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MAJOR ARTICLE

Evaluating HIV Viral Rebound Among Persons on Suppressive Antiretroviral Treatment in the Era of "Undetectable Equals Untransmittable (U = U)"

Sugi Min,[1] Fizza S. Gillani,[1,2] Su Aung,[1,2] Joseph M. Garland,[1,2] and Curt G. Beckwith[1,2]

[1]The Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA, and [2]The Miriam Hospital, Providence, Rhode Island, USA

Background. Studies have demonstrated that persons with HIV (PWH) maintaining viral suppression do not transmit HIV to HIV-negative partners through condomless sex, leading to the "Undetectable = Untransmittable (U = U)" prevention campaign. However, few studies have examined the durability of suppression in the era of U = U.

Methods. This retrospective cohort study was conducted in Providence, Rhode Island. PWH aged ≥18 years with documented viral suppression (defined as at least 1 viral load [VL] <200 copies/mL and no VL ≥200 copies/mL) in 2015 were included in the baseline cohort. Primary outcomes were viral suppression, viral rebound (at least 1 VL ≥200 copies/mL), or gap in VL monitoring assessed annually from 2016 to 2019. Those with viral rebound were assessed for resuppression within 6 months. Demographic and clinical characteristics associated with viral rebound or gaps in VL monitoring were investigated by bivariate analysis and logistic regression.

Results. A total of 1242 patients with viral suppression were included in the baseline cohort. In each follow-up year, 85%–90% maintained viral suppression, 2%–5% experienced viral rebound, and 8%–10% had a gap in VL monitoring. Among those with viral rebound, approximately one-half were suppressed again within 6 months. In the logistic regression models, retention in care was significantly associated with viral suppression, while younger age, black race, high school or equivalent education, non–men who have sex with men, and history of incarceration were significantly associated with viral rebound.

Conclusions. In the U = U era, most patients with viral suppression who are retained in care are likely to maintain viral suppression over time. Some patients require additional support for regular VL monitoring.

Keywords. monitoring; prevention; rebound; suppression; undetectable.

Several recent studies (HPTN 052, PARTNER, PARTNER 2, Opposites Attract) have demonstrated that people with HIV (PWH) on antiretroviral therapy (ART) who have suppressed viral load (VL), generally defined as <200 copies/mL, do not transmit HIV infection through condomless vaginal or anal sex to HIV-negative sexual partners [1–4]. Together, these studies provide strong evidence for the "Undetectable Equals Untransmittable (U = U)" HIV prevention campaign [5], a landmark prevention strategy endorsed by the Centers for Disease Control and Prevention [6], the National Institutes of Health [7], and international organizations such as the International AIDS Society [8] and UNAIDS [9].

The successful implementation of U = U to prevent the transmission of HIV, both at the individual patient and societal levels, depends on the durable and reliable maintenance of HIV viral suppression, which requires persistent adherence to ART and regular VL monitoring [7]. While more potent ART regimens helped increase rates of viral suppression in the US population over time [10], long-term adherence to HIV treatment can be challenging and affected by patient-related factors and circumstances. Certain patient characteristics, including youth [11–14], black race [15, 16], and history of incarceration [17–19], have previously been associated with barriers to successful treatment and adherence, increasing the risk of viremia in these populations, with important implications for the U = U strategy.

Several studies have examined the durability of viral suppression among those with a history of suppression in HIV clinic populations across multiple years of follow-up and analyzed characteristics associated with viral rebound [11, 20, 21]. The largest, conducted among 16 101 patients in HIV clinics across the United Kingdom, found a low rate of viral rebound (7.8 per 100 person-years) across 58 038 years of follow-up, with duration of viral suppression, more advanced age, and later

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Correspondence: Curt G. Beckwith, MD, Division of Infectious Diseases, The Miriam Hospital, 164 Summit Ave, Providence, RI 02906 (cbeckwith@lifespan.org).

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calendar year of ART initiation associated with maintaining viral suppression, while black race, lower pre-ART CD4 count, and higher pre-ART VLs were associated with viral rebound [11]. In contrast, an analysis in a Veterans Administration HIV clinic population in Washington, DC, found high probability of rebound (15%–26%) in the first 3 years of follow-up, but lower probability among patients with higher CD4 count and 3–6 years of sustained suppression [20]. Despite these important findings, the studies were conducted among majority male or more racially homogenous populations [11, 20, 21].

