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MAJOR ARTICLE

Risk of HIV Viral Rebound in the Era of Universal Treatment in a Multicenter Sample of Persons With HIV in Primary Care

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Background. Antiretroviral therapy (ART) is recommended for people with HIV (PWH), irrespective of CD4 cell count, to improve their health and reduce the risk of transmission to sexual partners through long-term viral suppression. We identified risk factors for viral rebound among patients with a period of stable viral suppression to inform counseling and monitoring.

Methods. We conducted a multisite, retrospective study of PWH with a 2-year period of sustained viral suppression in the United States using the Centers for AIDS Research Network of Integrated Clinical Systems cohort. We used multivariable logistic regression to identify characteristics independently associated with any viral rebound (viral load [VL] ≥200 copies/mL) and sustained viral rebound (VL ≥200 copies/mL followed by a VL that was also ≥200 copies/mL within 6 months), within 2 years of follow-up.

Results. Among 3496 eligible patients with a 2-year period of sustained viral suppression, most (90%) continued to have viral suppression over 2 additional years; 10% experienced viral rebound, and 4% experienced sustained viral rebound. In multivariable analyses, Black race, current smoking, integrase strand transfer inhibitor use, and 5- to 9-year duration of ART were positively associated, and being age ≥50 years was negatively associated, with any viral rebound. Only current smoking and 5- to 9-year (vs 2- to 4-year) duration of ART were positively associated, and being age ≥60 years was negatively associated, with sustained viral rebound.

Conclusions. Most people retained in clinical care and with HIV viral suppression on ART will have persistent viral suppression. However, some patients may benefit from additional treatment adherence support.

Keywords. HIV; antiretroviral therapy; long-term suppression; viral rebound; virologic failure.

HIV continues to cause substantial morbidity and mortality in the United States and globally [1, 2]. To improve the health and well-being of persons with HIV (PWH), the US Department of Health and Human Services recommended in 2012 offering antiretroviral therapy (ART) to all PWH irrespective of CD4 cell count [3]. Studies of PWH in early asymptomatic infection have identified health benefits of starting ART while CD4 counts remain >500 cells/μL rather than waiting until CD4 counts have declined [4–6]. Numerous studies have also demonstrated that people with a suppressed HIV viral load (VL), achieved through effective ART, do not transmit HIV infection through condomless vaginal or anal sex to HIV-negative partners [7–12].

First proposed in 2016, the "Undetectable equals Untransmittable" (U = U) HIV prevention campaign is based upon HIV "treatment as prevention" and is supported by the US Centers for Disease Control and Prevention, the International AIDS Society, and the Joint United Nations Programme on HIV/AIDS [13, 14]. While treatment as prevention is supported by strong empirical data and becoming part of mainstream clinical practice [15, 16], there are limited guidelines [17] for patients and providers to inform effective implementation, including optimal counseling and monitoring.

The success of treatment as prevention is based upon the persistence of viral suppression achieved through high levels of ART adherence [13]. However, HIV treatment is dynamic, and adherence can be affected by a myriad of factors such as stigma,

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domestic violence and trauma, substance use, depression, access to health insurance, and loss of housing [18, 19]. For PWH who depend on maintaining viral suppression to prevent transmission of HIV to sexual partners, viral rebound (typically defined as VL ≥200 copies/mL) increases the risk of HIV transmission. Although studies have identified factors that influence viral suppression after initiation of treatment (eg, age, race/ethnicity, treatment type, socioeconomic status, employment, food security) [20–22], risk factors for viral rebound among patients with demonstrated viral suppression are less understood. Identification of such risk factors could further inform guidelines for optimal implementation of treatment as prevention in the clinical setting, including the identification of patients for whom additional support may be useful.

The objective of this study was to identify risk factors for viral rebound among patients with a period of stable viral suppression (ie, persons potentially eligible to use treatment as prevention for HIV prevention based on established viral suppression). We analyzed data from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), a large, diverse clinical database of PWH from multiple US sites.

METHODS

Data Source

The multisite CNICS includes clinical data on PWH receiving care at 10 Centers for AIDS Research–affiliated clinics [23]. This study included data from 8 sites (Baltimore, Maryland; Birmingham, Alabama; Boston, Massachusetts; Chapel Hill, North Carolina; Cleveland, Ohio; San Diego, California; San Francisco, California; Seattle, Washington) that have participated in CNICS since 2010. Generally, the CNICS database includes information on participant demographics, risk factors, clinical encounters, diagnoses, HIV treatments, laboratory test results, and self-reported health measures and outcomes (eg, ART adherence, sexual behaviors, substance use, mental health symptoms, health-related quality of life). Institutional review boards at all sites approved participation in CNICS.

