 (25.0)	
4	282 (11.5)	140 (10.4)	142 (12.8)	
Age Group, Years				.002
15–29	1085 (44.3)	555 (41.2)	530 (47.9)	
30–39	1070 (43.6)	629 (46.7)	441 (39.9)	
40–49	297 (12.1)	162 (12.0)	135 (12.2)	
Sex				<.001
Female	1394 (56.9)	717 (53.3)	677 (51.2)	
Male	1058 (43.2)	629 (46.7)	429 (38.8)	
Marital Status				.063
Married	1545 (63.0)	874 (64.9)	671 (60.7)	
Previously married	773 (31.5)	407 (30.2)	366 (33.1)	
Never married	134 (5.5)	65 (4.8)	69 (6.2)	
Educational Attainment				.180
None	311 (12.7)	159 (11.8)	152 (13.7)	
Primary	1863 (76.0)	1042 (77.4)	821 (74.2)	
Secondary or more	278 (11.3)	145 (10.8)	133 (12.0)	
Primary Occupation				<.001
Agricultural or housework	425 (17.3)	204 (15.2)	221 (20.0)	
Trader or shopkeeper	534 (21.8)	289 (21.5)	245 (22.2)	
Bar/restaurant worker	300 (12.2)	163 (12.1)	137 (12.4)	
Fishing-related work	903 (36.8)	546 (40.6)	357 (32.3)	
Other	290 (11.8)	144 (10.7)	146 (13.2)	
Migration Status				<.001
Long-term resident	1879 (76.6)	1044 (77.6)	835 (75.5)	
In-migrant (0–2 years)	310 (12.6)	144 (10.7)	166 (15.0)	
In-migrant (>2 years)	169 (6.9)	114 (8.5)	55 (5.0)	
Data missing	94 (3.8)	44 (3.3)	50 (4.5)	
Number of Sexual Partners				.966
0–1	1368 (55.8)	749 (55.7)	619 (56.0)	
2–3	827 (33.7)	454 (33.7)	373 (33.7)	
>3	257 (10.5)	143 (10.6)	114 (10.3)	
Prior HIV test (self-report)	1830 (74.6)	1027 (76.3)	803 (72.6)	.036
ART use (self-report)	709 (28.9)	421 (31.3)	288 (26.0)	.004
HIV VL <400 copies/mL	980 (40.0)	581 (43.2)	399 (36.1)	<.001
HIV VL <1000 copies/mL	1066 (43.5)	625 (46.4)	441 (39.9)	.001

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; VL, viral load.

NOTE: Data are sample sizes and corresponding column percentages. Two-sided *P* values were determined from Pearson's χ^2 tests.

[a]Persons were excluded from the analytic cohort if they were loss to follow-up. Loss to follow-up was defined as not being observed in a follow-up survey and/or missing viral load data at a follow-up visit (ie, HIV-positive participants with only 1 baseline viral load measurement).

suppression (96.7%, 235 of 243), and loss of VL suppression (95.5%, 21 of 22).

Cross-Sectional Versus Longitudinal Measures of Viral Load Suppression

Overall, the population-level prevalence of a suppressed outcome (D-VLS or new/renewed suppression) was higher compared with cross-sectional assessments of VL suppression levels among the total HIV-positive population, including those without follow-up (Table 3), suggesting that participants lost-to-follow-up have relatively lower VL suppression levels compared to those with follow-up. Indeed, a comparison of VL suppression levels among those with and without follow-up showed significantly lower levels of suppression among those lost to follow-up at all 3 surveys (Supplementary Table S7).