Despite the promotion of U = U, there have been few studies examining the incidence of or risk factors for viral rebound among persons with known viral suppression and how often persons with viral suppression experience gaps in viral load monitoring. In light of the growing promotion and implementation of U = U globally, we conducted a study to characterize the durability of viral suppression at 2 suppression thresholds (<200 copies/mL and <20 copies/mL) and to identify patient characteristics associated with viral rebound and gaps in viral monitoring to identify at-risk populations who may need targeted support for successful uptake and use of the U = U prevention strategy.

METHODS

Study Setting

In this retrospective cohort study, we analyzed data from the Immunology Center in Providence, Rhode Island, the largest provider of HIV care in Southeastern New England. The Center is supported by the federal Ryan White program and has 1850 active patients, with a high baseline viral suppression rate (90.2%). Over 80% of the PWH in Rhode Island receive their care at the Immunology Center.

Study Population and Design

Data were extracted from the Immunology Center Database, a comprehensive relational (longitudinal) SQL Server data system that is populated through the electronic medical record. All patients with HIV treated in 2015 who were ≥18 years of age as of December 31, 2015, were eligible for study participation. Patients were included in the 2015 baseline cohort if they met the following criteria: at least 1 VL measurement <200 copies/mL between January 1, 2015, and December 31, 2015, and no VL measurements ≥200 copies/mL during the same time period. Our primary outcomes were assessed per calendar year during the follow-up period of January 1, 2016, through December 31, 2019, and included the proportions of patients from the baseline cohort who (1) maintained viral suppression, defined as having at least 1 VL measurement <200 copies/mL and no VL measurements ≥200 copies/mL; (2) had viral rebound, defined as having at least 1 VL ≥200 copies/mL; or (3) experienced a gap in VL monitoring, defined as having no VL data for that year. Those with documented viral rebound or a gap in VL monitoring in any given calendar year during the follow-up period were excluded from the cohort for the subsequent follow-up years. Among those who experienced viral rebound, we determined the proportion who subsequently returned to viral suppression within 6 months, which we defined as having at least 1 VL measurement <200 copies/L followed by no VL ≥200 copies/mL within 6 months of their first documented episode of viral rebound.

In a secondary analysis, we assessed outcomes using a more stringent definition of viral suppression, VL <20 copies/mL, which may more accurately depict a common threshold for viral suppression used by clinicians. In this analysis, inclusion criteria for the baseline cohort were at least 1 VL measurement <20 copies/mL and no VL measurements ≥20 copies/mL between January 1, 2015, and December 31, 2015. During the follow-up period, viral suppression was defined as at least 1 VL measurement <20 copies/mL and no VL measurements ≥20 copies/mL in a calendar year, and viral rebound was defined as at least 1 VL ≥20 copies/mL in a calendar year.

We described the baseline characteristics of the 2015 study cohort and identified factors that were associated with viral rebound or a gap in VL monitoring in the follow-up years. Covariates of interest included age (divided into 2 age groups, 18–44 years and 45–99 years as of December 31, 2015), race (categorized as White, Black, and other), and ethnicity (Hispanic and non-Hispanic). In addition, we examined a number of dichotomous variables that were assessed at the time of clinic intake including place of birth (United States and Puerto Rico vs non-US); primary HIV risk factor (men who have sex with men [MSM] vs non-MSM; injection drug use [IDU] vs non-IDU); history of psychiatric illness; history of noninjection substance use; housing status (stable vs unstable housing); and history of incarceration. We also included highest level of education attained. For each year of analysis, we determined the proportion of patients who were retained in care using the Health Resources and Services Administration definition [22]: having 2 HIV provider visits, separated by 3 months, within 1 year. We included retention in care during both the baseline calendar year 2015 and during the entire follow-up period.

Statistical Analysis

Incidence rate of viral rebound was determined by calculating the number of patients experiencing viral rebound per 100 person-years of follow-up, and confidence intervals were calculated by normal approximation to the Poisson distribution [23]. Follow-up time from the baseline year 2015 was assigned based on the year during which patients exited the study (due to viral rebound, gap in VL monitoring, or conclusion of the study), with study exit assumed to occur at the halfway point in the calendar year. Study exit in 2016, 2017, 2018, and 2019 was assigned 0.5, 1.5, 2.5, and 3.5 years of follow-up, respectively.