Study Design and Sample

We identified a subset of patients who initiated ART after CNICS enrollment and who could be eligible for treatment as prevention based on a 2-year period of stable viral suppression. We then identified persons who experienced viral rebound during the subsequent 2 years of follow-up. Among persons who experienced viral rebound, we determined whether the rebound was sustained, defined as having another sequential VL measurement ≥200 copies/mL within 6 months (Figure 1). Therefore, we analyzed up to 30 months of follow-up after the 2-year period of viral suppression. Patient eligibility criteria for the study included (1) CNICS enrollment; (2) started ART after CNICS enrollment; (3) 2-year period of sustained viral suppression between January 1, 2010, and December 31, 2016 (all VLs <200 copies/mL and within each year had at least 2 VL measurements separated by 6 months); and (4) at least 30 months of follow-up data available after the 2-year period of viral suppression. Each patient entered our analytical sample on the date they completed the 2-year period of viral suppression, which may have been after multiple years of ART.

Measures

Outcomes

The primary study outcome was viral rebound, defined as any VL ≥200 copies/mL during the 2-year follow-up period. Among persons who experienced viral rebound, we determined whether the rebound was sustained as a secondary outcome. Among those with any or sustained viral rebound, we determined the proportion with VLs >1500 copies/mL as a conservative estimate of increased risk for HIV transmission [24].

Sample Characteristics

We included demographics, HIV care–related measures, and health and behavioral time-varying measures that were repeatedly collected over time in CNICS. For measures that could vary over time, we used those reported closest to and before meeting study eligibility. Demographics included age, current sex, race, and ethnicity. HIV care–related measures included primary HIV risk factor; CD4 count; exposure to ART classes including non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (InSTIs), or none of these classes, indicating previous exposure to nucleoside reverse transcriptase inhibitors (NRTIs) only; duration of ART; duration of care at the CNICS site; and self-reported ART adherence (poor or worse/fair vs good/very good/excellent [25]). Sexual behavior measures included penile-vaginal sex and/or penile-anal sex in the past 6 months (categorized as with a condom, without a condom, or no sex). Other health measures included smoking status, health-related quality of life (EQ-5D instrument with a summary score [low, medium, and high] using the Shaw scoring algorithm [26]), and depression and anxiety symptoms (depression was classified into 2 categories: none or mild vs moderate, moderate severe, or severe [PHQ5 instrument] [27]; anxiety was measured using 3 categories: none, some symptoms, and panic disorder; binge drinking frequency [AUDIT-C instrument] [28]; and use of methamphetamines, cocaine, and opioids [ASSIST instrument] [29]).

Statistical Analyses

We described study sample characteristics using percentages, excluding patients with missing data from the denominator for each characteristic, or mean with SD for continuous data. We compared characteristics of patients who did and did not experience viral rebound using chi-square tests or Fisher exact

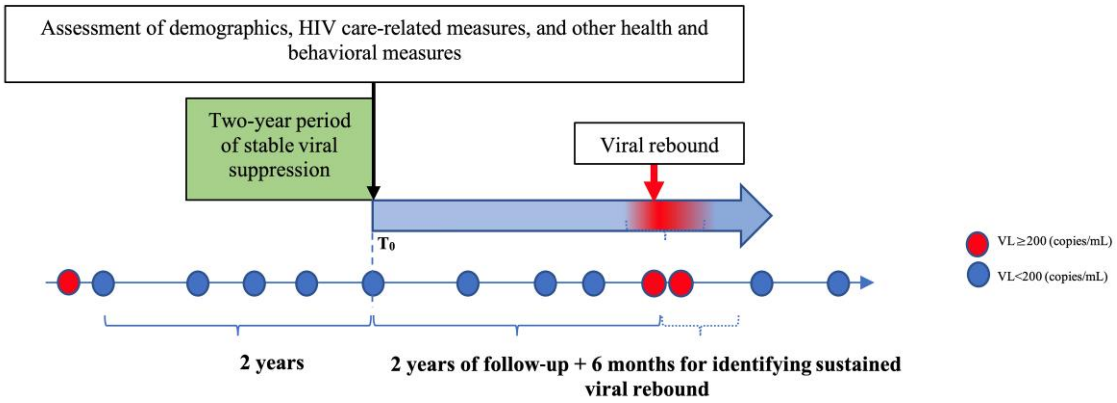

Figure 1. Cohort eligibility and assessment of viral rebound during follow-up. Abbreviation: VL, viral load.

