Clinical Infectious Diseases

MAJOR ARTICLE

Longitudinal Trends in the Prevalence of Detectable HIV Viremia: Population-Based Evidence From Rural KwaZulu-Natal, South Africa

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Background. The prevalence of detectable viremia has previously been used to infer the potential for ongoing human immunodeficiency virus (HIV) transmission. To date, no study has evaluated the longitudinal change in the prevalence of detectable viremia within the HIV-positive community (PDV_+) and the entire population (PDV_p) using data from a sub-Saharan African setting.

Methods. In 2011, 2013, and 2014, we obtained 6752 HIV-positive and 15 415 HIV-negative test results from a population-based surveillance system in the KwaZulu-Natal province of South Africa. We quantified the PDV_+ as the proportion of the 6752 HIV-positive results with a viral load >1550 copies/mL and the PDV_p as the proportion of the 6752 HIV-positive and 15 415 HIV-negative results with a viral load >1550 copies/mL.

Results. Between 2011 and 2014, the PDV_+ decreased by 16.5 percentage points (pp) for women (from 71.8% to 55.3%) and 10.6 pp for men (from 77.8% to 67.2%). However, a steady rise in the overall HIV prevalence, from 26.7% to 32.4%, offset the declines in the PDV_+ for both sexes. For women, the PDV_p decreased by only 2.1 pp, from 21.3% to 19.2%, but for men, the PDV_p actually increased by 1.6 pp, from 14.6% to 16.2%, over the survey period.

Conclusions. The PDV_+, which is currently being tracked under the UNAIDS 90-90-90 targets, may not be an accurate indicator of the potential for ongoing HIV transmission. There is a critical need for countries to monitor and report the prevalence of detectable viremia among all adults, irrespective of HIV status.

Keywords. HIV; viral load; detectable viremia; prevalence; South Africa.

By 2015, almost half of the 36.7 million people living with human immunodeficiency virus (HIV) were on combination antiretroviral therapy (ART) [1]. ART is expected to prevent the onward transmission of HIV by reducing the number of infected persons with detectable viremia [2, 3]. For this reason, the HIV-positive prevalence of detectable viremia (PDV_+), which is the proportion of all infected persons with a recent viral load above a copies/mL threshold, has been promoted as a sensitive biological index of ART program effectiveness. The PDV_+ has previously been used to monitor a community's uptake of ART [4, 5], and is central to the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 targets to have 90% of all ART-initiated patients achieve undetectable viremia by the year 2020 [6]. In addition, the PDV_+ has been used to quantify the potential for ongoing HIV transmission within a well-defined community or geographic area [4, 5, 7–9]. An assumption underlying the use of this measure is that higher levels of ART coverage will lower the PDV_+ and thus reduce the incidence of HIV infection within the general population.

However, one key limitation of the PDV_+ is that it does not account for the relative sizes of the HIV-infected and HIV-uninfected populations [10]. This information is important because the risk of acquiring HIV will depend not only on the number of infected persons with detectable viremia (ie, PDV_+) but also on the number of infected persons in the general population (ie, HIV prevalence), and the rate of sexual contact between them [10]. Thus, an improved biological index, which we call the population prevalence of detectable viremia (PDV_p) [11], can be obtained by multiplying the PDV_+ with the HIV prevalence (see Supplementary Figure 1). Aggregated viral load indices that account for the HIV prevalence have gained traction in the literature [12–15], and we recently showed that the PDV_p is significantly better than the PDV_+ at predicting the prospective risk of HIV infection [11].

Received 13 July 2017; editorial decision 29 October 2017; accepted 23 November 2017; published online November 25, 2017.

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Clinical Infectious Diseases® 2018;66(8):1254–60

DOI: 10.1093/cid/cix976

As far as we know, time trends in both the PDV_+ and the PDV_P have not been evaluated and compared using data from a sub-Saharan African population. In 2011, 2013, and 2014, we obtained 6752 HIV-positive and 15 415 HIV-negative test results from a population-based surveillance system in the KwaZulu-Natal province of South Africa. We quantified the PDV_+ as the proportion of the HIV-positive test results with a viral load >1550 copies/mL and then quantified the PDV_P as the proportion of the HIV-positive and HIV-negative test results with a viral load >1550 copies/mL. Using this population-based data, we had a unique opportunity to empirically estimate and compare the changes in both the PDV_+ and PDV_P measures over time.