Table 2. Overall Prevalence of Longitudinal HIV Viral Load Patterns and Stratified by Sociodemographic and Behavioral Characteristics

		No. of Visit-Pairs (%)			
Characteristic	N	Durable Suppression	New/Renewed Suppression	Loss of Suppression	Persistent Viremia
Total	1883	949 (50.4)	571 (30.3)	54 (2.9)	309 (16.4)
Index survey visit (midpoint date)					
(1) January 2012	855	251 (29.4)	400 (46.8)	32 (3.7)	172 (20.1)
(2) May 2015	1028	698 (67.9)	171 (16.6)	22 (2.1)	137 (13.3)
Community					
1	1010	543 (53.8)	285 (28.2)	33 (3.3)	149 (14.8)
2	205	105 (51.2)	65 (31.7)	4 (2.0)	31 (15.1)
3	478	212 (44.4)	157 (32.8)	15 (3.1)	94 (19.7)
4	190	89 (46.8)	64 (33.7)	2 (1.1)	35 (18.4)
Age Group, Years					
15–29	662	267 (40.3)	243 (36.7)	18 (2.7)	134 (20.2)
30–39	931	494 (53.1)	263 (28.2)	30 (3.2)	144 (15.5)
40–49	290	188 (64.8)	65 (22.4)	6 (2.1)	31 (10.7)
Sex					
Female	1029	599 (58.2)	292 (28.4)	25 (2.4)	113 (11.0)
Male	854	350 (41.0)	279 (32.7)	29 (3.4)	196 (23.0)
Marital Status					
Married	1219	620 (50.9)	362 (29.7)	37 (3.0)	200 (16.4)
Previously married	588	309 (52.6)	186 (31.6)	13 (2.2)	80 (13.6)
Never married	76	20 (26.3)	23 (30.3)	4 (5.3)	29 (38.2)
Educational Attainment					
None	230	121 (52.6)	71 (30.9)	3 (1.3)	35 (15.2)
Primary	1458	734 (50.3)	446 (30.6)	44 (3.0)	234 (16.0)
Secondary or more	195	94 (48.2)	54 (27.7)	7 (3.6)	40 (20.5)
Primary Occupation					
Agricultural or housework	293	154 (52.6)	92 (31.4)	6 (2.1)	41 (14.0)
Trader or shopkeeper	412	229 (55.6)	120 (29.1)	13 (3.2)	50 (12.1)
Bar/restaurant worker	225	127 (56.4)	61 (27.1)	10 (4.4)	27 (12.0)
Fishing-related work	744	319 (43.9)	237 (31.9)	20 (2.7)	168 (22.6)
Other	209	120 (57.4)	61 (29.2)	5 (2.4)	23 (11.0)
Migration Status					
Long-term resident	1551	774 (49.9)	485 (31.3)	44 (2.8)	248 (16.0)
In-migrant (0–2 years)	150	71 (47.3)	39 (26.0)	8 (5.3)	32 (21.3)
In-migrant (>2 years)	121	72 (59.5)	25 (20.7)	2 (1.7)	22 (18.2)
Alcohol Use[a]					
No	742	396 (53.4)	215 (29.0)	21 (2.8)	110 (14.8)
Yes	1141	553 (48.5)	356 (31.2)	33 (2.9)	199 (17.4)
Sexually Active[a]					
No	150	81 (54.0)	39 (26.0)	2 (1.3)	28 (18.7)
Yes	1733	868 (50.1)	532 (30.7)	52 (3.0)	281 (16.2)
Number of Sexual Partners[a]					
0–1	1241	650 (52.4)	384 (30.9)	31 (2.5)	176 (14.2)
2–3	497	237 (47.9)	149 (30.0)	18 (3.6)	93 (18.7)
>3	145	62 (42.8)	38 (26.2)	5 (3.5)	40 (27.6)
Self-Reported GUD Symptoms[a,b]					
No	1526	779 (51.0)	460 (30.1)	44 (2.9)	243 (15.9)
Yes	207	89 (43.0)	72 (34.8)	8 (3.9)	38 (18.4)
Consistent Condom Use[a,b]					
No	1571	776 (49.4)	489 (31.1)	48 (3.1)	258 (16.4)
Yes	160	92 (57.5)	41 (25.6)	4 (2.5)	23 (14.4)
Alcohol Use Before Sex[a,b]					
No	882	455 (51.6)	267 (30.3)	25 (2.8)	135 (15.3)
Yes	851	413 (48.5)	265 (31.1)	27 (3.2)	146 (17.2)
Transactional Sex[a,b]					
No	1327	674 (50.8)	418 (31.5)	34 (2.6)	201 (15.1)
Yes	406	194 (47.8)	114 (28.1)	18 (4.4)	80 (19.7)