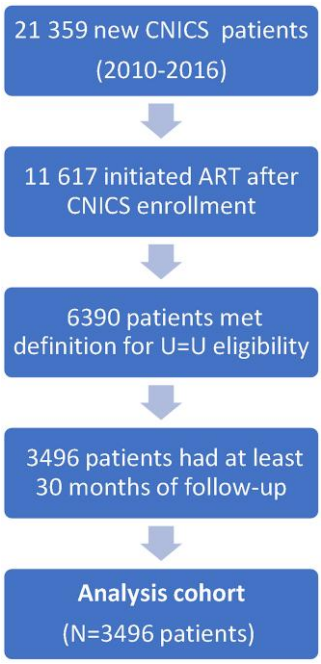

Figure 2. Inclusion criteria for the study cohort. Abbreviations: ART, antiretroviral therapy; CNICS, Centers for AIDS Research Network of Integrated Clinical Systems.

tests as appropriate for categorical variables and 2-sample Student *t* tests or Wilcoxon rank-sum tests as appropriate for continuous variables. To identify characteristics independently associated with viral rebound, we fit a multivariable logistic regression model, including characteristics that were associated with viral rebound ($P \lesssim .1$).

To utilize all available data and minimize bias due to missing data, we used multiple imputations to impute missing values for sample characteristics. To accommodate different missing data patterns, we used chained equation models assuming that data were missing at random conditional on other characteristics (R mice package, version 3.11.0) and imputed missing data iteratively until achieving stationary distributions to create 5 complete data sets. For each complete data set, we fit the multivariable logistic models, and results from across data sets were pooled using Rubin's rules [30]. For comparison purposes, we also completed the multivariable analyses using complete cases only.

We conducted analyses using R software (version 3.6.1). We used 2-sided tests, with a significance level of alpha = .05.

RESULTS

Between 2010 and 2016, 21 359 PWH enrolled in CNICS. Overall, 11 617 (54%) had initiated ART after CNICS enrollment; of these, 9776 (84%) had been on ART for at least 2 years, and 6390 (55%) had a 2-year period of sustained viral suppression. Of these, 3496 (55%) had at least 30 months of follow-up data for assessment of our study outcomes (Figure 2).

Characteristics of the Study Sample

Among the 3496 patients included the study, most were aged 30 to 59 (84%) and male (80%) (Table 1). Just over half (53%) were White, 38% were Black, and 16% were of Hispanic ethnicity. The primary HIV risk factor was male-to-male sexual contact (57%), followed by heterosexual contact (27%) and injection drug use (7%). Patients' average CD4 count (SD) was 615 (277) cells/μL, 52% had been on ART for 2 to 4 years, and 41% had received HIV care at the CNICS site for 2 to 4 years at study entry. Regarding ART exposure before entering the cohort, 65% had been exposed to 1 ART class, 28% to 2 classes, 6% to 3 classes, and <1% had not been exposed to NNRTIs, PIs, or InSTIs, indicating exposure to NRTIs only. Nineteen percent of the patients were on an InSTI at study entry, including 16% on a first-generation InSTI (raltegravir or elvitegravir) and 3% on a second-generation InSTI (dolutegravir). Most patients (90%) reported "good" or better adherence to ART.

At study entry, 54% of patients reported low or medium health-related quality of life, 18% reported moderate to severe