METHODS

Setting

The Africa Health Research Institute (AHRI) maintains a population-based surveillance system in the Umkhanyakude district of the northern KwaZulu-Natal province. Most of the surveillance area is poor and rural, with several informal periurban settlements and a single urban township [16]. The area is 438 km^2 in size with a population of approximately 90 000 people and 11 000 households.

HIV Surveillance Survey

AHRI has collected longitudinal data on households and individuals within the surveillance area since 2000. Every 6 months, trained field workers visit a key informant within the household to collect information on both resident and nonresident members. Biannual participation rates for household data collection are typically >95%. Nested within the AHRI cohort is the population-based HIV cohort. Field workers have visited households every 12 months since 2004 and identified eligible participants >15 years of age for HIV testing. After obtaining consent, the field workers extract blood according to the UNAIDS and World Health Organization Guidelines for Using HIV Testing Technologies in Surveillance. Of the eligible participants contacted, 78% agreed to be tested for HIV at least once in the 3 survey years. Participants from the AHRI and HIV cohorts were linked across the survey years and the data were stored in a SQL database server. The AHRI and HIV cohorts are described in greater detail elsewhere [16].

HIV Incidence and ART Usage

The AHRI surveillance area is situated at the epicenter of the global AIDS epidemic. Between 2004 and 2011, the crude HIV incidence was 2.6 new infections per 100 person-years (95% confidence interval [CI], 2.50–2.77) [17]. Incidence peaked at 6.6 new infections per 100 person-years in women aged 24 years and at 4.1 new infections per 100 person-years in males aged 29 years [17]. Since 2005, the HIV prevalence among men and women aged 15–54 years has increased steadily from 21.7% in 2005 to 28.7% in 2010 [18]. The increase in HIV prevalence has been attributed to ART-associated reductions in mortality [19].

ART can be accessed for free at any of the 17 primary healthcare clinics within or adjacent to the surveillance area [20]. When ART was first made available in 2004, the $CD4^+$ T-cell count eligibility criteria was <200 cells/μL. In 2010, treatment eligibility was extended to pregnant women with $CD4^+$ T-cell counts <350 cells/μL and patients with active tuberculosis. All patients with $CD4^+$ T-cell counts <350 cells/μL became eligible for ART in 2011. Approximately 32 of the HIV-participants in our study area were on ART in 2011.

Viral Load Measurements

All of the 5368 participants, aged 15–64 years, who tested HIV positive in 2011 (n = 2401), 2013 (n = 2510), and 2014 (n = 2611), provided dried blood spot (DBS) samples. The total number of DBS samples was 7522 as 32.4% of the 5368 participants tested HIV-positive in >1 survey year. From all 7522 DBS samples, we extracted nucleic acid with NucliSENS EasyMag (Bordeaux, France) and used the Generic HIV Viral Load kit (Biocentric) to quantify the viral load levels. As described in greater detail elsewhere [21], the quantification method has a lower detection limit of 1550 copies/mL. Due to insufficient specimens, we had to exclude 770 (10.24%) viral load samples. For the final analysis, we therefore used a total of 6752 viral load measurements from 4991 unique participants who tested HIV positive in 2011 (n = 2366), 2013 (n = 2135), and 2014 (n = 2251).

Prevalence of Detectable Viremia Measures

We calculated the PDV_+ for each survey year t as follows (we drop the subscript t as it is implicit throughout). Let v_i denote the ith viral load measurement for $i = 1,\ldots,n^+$, where n^+ is the number of HIV-positive test results, and let $y_i = 1$ if $v_i >$ 1550 copies/mL otherwise $y_i = 0$. Then, the $PDV_+ = \sum_{i=1}^{n^+} y_i / n^+$, which is the number of viral loads >1550 copies/mL divided by the number of HIV-positive test results. This PDV_+ measure is a true population estimator because the viral load measurements come from a representative sample of HIV-positive participants. For this reason, our analysis avoids the sampling biases typically associated with facility-based studies in which patients self-select into care [10].