Table 2. Continued

Characteristic	N	No. of Visit-Pairs (%)			
		Durable Suppression	New/Renewed Suppression	Loss of Suppression	Persistent Viremia
ART Use (Self-Report)					
No	274	28 (10.2)	31 (11.3)	20 (7.3)	195 (71.2)
Yes	1609	921 (57.2)	540 (33.6)	34 (2.1)	114 (7.1)

Abbreviations: ART, antiretroviral therapy; GUD, genital ulcer disease.

NOTE: Data are sample sizes and corresponding row percentages. Sociodemographic characteristics were ascertained at the index visit of the visit-pair. Behavioral characteristics and self-reported ART use were ascertained at the follow-up visit of the visit-pair.

[a]In the past year.

[b]Among sexually active participants only.

Although VL suppression increased among both those with and without follow-up, differences in VL suppression between the 2 groups increased over calendar time (33.1.% among those with follow-up vs 27.7% among those without follow up at survey 1; 84.4% vs 64.9% at survey 3). Of note, cross-sectional analyses at visit 3 included new enrollees, who were not eligible for the analytic cohort because they had no opportunity for follow-up.

Predictors of Persistent Human Immunodeficiency Virus Viremia

Table 4 shows sociodemographic and behavioral factors associated with persistent viremia relative to D-VLS or new/renewed suppression. Men were twice as likely as women to be persistently viremic (adjRR = 2.09, 95% CI = 1.47–2.95). Among men, younger age, particularly those <30, never married, and being an in-migrant were all significantly associated with having persistent viremia. Among women, persistent viremia was 2 and a half times more prevalent among those who had never been married compared with married women (adjRR = 2.46, 95% CI = 1.39–4.36).

In univariate analyses, increasing number of sexual partners and engagement in transactional sex were associated with persistent viremia in the overall population (Table 4). However, these associations were attenuated after stratification by sex, partly because younger men (<30), who were most likely to be persistently viremic, were also most likely to report multiple sexual partners (Supplementary Figure S2; Supplementary Tables S3 and S4).

In sensitivity analyses, associations with persistent viremia were insensitive to changes in VL suppression cutoffs (<1000 copies/mL) (Supplementary Table S8), restriction to data collected only during the second survey interval (Supplementary

Table 3. Prevalence of Cross-Sectional and Longitudinal HIV Viral Load Outcomes by Calendar Time

Prevalence of HIV VL Outcome	Survey Interval 1: January 2012–May 2015[a]		Survey Interval 2: May 2015–January 2017[a]	
	n/N	% (95% CI)	n/N	% (95% CI)
Overall				
Durable VL suppression	216/727	29.7 (26.5–33.1)	698/1028	67.9 (65.0–70.7)
New/renewed VL suppression	328/727	45.1 (41.5–48.8)	171/1028	16.6 (14.5–19.0)
Loss of VL suppression	32/727	4.4 (3.1–6.2)	22/1028	2.1 (1.4–3.2)
Persistently viremic	151/727	20.8 (18.0–23.9)	137/1028	13.3 (11.4–15.6)
Cross-sectional VL suppression[b]	1036/1583	65.5 (63.1–67.8)	1357/1734	78.3 (76.3–80.1)
Females				
Durable VL suppression	151/412	36.7 (32.1–41.4)	428/559	76.6 (72.9–79.9)
New/renewed VL suppression	189/412	45.9 (41.1–50.7)	73/559	13.1 (10.5–16.1)
Loss of VL suppression	15/412	3.6 (2.2–6.0)	10/559	1.8 (1.0–3.3)
Persistently viremic	57/412	13.8 (10.8–17.5)	48/559	8.6 (6.5–11.2)
Cross-sectional VL suppression[b]	659/899	73.3 (70.3–76.1)	779/937	83.1 (80.6–85.4)
Males				
Durable VL suppression	65/315	20.6 (16.5–25.5)	270/469	57.6 (53.0–62.0)
New/renewed VL suppression	139/315	44.1 (38.7–49.7)	98/469	20.9 (17.5–24.8)
Loss of VL suppression	17/315	5.4 (3.4–8.5)	12/469	2.6 (1.5–4.5)
Persistently viremic	94/315	29.8 (25.0–35.1)	89/469	19.0 (15.7–22.8)
Cross-sectional VL suppression[b]	377/684	55.1 (51.4–58.8)	578/797	72.5 (69.3–75.5)