Table 1. Baseline Characteristics of Patients With HIV in the Study Cohort

	Overall (n = 3496) No. (%)[c]	No Viral Rebound (n = 3145) No. (%)[c]	Any Viral Rebound[a] (n = 351)		Sustained Viral Rebound[b] (n = 127)	
			No. (%)[c]	P[d]	No. (%)[c]	P[d]
Age group						
<30 y	295 (8)	261 (8)	34 (10)	**.01**	9 (7)	**.01**
30–39 y	768 (22)	690 (22)	78 (22)	…	32 (25)	…
40–49 y	1278 (37)	1128 (36)	150 (43)	…	59 (46)	…
50–59 y	905 (26)	830 (26)	75 (21)	…	26 (20)	…
≥60 y	250 (7)	236 (8)	14 (4)	…	1 (1)	…
Sex (current)						
Female	574 (20)	510 (20)	64 (22)	.48	19 (18)	.83
Male	2319 (80)	2086 (80)	233 (78)	…	85 (82)	…
Race						
Black	1316 (38)	1156 (38)	160 (47)	**<.01**	52 (42)	.19
White	1825 (53)	1669 (54)	156 (46)	…	57 (46)	…
Other	283 (8)	257 (8)	26 (8)	…	14 (11)	…
Hispanic/Latino						
No	2640 (84)	2394 (85)	246 (82)	.20	86 (78)	**.09**
Yes	487 (16)	432 (15)	55 (18)	…	24 (22)	…
Quality of life						
Low	143 (10)	121 (9)	22 (16)	**.04**	5 (11)	.86
Medium	634 (44)	574 (44)	60 (44)	…	21 (46)	…
High	657 (46)	602 (46)	55 (40)	…	20 (43)	…
Depression symptoms						
None	1166 (82)	1065 (83)	101 (77)	**.10**	33 (77)	.42
Moderate or severe	254 (18)	223 (17)	31 (23)	…	10 (23)	…
Anxiety symptoms						
None	1386 (79)	1255 (79)	131 (76)	**.03**	44 (79)	.95
Some	196 (11)	182 (11)	14 (8)	…	7 (13)	…
Panic disorder	183 (10)	156 (10)	27 (16)	…	5 (9)	…
Binge alcohol use						
Never	1196 (68)	1070 (67)	126 (75)	**.04**	44 (80)	**.12**
Infrequent	478 (27)	446 (28)	32 (19)	…	9 (16)	…
Frequent	97 (5)	86 (5)	11 (7)	…	2 (4)	…
Smoking status						
Never	735 (41)	685 (42)	50 (29)	**<.01**	15 (26)	**<.01**
Past	440 (24)	409 (25)	31 (18)	…	6 (11)	…
Current	627 (35)	533 (33)	94 (54)	…	36 (63)	…
Methamphetamine use						
Never	1011 (66)	922 (66)	89 (61)	**.07**	32 (68)	1.0
Past	405 (26)	366 (26)	29 (27)	…	12 (26)	…
Current	125 (8)	106 (8)	19 (13)	…	3 (6)	…
Cocaine use						
Never	902 (58)	826 (59)	76 (51)	**<.01**	28 (58)	**.11**
Past	548 (35)	493 (35)	55 (37)	…	14 (29)	…
Current	97 (6)	78 (6)	19 (13)	…	6 (13)	…
Opiate use						
Never	1309 (88)	1188 (88)	121 (86)	.58	42 (95)	.19
Past or current	185 (12)	165 (12)	20 (14)	…	2 (5)	…
HIV transmission risk factor						
Heterosexual contact	951 (27)	849 (27)	102 (29)	**.02**	30 (24)	.22
IDU	262 (7)	223 (7)	39 (11)	…	16 (13)	…
MSM	1977 (57)	1799 (57)	178 (51)	…	69 (54)	…
MSM-IDU	221 (6)	195 (6)	26 (7)	…	9 (7)	…
Other or unknown	85 (2)	79 (3)	6 (2)	…	3 (2)	…
Vaginal sex in the past 6 mo						
With condom	212 (16)	190 (16)	22 (16)	.97	7 (12)	.24

Table 1. Continued

	Overall (n = 3496) No. (%)[c]	No Viral Rebound (n = 3145) No. (%)[c]	Any Viral Rebound[a] (n = 351)		Sustained Viral Rebound[b] (n = 127)	
			No. (%)[c]	P[d]	No. (%)[c]	P[d]
Without condom	93 (6.9)	83 (6.9)	10 (7.4)	…	1 (2)	…
No sex	1039 (77)	935 (77)	104 (76)	…	49 (86)	…
Anal sex in the past 6 mo						
With condom	228 (17)	213 (18)	15 (12)	.25	7 (13)	.74
Without condom	353 (26)	318 (26)	35 (27)	…	14 (27)	…
No sex	754 (57)	766 (56)	77 (61)	…	31 (60)	…
Vaginal/anal sex in the past 6 mo						
With condom	450 (33)	410 (33)	40 (29)	.59	16 (28)	.27
Without condom	434 (32)	391 (32)	43 (32)	…	15 (26)	…
No sex	486 (35)	433 (35)	53 (39)	…	26 (46)	…
CD4 count, mean ± SD, cells/μL	615 ± 277	617 ± 278	599 ± 275	.25[a]	574 ± 285	**.11**[a]
Duration of ART						
2–4 y	1825 (52)	1663 (53)	162 (46)	**<.01**	55 (43)	**.04**
5–9 y	959 (28)	834 (27)	125 (36)	…	46 (36)	…
≥10 y	712 (20)	648 (20)	64 (18)	…	26 (21)	…
No. of exposures to ART classes						
(NRTI only)	31 (0.9)	30 (1.0)	1 (0.3)	**.02**	0 (0)	**.02**
One	2287 (65)	2070 (66)	217 (62)	…	68 (54)	…
Two	973 (28)	873 (28)	100 (28)	…	49 (39)	…
Three	205 (5.9)	172 (5.5)	33 (9.4)	…	10 (7.9)	…
Duration of care at site						
2–4 y	1423 (41)	1296 (41)	127 (36)	.13	42 (33)	.17
5–9 y	1111 (31)	985 (31)	126 (36)	…	47 (37)	…
≥10 y	962 (28)	864 (28)	98 (28)	…	38 (30)	…
ART adherence						
Fair or poor	137 (10)	117 (9)	20 (15)	**.04**	4 (10)	.79
Good	1273 (90)	1161 (91)	112 (85)	…	38 (90)	…
Any InSTI use	590 (19)	524 (18)	66 (22)	**.09**	22 (21)	.43
InSTI type						
1st generation	499 (84)	442 (84)	57 (86)	.67	17 (78)	.37
2nd generation	91 (16)	82 (16)	9 (14)	…	5 (22)	…