We calculated the PDV_P for each survey year as follows: let n^- denote the number of HIV-negative test results and let N denote the total number of HIV-positive and HIV-negative test results, with $N = n^- + n^+$. For all HIV-negative test results we denote $y_i = 0$. Then, the $PDV_P = \sum_{i=1}^{N} y_i / N$, which is the number of viral loads >1550 copies/mL divided by the total number of HIV-positive and HIV-negative test results.

We note that the number of HIV-negative test results for each survey year was determined with $n_{as}^- = \left[n_{as}^+ - \left(n_{as}^+ \times H_{as}\right)\right] / H_{as}$, where H is the HIV prevalence and the subscripts a and s

denote the age group and sex, respectively. Overall, 15 415 HIV-negative test results were sampled from 11 522 unique participants. We used this proportional allocation approach [22] to determine n^- because 770 HIV-positive samples were excluded from the analysis due to insufficient specimens (as described in the previous section). Otherwise, we would underestimate the PDV_P if we did not sample the correct n^- using this approach.

Statistical Analysis

We performed summary statistics for the unadjusted and age- and sex-adjusted PDV_+, PDV_P, and HIV prevalence measures by year. To statistically assess the change in the PDV_+ and PDV_P measures over time, we used a generalized estimating equation (GEE) model with a logit link function. We chose a GEE model because 32.4% of the participants tested HIV positive in >1 survey year. We fitted 4 regression models using data from the HIV-positive participants only (ie, PDV_+) and from the HIV-positive and HIV-negative participants (ie, PDV_P). For model 1, we included a variable indicating the year of the HIV-positive (ie, viral load measurement) or HIV-negative test result. For model 2, we added a sex variable to the year variable of model 1, and for model 3 we added an age variable (>25 years) to the model 2 variables. For model 4, we added a sex-year interaction term to the model 3 variables to determine if the PDV_+ and PDV_P measures changed significantly for men and women over time.

RESULTS

For all participants with a viral load measurement, the median age was 35 (interquartile range [IQR], 27–45) years, and 79% were female. For the HIV-positive and HIV-negative participants, the median age was 31 (IQR, 21–47) years and 69% were female, as shown in Table 1.

Results show that the adjusted PDV_+ decreased by 13.86 percentage points (pp), from 73.76% in 2011 to 64.38% in 2013, and then to 59.90% in 2014 (Table 1 and Figure 1). During this time, the adjusted HIV prevalence increased from 26.73% in 2011 to 30.64% in 2013 and then to 32.36% in 2014. Thus, when we accounted for the HIV prevalence, the adjusted PDV_P decreased by only 0.92 pp, from 18.83% in 2011 to 18.80% in 2013 and then to 17.91% in 2014.

We observed marked differences in the adjusted PDV_+ and PDV_P measures by sex over time, as shown in Figure 2. Between 2011 and 2014, the PDV_+ for women decreased by 16.5 pp, from 71.8% to 55.3%, compared with a 10.6 pp decrease in the PDV_+ for men, from 77.80% to 67.18% (Supplementary Table 1). However, women had a higher HIV prevalence, 30.56% in 2011 and 35.61% in 2014, and therefore a higher PDV_P, which decreased by 2.1 pp, from 21.35% to 19.23% over the survey

Table 1. Summary Statistics for the Human Immunodeficiency Virus (HIV)–Positive Population Only and the Entire Population (HIV-Positive and HIV-Negative Participants) for the 2011, 2013, and 2014 Survey Years