Bivariate analyses including chi-square and Fisher exact tests were used to assess the marginal effect of demographic and clinical variables on whether a patient from the baseline cohort experienced viral rebound or a gap in VL monitoring during the follow-up period. To identify characteristics associated with viral rebound, we examined patients from the baseline cohort who had at least 1 VL measurement available during the follow-up years of 2016–2019 and compared characteristics between those with viral suppression during 2016–2019 with those of individuals who experienced an episode of viral rebound in any of the follow-up years. Similarly, to determine characteristics associated with gap in VL monitoring in a follow-up year, we examined all patients from the baseline cohort who had no viral rebound during the follow-up years. Among this group, characteristics were compared between patients who provided at least 1 VL test every calendar year and patients who had at least 1 calendar year with no VL test.

Logistic regression models with variable selection were used to examine the combined effects of patient-related factors (age, race, ethnicity, HIV risk factors, retention in HIV care) on the probability of experiencing viral rebound in the follow-up years. For all analyses, a P value <.05 was considered significant. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

The Institutional Review Board of The Miriam Hospital approved this study.

RESULTS

Study Population and Characteristics

In the 2015 baseline cohort, 1242 patients met our definition of HIV viral suppression at <200 copies/mL. The mean and median (interquartile range) age at the end of 2015 were 49 and 50 (41–57) years, respectively; 67.5% were aged 45 years or older; 72.5% identified as male at birth; 64.3% were White, 32.5% Black, and 3.2% other race; 76.0% were non-Hispanic; 67.2% were born in the United States or Puerto Rico; and 44.6% described themselves as MSM. At the time of clinic intake, 34.0% had some college education, 80.4% had stable housing, 7.6% had a history of incarceration, 37.8% had a history of psychiatric illness, 19.3% had injected nonprescription drugs, and 43.7% had a history of substance use. In 2015, 76.8% of the cohort were retained in care for the year, and 37.8% were retained in all 4 subsequent years (Table 1).

Table 1. Demographic Characteristics for the 2015 Baseline Cohort at the Time of Study Enrollment

	n = 1242, No. (%)
Sex at birth	
Female	342 (27.5)
Male	900 (72.5)
Race	
White	798 (64.3)
Black	404 (32.5)
Others	40 (3.2)
Ethnicity	
Hispanic	298 (24.0)
Non-Hispanic	944 (76.0)
Education	
High school or equivalent	450 (36.2)
Some college/college graduate	422 (34.0)
Not reported/unknown	370 (29.8)
Housing	
Stable	998 (80.4)
Unstable	244 (19.6)
MSM	
Yes	554 (44.6)
No	688 (55.4)
Age groups (as of 12/31/2015)	
18–44 y	404 (32.5)
45–99 y	838 (67.5)
Other risk factors	
History of incarceration	
Yes	91 (7.6)
No	1100 (92.4)
Missing	51
History of psychiatric illness	
Yes	436 (37.8)
No	719 (62.2)
Missing/unknown	87
Injected nonprescription drugs	
Yes	217 (19.3)
No	908 (80.7)
Missing/unknown	117
Substance use	
Yes	522 (43.7)
No	672 (56.3)
Missing/unknown	48
Country of birth	
USA/PR born	834 (67.2)
Foreign born	408 (32.8)
Retained in 2015	
Yes	954 (76.8)
No	288 (23.2)
Retained in all 4 subsequent y	
Yes	469 (37.8)
No	773 (62.2)

Abbreviation: MSM, men who have sex with men; PR, Puerto Rico.

Durability of Viral Suppression

Figure 1 outlines the breakdown of patients in the baseline cohort who experienced viral rebound or had a gap in VL monitoring during the follow-up period. After the first year of follow-up, 1052/1242 (84.7%) continued to meet the definition for HIV viral suppression, 63/1242 (5.1%) patients experienced viral rebound, and 127/1242 (10.2%) patients had no available VL data. Between the years 2015 and 2019, 84.7%–89.7% of patients who had viral suppression in a given year maintained suppression in the following year. The proportion of patients with viral suppression in a given year who experienced viral rebound in a subsequent

