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Changes in Population HIV RNA Levels in Mbarara, Uganda During Scale-Up of HIV Antiretroviral Therapy Access

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Abstract

Objective—In a rural Ugandan community scaling up antiretroviral therapy (ART), we sought to determine if population based HIV RNA levels (population viral load) decreased from 2011-2012.

Design—Serial cross-sectional analyses (May 2011, May 2012) of a defined study community of 6,300 persons in a district with HIV prevalence of 8%.

Methods—We measured HIV-1 RNA (viral load, VL) levels on all individuals testing positive for HIV during a five-day high-throughput multi-disease community health campaign in May, 2012 that recruited two-thirds of the population. We aggregated individual-level VL results into population viral load metrics including the proportion of individuals with an undetectable VL, and compared these VL metrics to those we previously reported for this geographic region in 2011.

Results—In 2012, 223/2,179 adults were HIV-seropositive (10%). Overall, among 208/223 HIV-seropositive adults in whom VL was tested, 53% had an undetectable VL (95% CI 46-60%), up from 37% (95% CI 30-45%; p=0.02) in 2011. Seven (3%) individuals had a VL>100,000 copies/mL in 2012, down from 21 (13%) in 2011 (p=0.0007). Mean log(VL) [geometric mean]

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was 3.18 log (95% CI 3.06-3.29 log) in 2012, down from 3.62 log (95% CI 3.46-3.78 log) in 2011 (p<0.0001). Similar reductions in population VL were seen amongst males and females.

Conclusions—Reductions in population VL metrics and a substantial increase in persons with an undetectable VL were observed in a rural Ugandan community from 2011-2012. These findings from a resource-limited setting experiencing rapid ART scale-up may reflect a population-level effectiveness of expanding ART access.

Keywords

Population HIV RNA levels; viral load; HIV antiretroviral therapy (ART); ART effectiveness; epidemiology

Introduction

HIV antiretroviral therapy (ART) access is being rapidly and systematically scaled up throughout Sub-Saharan Africa according to WHO guidelines . However, persistent challenges remain in ensuring that patients are retained and engaged as they progress through the intended ‘cascade of HIV care’ consisting of diagnosis, linkage to care, initiation of ART, and achievement of a long-term undetectable viral load .

One potential way to assess the effectiveness of ART delivery is to estimate metrics of ‘population viral load’, a term that represents the aggregate distribution of HIV RNA levels within a population and includes both persons with known diagnoses of HIV and persons who are as-yet undiagnosed [5]. Such metrics are an objective measure of success in achieving a full cascade of HIV care. Population viral load metrics include the proportion of the population with an undetectable viral load, as well as the median and geometric mean VL of the population. We previously reported a method for assessing population viral load in resource limited settings using a fingerprick-based blood plasma collection method deployed at a community-wide health campaign and showed that a substantial fraction of a community can be recruited and tested for HIV in a short one week period of time , and that population viral load metrics can thereby be calculated.

In the Mbarara District of southwestern Uganda, an agrarian region with an HIV prevalence of 8%, ART access has recently expanded via several new activities. First, the aforementioned community health campaign we conducted in 2011 recruited residents of a parish of 6,300 persons for HIV testing and actively linked HIV-positive persons to care, many of whom were eligible for ART initiation [6]. Concomitantly, in early 2011, the Uganda Ministry of Health changed its ART initiation guidelines to a threshold CD4+ cell count <350 instead of CD4+ <250 [7]. Lastly, our group initiated a clinical research study in this region offering ART to persons with CD4≥350 who were otherwise ineligible for government-sponsored ART [8].

In this environment of multi-modal ART scale-up activities, we sought to measure population viral load metrics in 2012, one year after our first measurement was made in 2011. We sought to determine if population viral load was lower during this period of ART

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expansion, and whether the proportion of the population with an undetectable viral load was higher in 2012 compared to 2011.

Methods

2011 and 2012 Community health screening and treatment campaigns

Fingerprick blood was collected for HIV-1 RNA (viral load) measurement during 5-day community-wide multi-disease screening and treatment health campaigns ("community health campaigns", CHC) in Kakyerere Parish, Mbarara District, southwestern Uganda (May 16-21, 2011 [6] and April 30-May 2, 2012 [9]). Both health campaigns received advance ethics and regulatory approval from the institutional review boards of Makerere University School of Medicine, Kampala, Uganda, and the University of California, San Francisco (UCSF), as well as from the Uganda National Council for Science and Technology (UNCST). Patients provided informed verbal consent for participation prior to each health campaign.