	Year					
Characteristic	2011		2013		2014	
HIV-positive population						
Dried blood spot samples, No.	2401		2510		2611	
Successful viral load measurements, No. (%)	2366	98.54	2135	85.06	2251	86.21
Viral load >1550 copies/mL	1663		1304		1237	
HIV-positive prevalence of detectable viremia (PDV_+)						
Unadjusted, mean (95% CI)	70.29	(66.95–73.75)	61.08	(57.81–64.48)	54.95	(51.93–58.1)
Age- and sex-adjusted, mean (95% CI)	73.76	(68.77–79.26)	64.38	(59.63–69.64)	59.90	(54.98–65.37)
Female sex, No. (%)	1877	79.33	1690	79.16	1794	79.70
Age, y, median (IQR)	35	(27–45)	35	(27–44)	35	(28–45)
HIV-positive and HIV-negative population						
Observations, No.	8626		6881		6660	
Population prevalence of detectable viremia (PDV_P)						
Unadjusted, mean (95% CI)	19.28	(18.36–20.23)	18.95	(17.94–20.01)	18.57	(17.55–19.64)
Age-sex adjusted, mean (95% CI)	18.83	(17.94–19.76)	18.80	(17.79–19.85)	17.91	(16.92–18.95)
HIV prevalence						
Unadjusted, mean (95% CI)	27.43	(26.33–28.56)	31.03	(29.73–32.37)	33.80	(32.42–35.22)
Age- and sex-adjusted, mean (95% CI)	26.73	(25.66–27.83)	30.64	(29.35–31.97)	32.36	(31.03–33.73)
Female, No. (%)	5832	67.61	4775	69.39	4730	71.02
Age, y, median (IQR)	31	(21–47)	30	(20–47)	31	(21–47)

Unadjusted and age-sex adjusted results for the HIV-positive prevalence of detectable viremia (PDV+), population prevalence of detectable viremia (PDV_P), and HIV prevalence measures are shown. The unadjusted PDV_P is obtained by multiplying the PDV+ by the HIV prevalence. For example, in 2011, there were 1663 HIV-positive participants with a viral load >1550 copies/mL. Therefore, the unadjusted PDV_+ = 1663/2366 (70.29%), the HIV prevalence = 2366/8626 (27.43%), and the PDV_P = 1663/8626 (19.28%). Multiplying the PDV_+ by the HIV prevalence (H) returns the PDV_P: $PDV_+ \times H = 70.29\% \times 27.43\% = 19.28\%$. We also report the age- and sex-adjusted PDV_+, PDV_P, and HIV prevalence measures.

Abbreviations: CI, confidence interval; HIV, Human Immunodeficiency Virus; IQR, interquartile range.

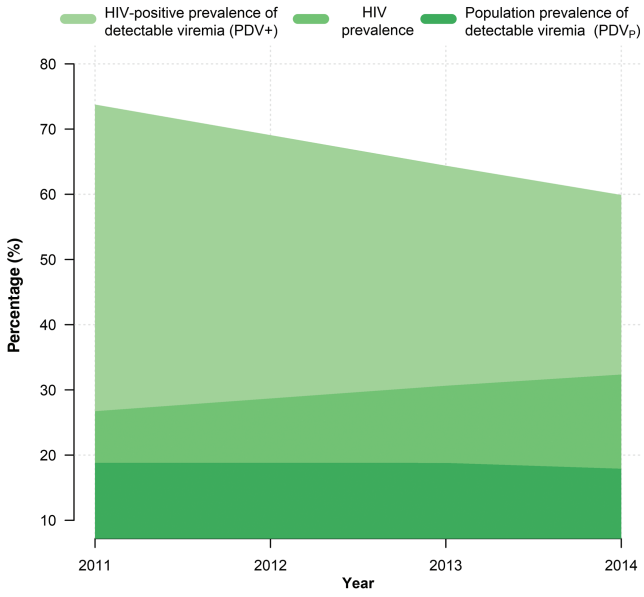

Figure 1. Time trends in the human immunodeficiency virus (HIV)–positive prevalence of detectable viremia (PDV_+), the population prevalence of detectable viremia (PDV_p), and the HIV prevalence over the 2011–2014 survey period.

period. For men, the HIV prevalence rose sharply from 19.63% in 2011 to 27.05% in 2014, which offset the decline in their PDV_+. Thus, the PDV_p for men actually increased by 1.6 pp over the survey period, from 14.58% to 16.18%.

The GEE model results show that the odds of detectable viremia within the HIV-positive population (PDV_+) was significantly lower in 2013 (0.647 [95% CI, .575–.727]; $P < .001$) and 2014 (0.490 [95% CI, .436–.551]; $P < .001$) compared with 2011 (Table 2). In addition, the odds of detectable viremia was significantly lower in women than men, but there was no difference between men and women over time, as shown by the 2 interaction terms in Table 2 ($P > .266$).