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; VL, viral load.

NOTE: Data are sample sizes and corresponding column percentages with logit-transformed 95% CIs. For longitudinal HIV VL patterns, this analysis excludes 128 visit-pairs for which the index visit was the first survey (midpoint date: January 2012) and the follow-up visit was the last survey (midpoint date: January 2017) to allow comparisons by time.

[a]The dates provided reflect the midpoint dates of index and follow-up survey round.

[b]The proportion of the total HIV-positive population suppressed at the end of the visit-interval; analysis includes all HIV-positive persons irrespective of whether they were in the analytic sample that contributed a follow-up visit(s) for analyses of longitudinal VL.

Table S9), and when excluding individuals who self-reported ART use and were persistently viremic (Supplementary Table S10). Furthermore, associations with viremia were similar among those who self-reported ART use (Supplementary Table S11). We also used inverse probability of selection weights, and we found no impact on study inferences related to factors associated with persistent viremia (Supplementary Tables S12 and S13).

Predictors of a Loss of Human Immunodeficiency Virus Viral Load Suppression

Relative to visit-pairs with D-VLS, loss of VL suppression was more common among men than women (RR = 1.91, 95% CI = 1.13–3.22) (Supplementary Table S14). Among men, being a recent in-migrant (RR = 2.65, 95% CI = 1.01–6.95) and reporting transactional sex in the past year (RR = 2.07, 95% CI = 1.02–4.22) were associated with loss of VL suppression. There were no statistically significant factors associated with this outcome among women.

DISCUSSION

Using population-based data among HIV-positive individuals living in 4 high prevalence fishing communities of Lake Victoria, we found significant increases in the population-level prevalence of D-VLS during the roll out of UTT. Moreover, among those who were initially viremic, the majority went on to achieve VL suppression consistent with increases in ART use over time. We also found a reduction in the proportion of suppressed persons who lost VL suppression over time. However, a substantial fraction of the population (~13%), whose risk profiles tended to be younger, male, and mobile with multiple sexual partners, remained persistently viremic despite UTT. Disparities in HIV treatment outcomes across demographic and risk groups may undermine the long-term success of UTT programs and elimination efforts, especially if these subgroups disproportionately contribute to onward HIV transmission [19].

Overall, we found that the population-level prevalence of VL suppression was high, among those who self-reported ART use (~90%), implying most HIV-positive persons were engaged successfully in treatment programs. Loss of suppression was relatively rare suggesting that the majority of viremic persons may not have begun rather than failed treatment. However, among the 16% with persistent viremia, one third self-reported ART use. In this population, we have previously shown that 99% of individuals who self-report ART use have >1 detectable antiretroviral drugs [20], indicating that approximately 33% of persistently viremic persons may be failing their prescribed therapy and/or were not optimally adherent. Although patients found to be failing first-line ART are recommended for switch to second-line therapy according to Ugandan MOH guidelines, we previously found delays in switching to second-line ART at clinics in our study area [21]. Delay and failure to switch to second-line treatment has been widely reported across sub-Saharan Africa and is associated with both increased risk of opportunistic infections and mortality [22]. It is notable that, among those who were persistently viremic in the most recent survey, ~20% reported not knowing that they were HIV-positive despite receiving prior HIV test results through RCCS. Such discrepancies may indicate that this group has heightened vulnerabilities to stigma, which has been associated with reduced treatment uptake and poorer outcomes in others settings [23–25].