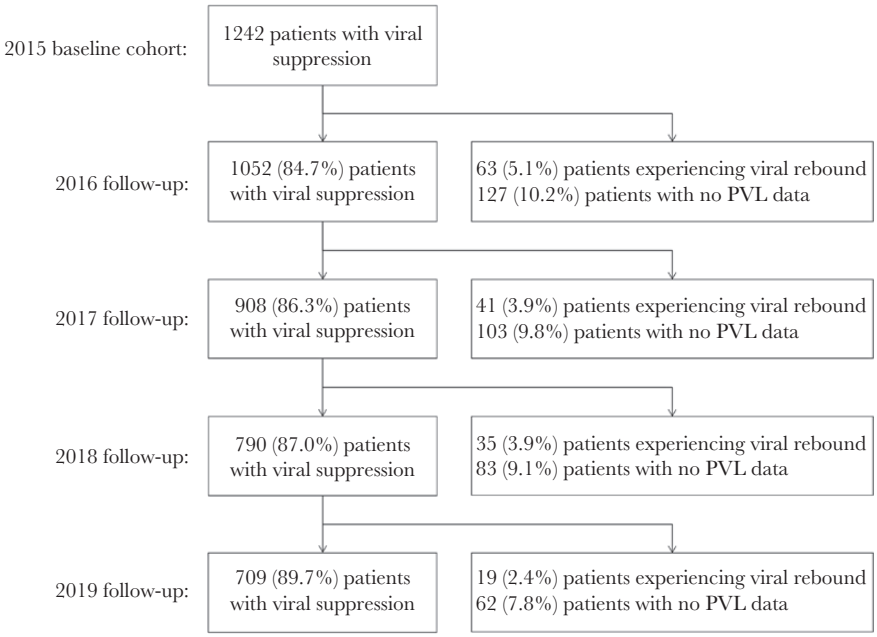

Figure 1. Study population diagram, with viral suppression defined as <200 copies/mL, including the proportion of participants each year who maintained viral suppression, experienced viral rebound, or did not have viral load data at our center. Abbreviation: PVL, plasma viral load.

year ranged from 2.4% to 5.1% (5.1%, 3.9%, 3.9%, and 2.4% for 2016–2019, respectively). The proportion of patients with viral suppression who experienced a gap in VL monitoring in a subsequent year ranged from 7.8% to 10.2% (10.2%, 9.8%, 9.1%, and 7.8% for 2016–2019, respectively). By the end of 2019, 709/1242 (57.1%) patients from the baseline cohort maintained viral suppression every year (Figure 2). Overall, 158/1242 (12.7%) had viral rebound over 3371 person-years of follow-up for the baseline cohort, for an incidence rate of viral rebound of 4.7 per 100 person-years (95% CI, 4.0–5.4), and 375/1242 (30.2%) exited the cohort due to a gap in VL monitoring.

Among 158 patients who experienced viral rebound during the follow-up period, 110 had at least 1 VL available in the 6-month period after their first VL ≥200 copies/mL, and 88/110 (80.0%) achieved viral resuppression during this subsequent 6-month period (36/44 [81.8%], 18/27 [66.7%], 19/24 [79.2%], and 15/15 [100%] annually during the years 2016 through 2019, respectively). Forty-eight patients did not have a VL available during the 6 months following their documented rebound, and therefore, resuppression during this period could not be assessed. In total, 88/158 (55.7%) who experienced viral rebound had documented viral suppression in the 6-month period following their rebound event.

In a secondary analysis using the more stringent definition of viral suppression of <20 copies/mL, the baseline cohort was comprised of 1061 patients. After the first year of follow-up, 835/1061 (78.7%) continued to meet the definition for HIV viral suppression, 116/1061 (10.9%) experienced viral rebound, and 110/1061 (10.4%) had no available VL data. Between the years 2015 and 2019, 78.7%–84.4% of patients with viral suppression in a given year maintained viral suppression in the following year. Among those with viral suppression in a given year, 8.4%–10.9% experienced viral rebound in a subsequent year, and 7.2%–10.4% had a VL monitoring gap in a subsequent year. By the end of 2019, 472/1061 (44.4%) patients from the baseline cohort, at the more stringent VL <20 copies/mL, maintained viral suppression every year; 295/1061 (27.8%) experienced viral rebound; and 294/1061 (27.7%) experienced a gap in VL monitoring. The incidence rate of viral rebound with suppression set at VL <20 copies/mL was 11.3 per 100 person-years (95% CI, 10.0–12.6).