The odds of detectable viremia within the entire population (PDV_p) was slightly lower in 2014 (0.911 [95% CI, .850–.977]; $P = .009$), but not in 2013 (0.968 [95% CI, .908–1.031]; $P = .31$), compared with 2011 (Table 3). Although the odd of detectable viremia was higher for women, these odds declined significantly over time when compared with men. We found a similar result when we stratified our analysis by sex (Supplementary Table 2).

DISCUSSION

Our study has quantified the temporal change in the HIV-positive prevalence of detectable viremia (PDV_+) and the population prevalence of detectable viremia (PDV_p) using data from a sub-Saharan African population. The results show that the PDV_+ decreased by almost 14 percentage points (PP), from 73.8% to 59.9%, over the 2011–2014 survey period. In this regard, the 17 healthcare clinics within or adjacent to our surveillance area have been effective in getting HIV-infected persons onto ART and then reducing their viral load levels over time. This is positive news for the global HIV treatment-as-prevention initiative as well as for our study community, which is considered to be at the epicentre of the global AIDS epidemic.

We compare our 40.1% prevalence of undetectable viremia in the HIV-positive community (ie, 100 − PDV_+) in 2014 with population-based studies undertaken in Malawi [23], Zambia [24], and Zimbabwe [25] in 2015–2016. In Malawi, the

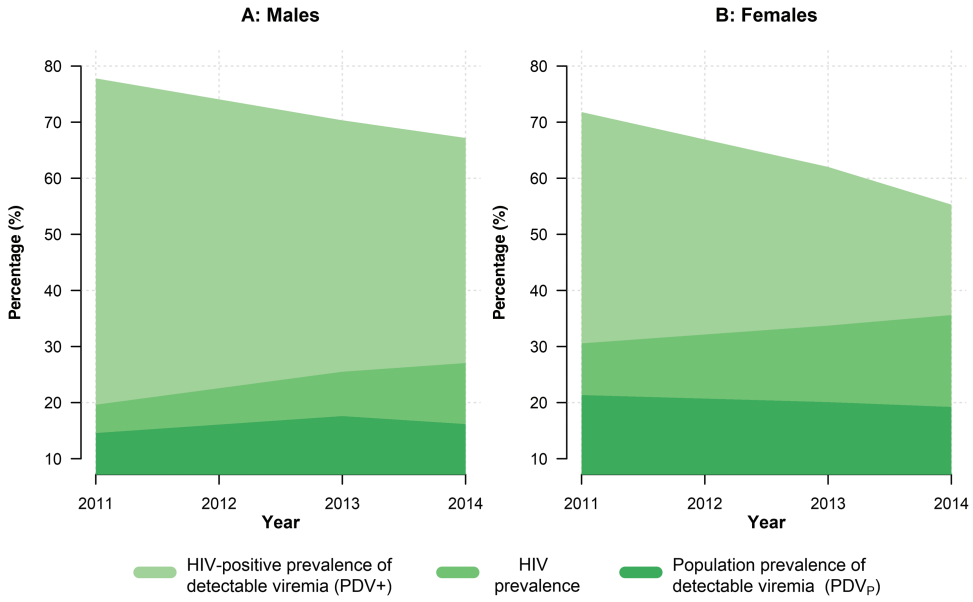

Figure 2. Time trends in the human immunodeficiency virus (HIV)–positive prevalence of detectable viremia (PDV_+), the population prevalence of detectable viremia (PDV_p), and the HIV prevalence over the 2011–2014 survey period for males (*A*) and females (*B*).