Abbreviations: ART, antiretroviral therapy; IDU, injection drug use; MSM, men who have sex with men; VL, viral load.

[a]VL of ≥200 copies/mL during the first 2 years of follow-up.

[b]VL of ≥200 copies/mL during the first 2 years of follow-up that was followed by a second VL of ≥200 copies/mL within 6 months. This is a subset of patients with any viral rebound.

[c]Cells for specific characteristics may not sum to the column total due to missing data. Percentages were calculated among patients with known values.

[d]Chi-square test or Fisher exact test, as appropriate, compared with sustained viral suppression. Bold indicates $P \leq .1$.

[e]Student t test or Wilcoxon rank-sum test, as appropriate, compared with sustained viral suppression.

depression symptoms, and 21% reported anxiety symptoms or panic disorder. Additionally, 32% reported at least some binge drinking of alcohol, 59% reported ever smoking, 41% reported ever using cocaine, 34% reported ever using methamphetamines, and 12% reported ever using opiates. Among 2118 patients (61%) who reported sexual behaviors, 23% reported any vaginal sex (7% condomless), 43% reported any anal sex (26% condomless), and 65% reported either vaginal or anal sex (32% condomless) in the prior 6 months.

Longitudinal Analyses

During the 2-year follow-up period, most patients (n = 3145, 90%) had sustained viral suppression (Figure 3). Overall, 351 patients (10%) experienced any viral rebound, and 127 (4%) experienced sustained rebound. Among those with any viral rebound, 95 (27%) did not have a second viral load within 6 months to confirm absence of sustained viral rebound yet remained classified as having any viral rebound. Among those with any viral rebound, the median time to first viral rebound (interquartile range [IQR]) was 13.1 (6.8–19.0) months, and 261 (62%) had VLs >1500 copies/mL, indicating increased transmission risk of HIV. Among those with sustained viral rebound, the median time to first sustained viral rebound (IQR) was 12.6 (6.9–19.0) months, the time to the second viral load test (after the first detectable VL) was a median (IQR) of 56 (23–116) days, and 96 (76%) had VLs >1500 copies/mL.

In univariable analyses, compared with patients with sustained viral suppression, those with any viral rebound were

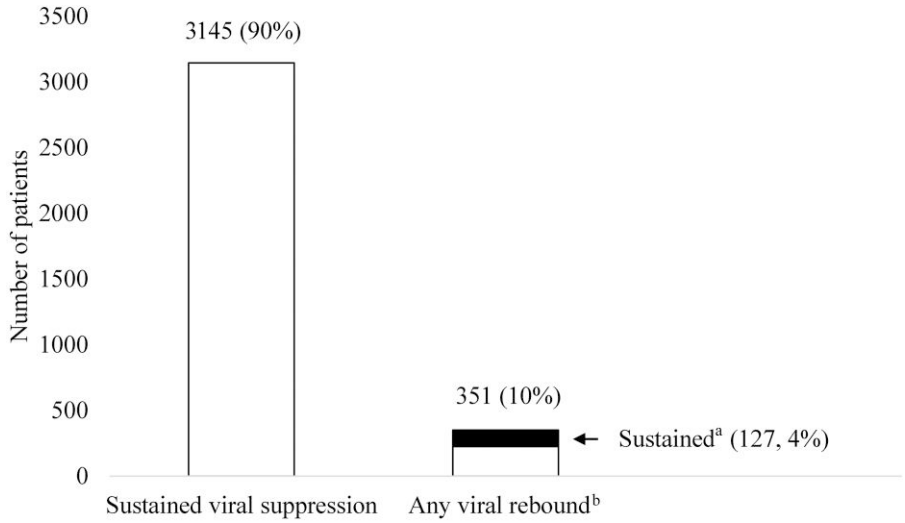

Figure 3. HIV treatment outcome over 2 years of follow-up. [a]VL of ≥200 copies/mL during the first 2 years of follow-up that was followed by a second VL of ≥200 copies/mL within 6 months. [b]VL of ≥200 copies/mL during the first 2 years of follow-up. This is a subset of patients with any viral rebound. Abbreviation: VL, viral load.