Characteristics Associated With Viral Rebound

In the bivariate analysis among 867/1242 patients who had at least 1 VL result during the follow-up period between 2016 and 2019 (Table 2), several variables were significantly associated with viral rebound in any of the follow-up years including Black race ($P = .004$), high school or equivalent educational ($P = .003$), non-MSM ($P = .017$), age 18–44 years ($P = .002$), and history of incarceration ($P = .007$). Retention in care, both during 2015 and in all 4 follow-up years, was associated with viral suppression ($P = .003$ and $P < .0001$, respectively). In the multivariate stepwise regression analysis, there was a negative association between age ≥45 years (odds ratio [OR], 0.977; 95% CI, 0.961–0.994) and retention in care in all follow-up years (OR, 0.41; 95% CI, 0.284–0.591) with viral rebound. There was a positive association between Black race (OR, 1.610; 95% CI, 1.095–2.368) and viral rebound.

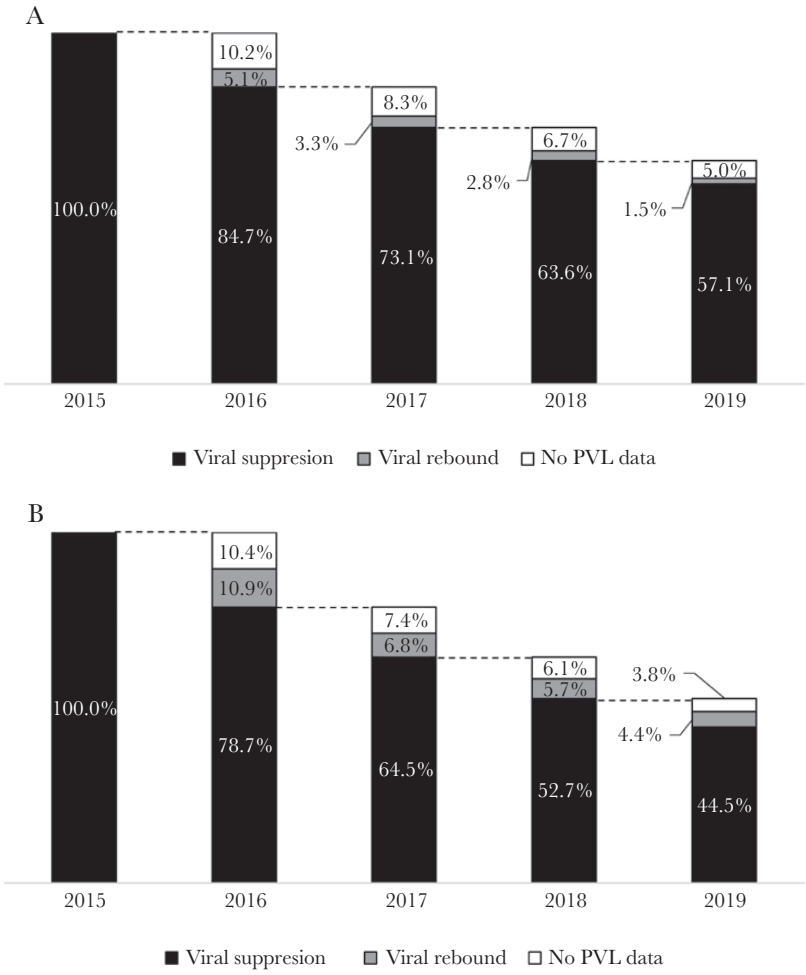

Figure 2. A year-by-year breakdown of the study cohort, with viral suppression defined as (A) <200 copies/mL and (B) <20 copies/mL. Percentages represent proportions of the 2015 baseline cohort who had viral suppression, viral rebound, or no viral load data. Abbreviation: PVL, plasma viral load.

Characteristics Associated With a Gap in VL Monitoring

In the bivariate analysis among 1084/1242 patients who had viral suppression for the entire study period or had a follow-up year with no VL data (Table 3), we found that retention in care was associated with the availability of VL testing every year during the study period ($P < .0001$ for both retention in 2015 and retention in all follow-up years). History of substance use ($P = .0023$), psychiatric illness ($P = .0284$), and some college education ($P = .0274$) were associated with a gap in VL monitoring. Male sex at birth ($P = .0343$), being an MSM ($P = .0326$), birth in the United States or Puerto Rico, and unknown place of birth ($P = .0119$) were additional characteristics that were associated with a gap in VL monitoring.