Table 2. Regression Results Showing the Relative Odds of a Detectable Viral Load for the Human Immunodeficiency Virus (HIV)–Positive Population, Adjusting for Year, Age, and Sex

	Model 1			Model 2			Model 3			Model 4		
	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value
Year (Ref: 2011)												
2013	0.647	(.575–.727)	<.001	0.646	(.575–.726)	<.001	0.649	(.577–.729)	<.001	0.749	(.565–.993)	.044
2014	0.490	(.436–.551)	<.001	0.49	(.436–.551)	<.001	0.495	(.44–.556)	<.001	0.498	(.379–.654)	<.001
Female sex				0.700	(.611–.801)	<.001	0.680	(.594–.779)	<.001	0.721	(.573–.908)	.005
Age (>25 y)							0.605	(.521–.702)	<.001	0.605	(.521–.702)	<.001
2013 * Female										0.839	(.616–1.144)	.266
2014 * Female										0.993	(.735–1.343)	.966
Constant	2.508	(2.294–2.741)	<.001	3.33	(2.89–3.837)	<.001	5.167	(4.26–6.268)	<.001	4.922	(3.848–6.295)	<.001
HIV tests, No.	6752			6752			6752			6752		
Participants, No.	4991			4991			4991			4991		

Abbreviations: CI, confidence interval; HIV, Human Immunodeficiency Virus; OR, odds ratio.

prevalence of undetectable viremia (<1000 copies/mL) in the HIV-positive community was 67.6% (95% CI, 65.0%–70.2%) among 15- to 64-year-olds, 59.8% (95% CI, 57.4%–62.2%) among 15- to 59-year-olds in Zambia, and 60.4% (95% CI, 58.3%–62.5%) among 15- to 64-year-olds in Zimbabwe. These estimates are markedly higher than our PDV_+ result, despite a lower detection level. It is likely that these differences would be slightly smaller in 2015–2016, if our PDV_+ continued to decrease as it did over the survey period. Nevertheless, we acknowledge that our 40.1% estimate is well below the UNAIDS target of 73% (ie, $90\times90\times90$) to be achieved by 2020.

In addition to quantifying a community's exposure to ART, the PDV_+ has also been used to infer the potential for ongoing HIV transmission at the population level [2–5, 7]. However, measures such as the PDV_+ have been criticized by Miller et al [10] and others [11–15] because they do not account for the relative sizes of the infected and uninfected populations (ie, HIV prevalence). Following this work, we multiplied the PDV_+ by the HIV prevalence to construct a measure called the population prevalence of detectable viremia (PDV_p) [11]. This measure enabled us to account for the high HIV prevalence in the AHRI study area, which increased from 26.7% to 32.4% over the 2011–2014 period. Our results show that the steady rise in the HIV prevalence offset the gains made by the declining PDV_+. Thus, the PDV_p only decreased by <1 pp, from 18.8% in 2011 to 17.9% in 2014.

We also observed significant differences in the PDV_+ and PDV_p measures by sex over time. For example, the PDV_+ for women decreased by 16.5 pp between 2011 and 2014, from 71.8% to 55.3%, when compared with a decrease of 10.6 pp for men, from 77.8% to 67.2%. Previous research has shown that women have more frequent contact with the healthcare system, due in large part to their antenatal treatment and care needs, where they can initiate ART early and have their viral loads monitored [26, 27]. However, because women had a higher HIV prevalence, they also had a higher overall PDV_p, which decreased by 2.1 pp, from 21.3% to 19.2%, over the survey period. Importantly, we found that men had a greater increase in their HIV prevalence over time, which offset the decline in

Table 3. Regression Results Showing the Relative Odds of a Detectable Viral Load for the Human Immunodeficiency Virus (HIV)–Positive and HIV-Negative Population by Year, Adjusting for Sex and Age

	Model 1			Model 2			Model 3			Model 4		
	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value
Year (Ref: 2011)												
2013	0.968	(.908–1.031)	.310	0.964	(.905–1.026)	.248	0.962	(.903–1.024)	.222	1.163	(1.018–1.328)	.026
2014	0.911	(.850–.977)	.009	0.904	(.844–.968)	.004	0.878	(.82–.94)	<.001	1.049	(.903–1.219)	.532
Female sex				1.708	(1.568–1.861)	<.001	1.461	(1.337–1.595)	<.001	1.674	(1.487–1.884)	<.001
Age (>25 y)							3.029	(2.761–3.322)	<.001	3.036	(2.767–3.33)	<.001
2013 * Female										0.785	(.675–.912)	.002
2014 * Female										0.798	(.674–.944)	.009
Constant	0.246	(.234–.258)	<.001	0.169	(.156–.183)	<.001	0.089	(.081–.097)	<.001	0.080	(.071–.089)	<.001
HIV tests, No.	22 167			22 167			22 167			22 167		
Participants, No.	16 319			16 319			16 319			16 319		

Abbreviations: CI, confidence interval; HIV, Human Immunodeficiency Virus; OR, odds ratio.

their PDV_+. Thus, the PDV_p for men actually increased by 1.6 pp, from 14.6% in 2011 to 16.2% in 2014.