younger; more likely to be Black; more often reported low quality of life, depression symptoms, anxiety symptoms, current smoking, current methamphetamine use, and current cocaine use; more often had injection drug use as their primary HIV risk factor; and had longer duration of ART (54% vs 47% for 5 years or longer). Exposure to a greater number of ART classes was significantly associated with any viral rebound ($P = .02$) and sustained viral rebound ($P = .02$). Those with any viral rebound were more often on an InSTI at study entry compared with those with sustained viral rebound (22% vs 18%), but the difference was not statistically significant ($P = .09$). No obvious patterns were observed between viral rebound and InSTI generations. Patients with any viral rebound less often reported good or better ART adherence and any binge drinking (all $P \lesssim .1$).

In multivariable analyses, we included the independent variables with $P \lesssim .1$ in the regression model. Because of the collinearity between the duration of ART and exposure to ART classes, we included only the duration of ART, not both. Multivariable analyses showed that only Black race, current smoking, InSTI use, and 5- to 9-year duration of ART were positively associated with any viral rebound, and only age 50 or older was negatively associated with any viral rebound (Figure 4). Specifically, compared with patients aged 29 and younger, those aged 50 to 59 (adjusted odds ratio [aOR], 0.52; 95% CI, 0.32–0.84) and 60 years and older (aOR, 0.31; 95% CI, 0.16–0.63) had lower odds of any viral rebound, respectively. In contrast, Black PWH had higher odds than White patients of experiencing any viral rebound (aOR, 1.36; 95% CI, 1.02–1.81), patients reporting current smoking had higher odds of viral rebound than those who did not (aOR, 1.42; 95% CI, 1.01–2.00), and patients who used InSTI had higher odds of viral rebound than those who did not (aOR, 1.45; 95% CI, 1.06–1.97). Compared with patients who had been on ART for 2 to 4 years at study entry, those on ART for 5 to 9 years had higher odds of viral rebound (aOR, 1.67; 95% CI, 1.28–2.18).

In univariable analyses, compared with patients with sustained viral suppression, those who experienced sustained viral rebound were generally younger; more likely to be Hispanic; more often reported current smoking and cocaine use; had lower CD4 counts (median, 574 vs 617 cells/μL); and less often reported infrequent binge drinking (all $P \lesssim .1$). However, in multivariable analyses, only current smoking (aOR, 1.92; 95% CI, 1.11–3.33) and 5- to 9-year compared with 2- to 4-year duration of ART (aOR, 1.76; 95% CI, 1.16–2.68) were positively associated with sustained viral rebound, and only age 60 or older compared with 29 and younger was negatively associated (aOR, 0.09; 95% CI, 0.01–0.75) with sustained viral rebound (Figure 5).

The results were similar when including only cases with complete information on all covariates (Supplementary Figures 1 and 2).

DISCUSSION

In this multisite retrospective study of PWH in the United States, viral rebound was infrequent among patients with at least 2 years of consistent viral suppression. Overall, 10% of patients experienced any viral rebound, while only 4% experienced sustained viral rebound. Among patients who experienced viral rebound during the 2-year follow-up period, the median times until first viral rebound and first sustained