DISCUSSION

In this study, we examined the durability of HIV viral suppression among our HIV clinic population in RI and identified patient characteristics associated with viral rebound or gaps in VL monitoring during the 4-year follow-up period, information critical to the implementation of U = U in the clinic setting. Few studies have examined rates of viral rebound specifically among individuals with previously demonstrated viral suppression, who may present different risk profiles from the general HIV population. To our knowledge, this study was the first to do so since the launch of the U = U strategy. Our findings highlight specific groups of PWH who may be at higher risk of rebound or have gaps in VL monitoring who may need targeted support to successfully utilize U = U.

In a given year of follow-up, most patients in the 2015 baseline cohort maintained viral suppression, and over one-half maintained suppression through 4 years of follow-up. The rate of viral rebound in our study was low overall (4.7 per 100 person-years; 95% CI, 4.0–5.4), and greater than half (55.7%) of those experiencing viral rebound had documented resuppression within 6 months. The incidence of rebound was lowest in those demonstrating longer periods of viral suppression, consistent with previous findings demonstrating that patients with multiple years of viral suppression have decreased risk of viral

Table 2. Demographic and Clinical Characteristics Comparing the Groups With Viral Suppression and Viral Rebound

Demographic Variables	Total, No. (%)	Patients With Viral Suppression, No. (%)	Patients With Viral Rebound, No. (%)	*P* Value
	n = 867 (100.0%)	n = 709 (81.8%)	n = 158 (18.2%)	
Sex at birth				.055
Female	258 (29.8)	201 (77.9)	57 (22.1)	
Male	609 (70.2)	508 (83.4)	101 (16.6)	
Race				.004
White	553 (63.8)	470 (85.0)	83 (15.0)	
Black	287 (31.0)	217 (75.6)	70 (24.4)	
Others	27 (3.1)	22 (81.5)	5 (18.5)	
Ethnicity				.151
Hispanics	219 (25.3)	172 (78.5)	47 (21.5)	
Non-Hispanics	648 (74.7)	537 (82.8)	111 (17.1)	
Education				.003
High school or equivalent	335 (38.6)	265 (79.1)	70 (20.9)	
Some college/college graduate	268 (30.9)	237 (88.4)	31 (11.6)	
Not reported/unknown	264 (30.5)	207 (78.4)	57 (21.6)	
Housing				.665
Stable	702 (81.0)	576 (82.0)	126 (18.0)	
Unstable	165 (19.0)	133 (80.6)	32 (19.4)	
MSM				.018
Yes	364 (42.0)	311 (85.4)	53 (14.6)	
No	503 (58.0)	398 (79.1)	105 (20.9)	
Age groups (as of 12/31/2015)				.002
18–44 y	273 (31.5)	207 (75.8)	66 (24.2)	
45–99 y	594 (68.5)	502 (84.5)	92 (15.6)	
Other risk factors				
History of incarceration				.007
Yes	65 (7.8)	45 (69.2)	20 (30.8)	
No	773 (92.2)	639 (82.7)	134 (17.3)	
Missing	29			
History of psychiatric illness				.204
Yes	290 (35.9)	232 (80.0)	58 (20.0)	
No	517 (64.1)	432 (83.6)	85 (16.4)	
Missing/unknown	60			
Injected nonprescription drugs				.088
Yes	153 (19.4)	118 (77.1)	35 (22.9)	
No	637 (80.6)	529 (83.0)	108 (17.0)	
Missing/unknown	77			
Substance use				.149
Yes	345 (41.1)	275 (79.7)	70 (20.3)	
No	494 (58.9)	413 (83.6)	81 (16.4)	
Missing/unknown	28			
Country of birth				.127
USA/PR born[a]	556 (64.1)	463 (83.3)	93 (16.7)	
Foreign born	311 (35.9)	246 (79.1)	65 (20.9)	
Retained in 2015				.003
Yes	694 (80.0)	581 (83.7)	113 (16.3)	
No	173 (20.0)	128 (74.0)	45 (26.0)	
Retained in all 4 subsequent y				<.0001
Yes	444 (51.2)	392 (88.3)	52 (11.7)	
No	423 (48.8)	317 (74.9)	106 (25.1)	

Abbreviation: MSM, men who have sex with men.