This study adds to the growing body of evidence showing that men and younger persons are less likely to be engaged in HIV treatment and prevention services (5, 27–30). Here, we found that persistent viremia was approximately twice as common among men compared with women and among adolescents and young adults under 30 years old compared with persons 40 years old and older. At the final follow-up visit after UTT was fully implemented, approximately one fifth of all men were

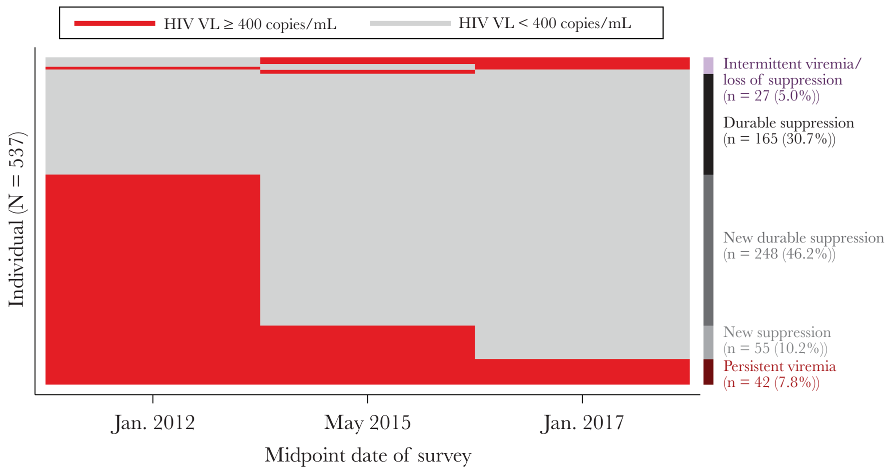

Figure 1. Longitudinal patterns in human immunodeficiency virus (HIV) viral load (VL) suppression among a closed population of HIV-positive participants observed at all 3 surveys. Note: Each row (ie, line) represents the viral load trajectory of a single study participant. The x-axis is not drawn to scale.

Table 4. Sociodemographic and Behavioral Factors Associated With Persistent Viremia Relative to Durable or New/Renewed Viral Suppression