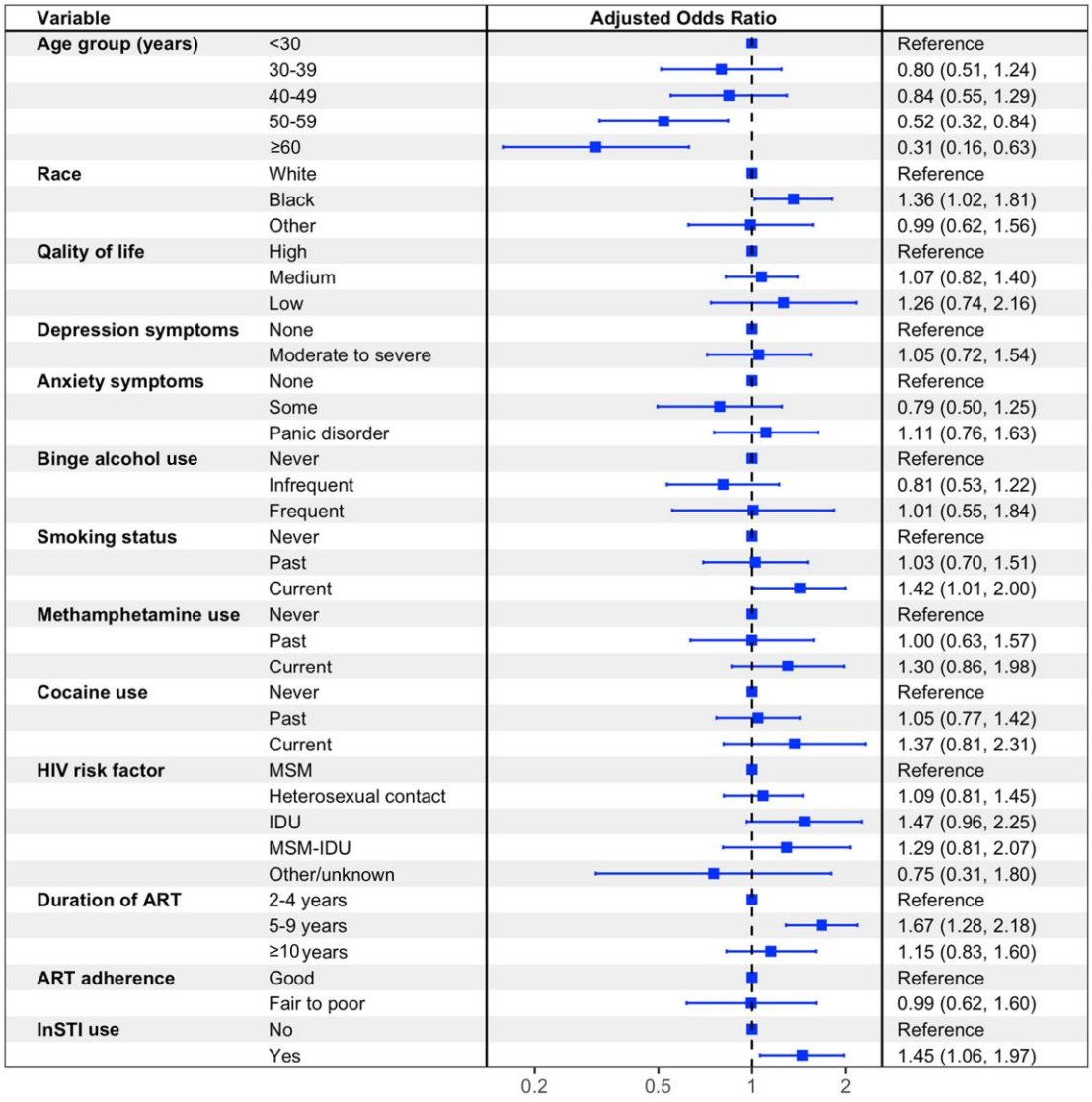

Figure 4. Characteristics independently associated with any viral rebound[a] (A) and sustained viral rebound[b] (B). [a]VL of ≥200 copies/mL during the first 2 years of follow-up. [b]VL of ≥200 copies/mL during the first 2 years of follow-up that was followed by a second VL of ≥200 copies/mL within 6 months. This is a subset of patients with any viral rebound. Abbreviation: VL, viral load.

viral rebound were ~13 months. Older patients (aged 50 years and older) were less likely to experience viral rebound, while Black patients, those who smoked, those using InSTIs, and those who had been on ART for a moderate duration (5 to 9 years) were more likely to experience viral rebound. Similarly, older patients (60 years and older) were also less likely to experience sustained viral rebound. There were no differences between those who did and did not experience viral rebound with respect to sexual behaviors, including vaginal or anal sex without a condom.

Our study suggests that a relatively small percentage of people in stable HIV care on ART experience viral rebound once they have achieved sustained viral suppression, highlighting that once viral suppression is achieved, it is maintained by most patients who are retained in care, which bodes well for their long-term health. The data also suggest that treatment as prevention can be an important and viable primary HIV prevention strategy for most patients with viral suppression. A very low number of patients had sustained viral rebound (4%), which is reassuring given the increased risk of HIV transmission to HIV-negative sexual partners with sustained viremia. In sum, viral suppression remained highly durable in this population of patients engaged in care at CNICS sites.

Prior studies had results generally consistent with our findings, although the definition of viral rebound and timeframe of follow-up have varied substantially across studies. A multisite study of Canadian MSM with HIV found that, among those who achieved viral suppression, 12% experienced viral rebound