[a]Includes 75 who have birth place = unknown.

rebound [11, 24, 25]. Current viral monitoring guidelines are consistent with this finding, recommending that VL testing should occur every 3–4 months after VL is initially suppressed to <200 copies/mL, and then at 6-month intervals after patients maintain consistent suppression for >2 years [26]. Overall, our rate of viral rebound was lower than that of the UK CHIC Study

Table 3. Demographic and Clinical Characteristics Comparing Groups With Viral Suppression and Gaps in VL Monitoring

Demographic Variables	Total, No. (%)	Patients With Viral Suppression, No. (%)	Patients With Gap in VL Monitoring, No. (%)	*P* Value
	n = 1084 (100.0)	n = 709 (65.4)	n = 375 (34.6)	
Sex at birth				.034
Female	285 (26.3)	201 (70.5)	84 (29.5)	
Male	799 (73.7)	508 (63.6)	291 (36.4)	
Race				.922
White	715 (66.0)	470 (65.7)	245 (34.3)	
Black	334 (30.8)	217 (65.0)	117 (35.0)	
Others	35 (3.2)	22 (62.9)	13 (37.1)	
Ethnicity				.236
Hispanics	251 (23.1)	172 (68.5)	79 (31.5)	
Non-Hispanics	833 (76.9)	537 (64.5)	296 (35.5)	
Education				.027
High school or equivalent	380 (35.0)	265 (69.7)	115 (30.1)	
Some college/college graduate	391 (36.1)	237 (60.6)	154 (39.4)	
Not reported/unknown	313 (28.9)	207 (66.1)	106 (33.9)	
Housing				.362
Stable	872 (80.4)	576 (66.1)	296 (33.9)	
Unstable	212 (19.6)	133 (62.7)	79 (37.3)	
MSM				.033
Yes	501 (46.2)	311 (62.1)	190 (37.9)	
No	583 (53.8)	398 (68.3)	185 (31.7)	
Age groups (as of 12/31/2015)				.052
18–44 y	338 (31.2)	207 (61.2)	131 (38.8)	
45–99 y	746 (68.8)	502 (67.3)	244 (32.7)	
Other risk factors				
History of incarceration				.635
Yes	71 (6.9)	45 (63.4)	26 (36.6)	
No	966 (93.1)	639 (66.2)	327 (33.8)	
Missing	47			
History of psychiatric illness				.028
Yes	378 (37.4)	232 (61.4)	146 (38.6)	
No	634 (62.6)	432 (68.1)	202 (31.9)	
Missing/unknown	72			
Injected nonprescription drugs				.740
Yes	182 (18.5)	118 (64.8)	64 (35.2)	
No	800 (81.5)	529 (66.1)	271 (33.9)	
Missing/unknown	102			
Substance use				.002
Yes	452 (43.3)	275 (60.8)	177 (39.2)	
No	591 (66.7)	413 (69.9)	178 (30.1)	
Missing/unknown	41			
Country of birth				.012
USA/PR born	644 (59.4)	403 (62.6)	241 (37.4)	
Foreign born	343 (31.6)	246 (71.7)	97 (28.9)	
Unknown	97 (9.0)	60 (61.9)	37 (38.1)	
Retained in 2015				<.0001
Yes	841 (77.6)	581 (69.1)	260 (30.9)	
No	243 (22.4)	128 (52.7)	115 (47.3)	
Retained in all 4 subsequent y				<.0001
Yes	417 (38.5)	392 (94.0)	25 (6.0)	
No	667 (61.5)	317 (47.5)	350 (52.5)	

Abbreviation: MSM, men who have sex with men.

(7.8 per 100 person-years; 95% CI, 7.6–8.0), though there were important differences in study design, including a much earlier and longer period of eligibility (1998–2013), and definitions of viral rebound [11]. With adequate viral monitoring and adherence counseling, many patients experiencing rebound can expect to return to suppression without regimen switch [27, 28].

The majority of persons in our study who experienced viral rebound subsequently achieved suppression, providing additional reassurance in the context of U = U.