	Overall		Females		Males	
Characteristic	RR (95% CI)	adjRR (95% CI)	RR (95% CI)	adjRR (95% CI)	RR (95% CI)	adjRR (95% CI)
Index Survey Visit (Midpoint Date)						
(1) January 2012	**1.53 (1.29–1.83)**	**1.73 (1.41–2.11)**	**1.63 (1.20–2.22)**	**1.74 (1.23–2.47)**	**1.49 (1.21–1.84)**	**1.79 (1.40–2.29)**
(2) May 2015	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Age Group, Years						
15–29	**1.91 (1.28–2.83)**	**1.80 (1.19–2.71)**	**2.06 (1.01–4.21)**	1.45 (0.69–3.08)	**2.31 (1.45–3.69)**	**1.94 (1.18–3.19)**
30–39	1.46 (0.99–2.16)	**1.55 (1.04–2.29)**	1.37 (0.68–2.76)	1.23 (0.59–2.54)	**1.74 (1.10–2.76)**	**1.67 (1.04–2.68)**
40–49	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Sex						
Female	Ref.	Ref.	-	-	-	-
Male	**2.11 (1.67–2.68)**	**2.09 (1.47–2.95)**	-	-	-	-
Marital Status						
Married	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Previously married	0.82 (0.64–1.05)	0.95 (0.74–1.21)	**0.65 (0.43–0.96)**	0.69 (0.46–1.04)	1.08 (0.80–1.45)	1.15 (0.85–1.54)
Never married	**2.38 (1.71–3.31)**	**1.88 (1.34–2.62)**	**2.57 (1.43–4.60)**	**2.46 (1.39–4.36)**	**2.15 (1.46–3.17)**	**1.53 (1.02–2.31)**
Educational Attainment						
None	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Primary	1.07 (0.75–1.54)	1.02 (0.71–1.45)	1.13 (0.63–2.03)	1.05 (0.59–1.88)	1.01 (0.65–1.58)	1.01 (0.65–1.57)
Secondary or more	1.38 (0.87–2.18)	1.51 (0.96–2.36)	1.65 (0.81–3.38)	1.51 (0.75–3.06)	1.44 (0.82–2.52)	1.52 (0.87–2.67)
Primary Occupation						
Agricultural or housework	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Trader or shopkeeper	0.88 (0.58–1.34)	0.82 (0.54–1.26)	0.86 (0.53–1.40)	0.93 (0.57–1.50)	0.69 (0.30–1.57)	0.59 (0.26–1.35)
Fishing-related work	**1.62 (1.16–2.28)**	0.96 (0.63–1.46)	0.96 (0.47–1.95)	1.01 (0.49–2.10)	0.95 (0.49–1.85)	0.81 (0.43–1.52)
Other	0.84 (0.55–1.26)	0.81 (0.54–1.21)	0.77 (0.48–1.24)	0.83 (0.52–1.32)	0.87 (0.39–1.94)	0.76 (0.35–1.66)
Migration Status						
Long-term resident	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
In-migrant (0–2 years)	1.37 (0.98–1.91)	**1.91 (1.34–2.73)**	1.38 (0.82–2.31)	1.75 (0.95–3.21)	**1.64 (1.09–2.47)**	**2.09 (1.35–3.23)**
In-migrant (>2 years)	1.12 (0.75–1.68)	1.46 (0.97–2.18)	0.61 (0.25–1.46)	0.82 (0.33–2.04)	**1.64 (1.09–2.47)**	**2.03 (1.30–3.17)**
Alcohol Use[a]						
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	1.18 (0.93–1.48)	0.98 (0.77–1.24)	1.05 (0.72–1.53)	1.01 (0.69–1.48)	0.90 (0.67–1.21)	0.95 (0.69–1.29)
Number of Sexual Partners[a]						
0–1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
2–3	**1.33 (1.05–1.70)**	0.93 (0.73–1.20)	1.13 (0.70–1.83)	1.04 (0.65–1.68)	0.99 (0.74–1.32)	0.90 (0.68–1.20)
>3	**1.96 (1.46–2.65)**	1.20 (0.88–1.64)	1.52 (0.54–4.33)	1.35 (0.55–3.30)	1.33 (0.95–1.86)	1.18 (0.85–1.64)
Self-Reported GUD Symptoms[a,b]						
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	1.16 (0.85–1.59)	1.21 (0.90–1.64)	1.17 (0.73–1.90)	1.12 (0.69–1.83)	**1.57 (1.07–2.30)**	1.28 (0.89–1.85)
Consistent Condom Use[a,b]						
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	0.87 (0.58–1.30)	0.97 (0.65–1.44)	0.86 (0.43–1.74)	1.03 (0.51–2.11)	0.90 (0.56–1.44)	0.95 (0.58–1.54)
Alcohol Use Before Sex[a,b]						
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	1.12 (0.90–1.41)	0.95 (0.75–1.20)	0.85 (0.55–1.31)	0.89 (0.57–1.37)	0.96 (0.73–1.26)	0.98 (0.74–1.32)
Transactional Sex[a,b]						
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	**1.33 (1.05–1.68)**	1.15 (0.91–1.46)	1.07 (0.66–1.75)	1.07 (0.65–1.74)	1.27 (0.97–1.66)	1.20 (0.92–1.57)

Abbreviations: adjRR, adjusted relative risk ratio; CI, confidence interval; GUD, genital ulcer disease; Ref., referent; RR, relative risk ratio.