Kakyerere Parish is a geographic area whose 2011 population was estimated as 6,300 persons [10]. As previously described [6], the 2011 health campaign offered HIV testing as follows: after adults completed an anonymous questionnaire ascertaining prior knowledge of HIV diagnosis, point-of-care fingerprick-based HIV testing was performed (Determine, Inverness), followed by confirmatory testing if indicated (STAT-PAK [Chembio Diagnostic Systems] and UniGold RecombiGen [Trinity]) according to Ugandan testing guidelines [11]. Participants who tested HIV-positive were provided with a referral appointment to the health center serving Kakyerere Parish (Bwizibwera Health Center) for intake into HIV care.

In 2012, the health campaign was repeated with similar procedures, but was preceded by a baseline census of the parish for more accurate estimation of its population, and to better estimate the uptake of the campaign relative to the parish population [9]. Participants underwent digital fingerprint measurement during census enumeration (U Are U 4500 Reader, Digital Persona, Redwood City, CA), and their attendance at the 2012 community health campaign was recorded by matching a digital fingerprint obtained upon arrival at the campaign to those obtained during the baseline census. Participants diagnosed with HIV in 2012 were offered linkage to care appointments as in 2011. In addition, in 2012, participants were asked if they had attended the 2011 health campaign.

HIV-1 plasma RNA and CD4+ T-cell count measurements

Persons testing positive for HIV in 2012 had a plasma HIV-1 RNA level measured via a fingerprick-derived blood sample that was collected at the community health campaign, processed in a central laboratory and tested using a modified commercial assay (RealTime HIV-1 Viral Load, Abbott) reported previously by our group [5]. This fingerprick-adapted assay has a lower limit of detection of 486 copies HIV-1 RNA/mL due to reduced input volume and incorporation of a dilution factor of 12.14-fold into the final result. Fingerprick viral load results correlate well with phlebotomy-derived results, and this modified technique is compatible with the demands of high-throughput health campaigns where phlebotomy is infeasible (due to the time and expertise needed, the requirement for sample storage capability, and biosafety concerns). Plasma HIV RNA levels were categorized as

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either (1) undetectable, (2) detectable with VL<486 copies/mL to 10,000 copies/mL, (3) VL 10,001-100,000 copies/mL, or (4) VL >100,000 copies/mL. HIV-1 RNA copy numbers below 486 copies/mL were determined from valid raw Ct values by extrapolation against the assay standard curve, and multiplied by the appropriate dilution factor to account for the reduced sample input volume. CD4+ T-cell counts were measured using the point-of-care PIMA platform (Alere), yielding results in 20 minutes that correlate well with phlebotomy-derived samples [12].

ART scale-up in Kakyerere Parish, 2011-2012

In early 2011, the Uganda Ministry of Health revised its CD4+ T-cell count threshold for ART initiation from 250 cells/uL to 350 cells/uL in concert with WHO guidelines . This new national recommendation was operationalized at the health center serving Kakyerere Parish (Bwizibwera Health Center) with assistance from a PEPFAR-supported implementing partner (Mulago-Mbarara Joint AIDS Program).

Additionally, in September 2011, our research group initiated a single-arm clinical trial studying ART administration to individuals who had CD4+ counts ≥350 cells/uL and were thus above the national guideline threshold. This study (EARLI: Early Antiretroviral Therapy in Resource Limited Settings in Patients with High CD4+ Cell Counts, NCT: 01479634) is based at Bwizibwera Health Center, the clinic serving the community where the 2011 and 2012 health campaigns were conducted. The EARLI Study began enrolling high CD4+ count individuals within a 25km radius in September 2011 and reached a target enrollment of 200 individuals. Therefore, residents of Kakyerere Parish with CD4+≥350 were eligible for screening and potentially for ART initiation, further expanding ART access locally. The EARLI Study has received ethical/regulatory approval from Makerere University School of Medicine, UCSF, UNCST, and the Uganda National Drug Authority (NDA).

Estimation of population RNA metrics

Within each of the two community health campaigns (2011 and 2012), we assessed the distribution of VL values among HIV-positive individuals by computing three sets of metrics: (1) the proportion of participants with an undetectable VL (with 95% binomial confidence intervals), as well as the proportion with VL values in three higher strata (<486 [detectable]-10,000 copies/mL, 10,001-100,000 copies/mL, and >100,000 copies/mL); (2) the median VL with interquartile range (IQR); and (3) the mean log(VL), i.e. the geometric mean VL, with 95% confidence intervals. Population viral load metrics for 2011 were reported previously [5].

We compared the 2011 and 2012 proportions of participants with undetectable VL via chi-square tests, median VLs via rank sum tests, and geometric mean VLs via two-sample t-tests. Analyses were performed in Stata 12/SE (Stata Corp., College Station, TX).