In both bivariate and stepwise analyses, retention in care was the characteristic most associated with long-term viral suppression, a finding consistent with other studies [21, 29–31]. While the benefits of continuous retention in care on HIV outcomes are clear, retention can be challenging for patients, given that >50% of diagnosed PWH were not retained in care in 2016 according to the Centers for Disease Control and Prevention [32]. As the majority of HIV transmissions occur from people who know their diagnosis but are not retained in care [33], strategies to help patients address barriers to care and improve retention are critical to the success of the U = U initiative. Our findings further assert the need to target high-risk groups, such as younger adults with HIV, as the association between retention and viral suppression appears strongest in this group [34].

In our analysis, younger patients were more likely to experience viral rebound during the follow-up period, echoed by other studies demonstrating that youth, particularly adolescents and young adults, is associated with lower rates of suppression, with disparities persisting even with similar levels of linkage to care compared with older adults [11–14]. Nance et al. reported that each decade of age correlated with a 5% increase in number of VL tests confirming suppression [10]. Additionally, black race and history of incarceration were also associated with viral rebound. Prior studies showed that viral rebound among formerly incarcerated patients, particularly among those with multiple incarcerations, is more common compared with persons without a history of incarceration, attributable to poorer access to care and challenges with adherence [17–19, 35]. However, racial disparities in viral suppression outcomes seem to persist even in settings of apparent equal access to care (ie, military bases and clinical trials) [15, 16].

Among our cohort, more patients experienced a calendar year of absent VL testing than documented viral rebound, particularly those with a history of psychiatric illness and substance use. It is important to note that a gap in VL monitoring does not necessarily imply falling out of care, as patients may have remained in care, either at our clinic or elsewhere, with a temporary gap in VL monitoring. The actual clinical risks associated with gaps in VL monitoring for patients with a history of successful viral suppression are currently not known; thus it is especially vital for those using U = U as their primary HIV prevention strategy to be regularly monitored for suppression and address any barriers to regular VL testing.

In our secondary analysis using the stricter definition of viral suppression (<20 copies/mL), the detection threshold commonly used with many current VL assays, we saw a ~2-fold increase in the rate of viral rebound compared with the 200 copies/mL threshold. The studies upon which U = U is based demonstrated that using a threshold of 200 copies/mL is effective for the purposes of HIV prevention, and our findings suggest that clinicians using the 20 copies/mL detection threshold for the purposes of U = U may be overly stringent. Educational initiatives to improve our understanding of data supporting U = U are needed for both patients and providers to increase uptake and facilitate rollout of this important HIV prevention strategy.

This study has several important limitations. It is unclear whether viral rebound in our cohort represented true virologic failure with increased risk of viral transmission, or a transient "viral blip" with rapid return to suppression without significant clinical intervention, as we did not assess the magnitude of viral rebound beyond the 200 copies/mL threshold. Furthermore, in our assessment of viral resuppression after rebound, we did not analyze whether the patient received additional counseling or change in ART regimen [11]. We were unable to fully determine the extent to which our results are generalizable for PWH who use U = U, as we did not assess the use of U = U or other HIV prevention strategies (ie, condom use, pre-exposure prophylaxis) among our study population, nor did we address patients' knowledge of their VL status. Previous studies have demonstrated that PWH may inaccurately report their VL status [36], particularly as viral suppression status may have changed [37], highlighting the importance of regularly assessing patients' VL status and its implications on viral transmission to their serodiscordant partners, information critical to the success of U = U. Prospective studies examining the durability of viral suppression among patients counseled on the U = U strategy and among those who have specifically declared use of U = U are needed to assess the patient-level impact of U = U–specific counseling and monitoring strategies. Finally, further research is needed with larger data sets and longer periods of follow-up to examine risk factors predicting viral rebound and to better inform optimal monitoring of patients relying on the U = U strategy to prevent HIV transmission to their serodiscordant partners.

In conclusion, most patients in our HIV clinic population in Rhode Island with a history of viral suppression maintained suppression over a number of years, and approximately one-half of patients experiencing viral rebound went on to achieve resuppression within 6 months. With appropriately scheduled viral monitoring, adherence counseling, and follow-up, these patients are at low risk for viral rebound and HIV transmission to their sexual partners. Certain patient groups, including younger adults, those with history of incarceration, and patients who are not retained in care, are at increased risk of experiencing rebound or gaps in VL monitoring, and thus may benefit from targeted counseling to promote adherence and follow-up if they prioritize U = U as their primary HIV prevention strategy.

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