We have previously exploited the substantial space-time heterogeneity in ART scale-up over 8 years to demonstrate independent reductions in the individual risk of HIV acquisition with increasing ART exposure [17, 28, 29]. In more recent work, we used viral load survey data from 2011 to show that the prospective risk of HIV acquisition (5 years of follow-up) was independently associated with the PDV_p (adjusted hazard ratio [aHR], 1.07, $P < .001$) but not the PDV_+ (aHR, 1.005, $P = .4$) [11]. Barring substantial changes in sexual behavior, one might expect that the minimal change in the PDV_p would translate into a minimal change in the crude HIV incidence rate. In this regard, we report elsewhere that the crude HIV incidence rate has been relatively stable in the AHRI study population between 2008 and 2016 [30, 31]. Thus, at an ecological level, the HIV incidence rate corresponds with the PDV_p, rather than declining in relation to the marked decrease in the PDV_+. These findings, and the results from our earlier work [11], provide further empirical support for the PDV_p's utility as a measure of the potential for HIV transmission.

The PDV_p will not capture all the fundamental phenomena that underlie HIV transmission dynamics within a population. To better quantify the potential for HIV transmission, it would be ideal to use population-based surveillance systems to collect information on the number and patterns of condomless sex acts. But reliable self-report data is often difficult to obtain, and not all countries will have population-based surveillance systems, which are costly to establish and maintain. Public healthcare facilities can be a more affordable and convenient source of data. However, 2 recent studies have shown that facility-based PDV_+ measures are poor indicators of the incidence of HIV infection [11, 12].

One potential limitation of the study is that 22% of the participants refused to take an HIV test during the survey period. In a previous study, Larmarange et al [32] found that HIV-infected participants were significantly less likely than HIV-uninfected participants to consent to an HIV test during a single survey round. This refusal rate could potentially bias both the HIV prevalence and PDV_p measures downward. However, 2 recent studies have confirmed that survey nonparticipation in this community did not lead to large biases in the cross-sectional estimation of the HIV prevalence [33, 34]. Furthermore, it is unlikely that the 22% refusal rate would bias the PDV_+ measure, as viral load measurements were obtained from all of the HIV-positive test results.

The PDV_+ has been promoted as a proxy for ART program effectiveness. In recent years, it has gained traction in light of the UNAIDS target to have 90% of all ART-initiated persons achieve and maintain undetectable viremia by the year 2020 [6]. But while the PDV_+ may reflect an infected community's exposure to ART, it may not tell us enough about the potential for HIV transmission within the general population. Recent work has therefore begun to promote the PDV_p as a more sensitive biological measure for this purpose, primarily because it accounts for the underlying prevalence of HIV [10–15]. We therefore highlight the need for countries to monitor and report the prevalence of detectable viremia among all adults, irrespective of HIV status.

Supplementary Data

Supplementary materials are available at *Clinical 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

Financial support. This work was supported by the National Institutes of Health (NIH) (grant numbers R01HD084233 and R01AI124389) , T.d.O., A.T., and a South African Medical Research Council flagship grant (grant number MRC-RFA-UFSP-01-2013/UKZN HIVEPI). Funding for the Africa Health Research Institute's Demographic Surveillance Information System and Population-Based HIV Survey was received from the Wellcome Trust. F. T. was was supported by a UK Academy of Medical Sciences Newton Advanced Fellowship (award number NA150161). J. H. was supported by the NIH (grant numbers R01AI108490 and R01AI127232). T. B. was supported by the Alexander von Humboldt Foundation through the endowed Alexander von Humboldt Professorship funded by the German Federal Ministry of Education and Research, as well as by the Wellcome Trust, the European Commission, the Clinton Health Access Initiative, and by the NIH (grant numbers D43-TW009775 and R01-AI112339).

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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