To examine the potential impact of a change in the sex distribution of sampled adults between 2011 and 2012 on population viral load results, we compared the VL distribution (as described above) within the male and female populations of the 2011 and 2012 community health campaigns.

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Finally, to examine whether changes in population viral load metrics were related to whether individuals had been connected to HIV care for a longer time (and thus more likely to have been offered ART if eligible), we compared the VL distribution of 2012 health campaign participants who reported attending the health campaign for the first time in 2012 ("2012 first-time testers") versus persons who also participated in 2011 ("2012 repeat testers").

Results

Community health campaign participants in 2011 and 2012

In 2011, a total of 4,343 individuals from Kakyerere Parish participated in the health campaign, including 2,323 adults ≥18 years old, of whom 2,282 adults underwent HIV testing (Table 1, reproduced from [6]). This represented a 72% community participation rate based on Ugandan Bureau of Statistics data. In 2012, 4,879 individuals (2,687 adults) participated, of whom 4,282 were Parish residents (2,204 adult residents), achieving an estimated 63% community participation based on the population enumerated (n=6,844) during the census done before the campaign [9]. Of the 2,204 adult parish residents participating in the 2012 health campaign, 2,197 (99.7%) underwent HIV testing.

In both 2011 and 2012, community health campaign participants were young, with a median age of 18-19 years, and predominantly female (34% male in 2011, 46% male in 2012, Table 1). Overall, in 2011, 179/2,282 adults (7.8%) were HIV-positive, while in 2012, the prevalence was 223/2,197 (10%). CD4+ T cell counts were measured in 184/223 HIV-positive adults; the median CD4+ count was 423 cells/uL (IQR 307-611 cells/uL). The fraction of participants self-reporting their HIV positive status as a new diagnosis was 46% in 2011 and 47% in 2012. CD4+ counts were similar between persons self-reporting their HIV status as a new diagnosis (n=85; median CD4+ count 445 cells/uL, IQR 306-617) compared to a previously known diagnosis (median CD4+ count 424 cells/uL, IQR 313-609; p=0.81). Viral load was successfully determined in 92-93% of HIV-positive participants in both years (Table 1, and reproduced from).

Population-level HIV RNA Metrics

As shown in Table 2, 37% (95% CI, 30-45%) of adult participants in 2011 had an undetectable VL [5] while in 2012 this was substantially higher at 53% undetectable (95% CI, 46-60%, p=0.02). Examining the distribution of detectable VL values, we found that individuals with VL>100,000 copies/mL comprised 13% (95% CI, 8-18%) of the sample in 2011, but only 3% of the sample in 2012 (95% CI, 1.4-6.8; p=0.0007). The median VL was 2,185 copies/mL (IQR, <486-33,045 copies/mL) in 2011 and was lower in 2012: <486 (IQR, <486-5,931 copies/mL; p=0.0001). Lastly, the mean log(VL)— i.e., the geometric mean VL—was 3.62 log copies/mL in 2011 (95% CI, 3.46-3.78 log), and substantially lower in 2012: 3.18 log copies/mL (95% CI, 3.06-3.29 log; p<0.0001, Table 1 and [5]). Among persons with both VL and CD4+ count measured, median CD4+ T cell counts did not differ substantially between persons with undetectable VL (n=97; 419 cells/uL [IQR 303-617]) compared to persons with detectable viremia (n=79; 452 cells/uL [IQR 323-593]; p=0.46).

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To examine whether the lower population viral load metrics we observed in 2012 might be due to changes predominantly within either males or females alone, we examined the VL distribution within sex for 2011 and 2012 (Table 3). From 2011 to 2012, virologic suppression among female participants increased from 40% to 54% (+14%; p=0.022), and increased to a similar degree among male participants, rising from 37% to 52% (+15%, p=0.097). Persons with VL>100,000 c/mL declined from 12% to 4% among females (p=0.018), and declined from 27% to 2.5% among males (p<0.001). Geometric mean VL also declined among females from 3.65 log in 2011 (95% CI, 3.47-3.82 log) to 3.18 log in 2012 (95% CI, 3.03-3.32 log; p=0.001) as well as among males (from 3.55 log in 2011 (95% CI, 3.17-3.93 log) to 3.18 log in 2012 (95% CI, 2.99-3.36 log; p=0.047); Table 3 and [5]).