NOTE: Relative risks of persistent viremia were estimated from modified Poisson regression models with generalized estimating equations, an independent correlation matrix, and robust standard errors. Visit-pairs characterized by durable or new/renewed HIV viral load suppression served as the comparison group. Adjusted RRs were estimated from multivariate models that included adjustment for all sociodemographic covariates shown (age group, sex, marital status, educational attainment level, primary occupation, and migration status), as well as the survey period of the index visit of the visit-pair. Estimates in bold had a 2-sided Wald *P* value less than .05.

[a]In the past year.

[b]Among sexually active participants.

classified as persistently viremic compared with only 9% of women. Loss of suppression was also more common among men. Poor uptake of HIV testing and treatment among men has been linked to cultural and structural factors including gender norms, masculinity, stigma, and a female-focused health system within Africa [30]. In addition to showing that persistent viremia is more common among men and youth, we find that these same groups were also the most likely to report multiple sexual partners, indicating overlap in behavioral and demographic risk factors associated with viremia. Men reporting transactional sex were also at increased risk of persistent viremia, although women who reported transactional sex were not. Taken together, these data emphasize the need for targeted efforts to men and youth.

We also found that migrants were significantly more likely to be persistently viremic, consistent with cross-sectional data from Rakai and elsewhere demonstrating lower levels of ART use and VL suppression in mobile persons [31–33]. Furthermore, we show participants with no follow-up and not included in our analytic cohort had lower levels of VL suppression compared with those with follow-up visits. Thus, cross-sectional measurements of VL suppression tended to be lower than those obtained among our longitudinal analytic cohort. We have previously shown that the vast majority (>90%) of participants lost to follow-up in these same communities are predominately lost as a result of migration or mobility related to work and school travel rather than refusal to participate (~1%) [16]. It is unclear whether lower VL among mobile and migrating persons is because they remain outside the purview of ART programs or because they are experiencing interruptions in care. We found that viral rebound was more common among migrants, suggesting that migrating persons likely suffer from treatment interruptions, indicating the need for strategies to ensure continuity in care for this population.

This study has limitations. First, ART use was self-reported and we could not verify ART initiation or drug regimen through clinical records. We also did not assess HIV drug resistance. Second, there was substantial loss to follow-up, which was associated with being male, young, and migrants, all factors associated with viremia. Although the nonmobile population may have high levels of D-VLS, rates are likely lower among more mobile factions of society, which are difficult to capture in population-based studies. Indeed, we show those lost to follow-up, typically due to mobility and migration, have lower levels of VL suppression. Thus, our estimates of the proportions of the population with persistent and rebound viremia should be considered as lower bounds. Future research on "hard-to-reach" mobile populations is needed to determine the extent to which nonmobile resident populations provide biased population-level estimates of D-VLS and viremia. Although we found similar results using inverse probability of selection weights, the analysis may still be biased if those who did not participate or were lost to follow-up were different on unmeasured factors associated with viremia. Third, this analysis largely focused on individual rather than health systems factors that may contribute to virologic failure. Our results suggest that delay and failure to switch to second-line treatment may be one such health systems factor accounting for a large fraction of viremia. Of note, we previously found distance to clinic had no significant impact on viremia in these communities, suggesting that geographic access to ART may not be a major driver of viremia in our study population [34]. Finally, these data were collected in high prevalence (~40%) fishing communities, which are not representative of most of sub-Saharan Africa. However, our findings are consistent with research from across the continent showing men, young persons, and migrants populations are critical to the success of ART-based HIV control efforts [26, 32, 35].

CONCLUSIONS

In summary, we find increases and high levels of D-VLS in high HIV prevalence fishing communities on Lake Victoria after implementation of UTT. However, we also find that a substantial fraction of the population remains persistently viremic and that men, young persons, and recent migrants were most likely to be persistently viremic, and thus most likely to be contributing to onward HIV transmission. Achieving the UNAIDS treatment targets and elimination goals will require surveillance of population-level VL and interventions targeting persons most likely to remain viremic despite implementation of UTT.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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