Lastly, we examined whether a higher fraction of HIV-infected persons who self-identified as having tested at both the 2011 and 2012 campaigns (termed “2012 repeat testers”) had an undetectable VL in 2012 compared to the group who self-identified as testing in 2012 for the first time (termed “2012 first-time testers”). This was motivated by the idea that repeat testers may have had more time to become eligible for ART, initiate therapy, and achieve lower viral loads prior to their measurement at the 2012 campaign. Of the 208 total adult HIV-positive participants in the 2012 campaign, repeat participation was ascertained in 197. Overall, 115 individuals identified as first-time testers, 82 as repeat testers, 5 reported an unknown status, and in 6 participants this question was not answered. As shown in Table 4, virologic suppression among 2012 first-time testers (n=115/197) was 46% (95% CI, 37-56%), and among 2012 repeat testers (n=82/197) was higher at 66% (95% CI, 55-76%; p=0.006). Median VL in both groups was <486 copies/mL. Geometric mean VL was lower among 2012 repeat testers compared to 2012 first-time testers (3.05 log vs. 3.25 log; p=0.083).

Discussion

We report here a substantial reduction in population viral load metrics in a rural southwest Ugandan geographic region from 2011 to 2012, finding that the proportion of residents with an undetectable viral load was higher, and that the median and geometric mean VL were both lower. To our knowledge, this is the first report from a resource-limited region in Sub-Saharan Africa detailing population viral load metrics over time during a period of expanding antiretroviral therapy scale-up activities.

Our findings suggest a rising level of success in diagnosing and treating patients, and of retention through the cascade of care that culminates in ART-mediated virologic suppression. That 53% of HIV-positive participants in the 2012 health campaign had an undetectable viral load places this metric near results from certain resource-rich settings in the U.S. such as Washington D.C., where 57% of the population was virologically suppressed in 2008 [13]. However, despite improvements, there remains a substantial proportion (47%) of the HIV-positive population with measurable viremia, likely representing individuals with as-yet undiagnosed HIV, persons in care but still ineligible for ART by Ugandan guidelines (CD4<350), and persons on ART experiencing virologic failure. Although we offered ART access to individuals with CD4+ counts >350 cells/uL living in this geographic unit, the EARLI study was only in operation for 6 months prior to

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the 2012 health campaign; the impact of this expanded ART access may have been too early to ascertain, and may be more evident in future assessments.

Our results come at a time of expanding interest within resource-limited settings in the potential impact of expanding ART access on HIV transmission and incident HIV. The largest and most comprehensive study on this question is a report by Tanser et al. who showed within a large longitudinal population based cohort in rural Kwa-Zulu Natal, South Africa, regions with higher fractions of residents receiving ART had markedly lower HIV incidence rates over time than regions with lower rates of ART uptake [14]. One presumed mechanism for this encouraging and important finding is that individuals' levels of HIV RNA were decreased by expanding ART coverage, leading to less transmission. Although this report did not enumerate individuals' viral load characteristics over time, South Africa is one of the few locations where viral load testing is a part of routine care, so future evidence may emerge strengthening the link between population viral load metrics and ART effectiveness.

Our results lend strength to the theoretical mechanistic link between ART, population viral load metrics, and HIV transmission—a link that will be tested in upcoming large-scale cluster randomized trials that will compare strategies of universal antiretroviral therapy at all CD4+ cell counts ('test and treat') versus standard CD4-guided therapy . Many of the upcoming trials will measure individual participant viral loads during multi-year observation, and will track incident HIV as a primary outcome, offering the potential to causally link ART scale-up, population viral load metrics, and HIV transmission.

Interpretation of our findings should be considered in light of our study approach. Due to the anonymous registration of the 2011 health campaign, individual participants could not be linked across the two health campaigns. As such, we could not precisely determine the degree to which individual viral loads decreased from 2011 to 2012. However, our findings are unlikely to be primarily driven by different individuals attending the 2011 vs. 2012 health campaigns since they reached 64-72% of the Parish population each year. A related issue is that our community sampling was unlikely to be totally random, introducing the possibility of bias if there were systematic differences between persons attending versus not attending the health campaigns. Missing individuals, for example, could have introduced both upward and downward bias in either or both years[17]. Non-attendees may have had higher rates of undiagnosed HIV and may have raised VL metrics. Conversely, HIV-positive persons on ART may not have attended if they felt they would not benefit from the community campaign services. Had they participated, population VL reductions may have been larger. We did assess gender participation and found that both males and females showed similar declines in in population viral load metrics despite different levels of participation.

In summary, by utilizing a fingerprick-based viral load ascertainment performed within the context of high-throughput community-wide health campaigns, we demonstrate here that population viral load metrics were substantially lower in 2012 than 2011 in a rural Ugandan community undergoing rapid ART scale-up activities. This included a greater fraction of individuals with an undetectable viral load, and lower viral load levels in viremic

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individuals. Our results suggest that periodic estimations of population viral load may be provide useful, time-updated information about the effectiveness of ongoing ART delivery, particularly during the current era of expanding ART eligibility and delivery in Sub-Saharan Africa.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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