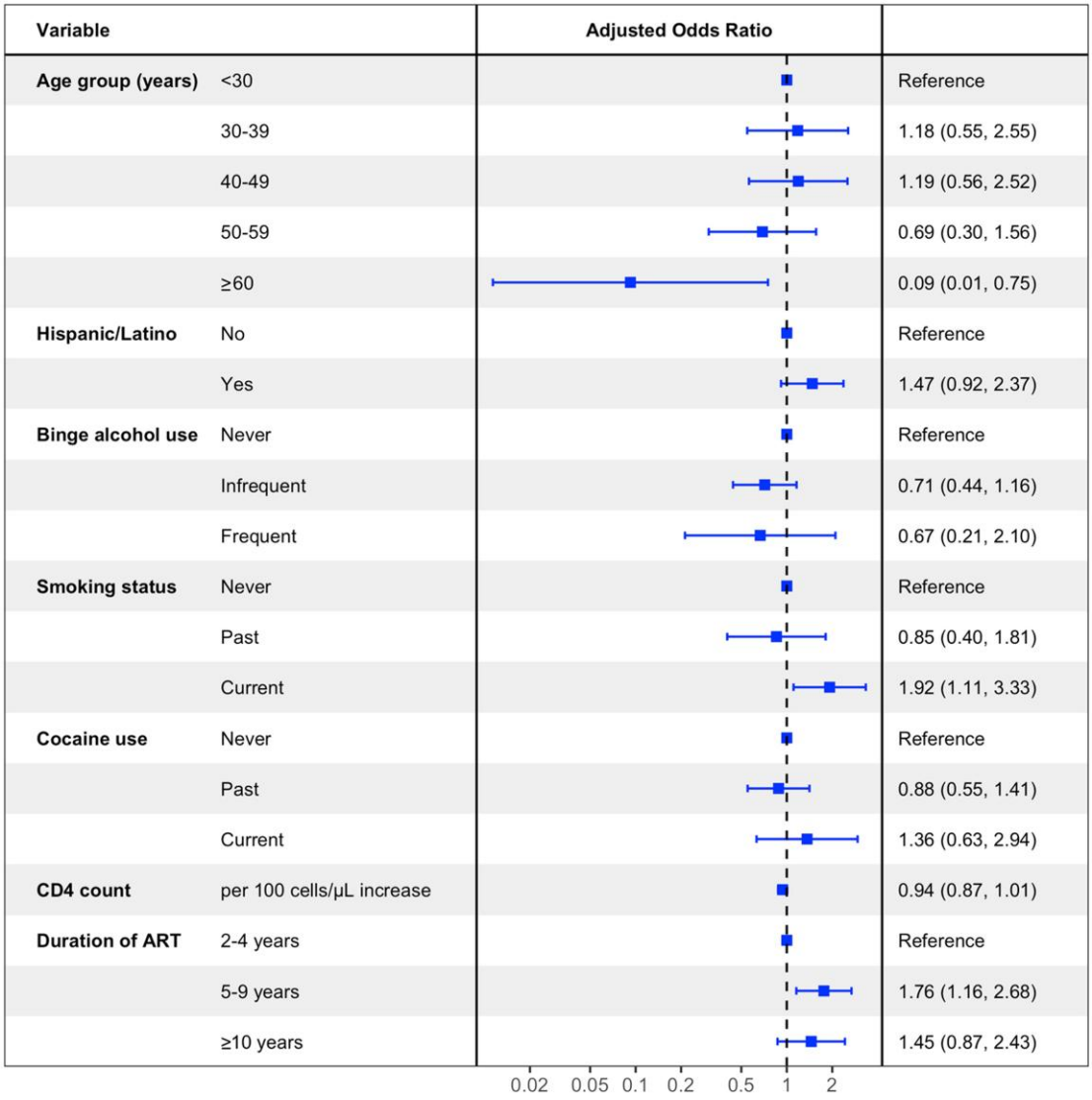

Figure 5. Characteristics independently associated with sustained viral rebound[a]. [a]VL of ≥200 copies/mL during the first 2 years of follow-up that was followed by a second VL of ≥200 copies/mL within 6 months. This is a subset of patients with any viral rebound. Abbreviation: VL, viral load.

(defined as 2 VLs of >200 copies/mL ≥30 days apart) within roughly 5 years of follow-up [31]. Additionally, in an interim analysis of a cohort of MSM with HIV in Atlanta, Georgia, 10% of White MSM and 20% of Black MSM experienced incident loss of viral suppression (defined as >40 copies/mL) over 24 months [32]. Finally, a study from Providence, Rhode Island, evaluated viral rebound among PWH in care and found that 2%–5% of those with viral suppression experienced viral rebound (VL ≥200 copies/mL) per year; half were resuppressed again within 6 months [33].

Although viral suppression was durable in our study and all patients remained engaged in care, we identified some patients who were more likely to experience any viral rebound, including younger patients, Black patients, those using first-generation InSTIs, those on ART for at least 5 but <10 years, and those who smoked. The prior studies in Rhode Island [33] and of MSM in Atlanta [32] also found that Black patients experienced higher risk of viral rebound once viral suppression was achieved. In our study, Black PWH had a higher rate of any viral rebound despite being engaged in care yet did not disproportionately experience sustained viral rebound. The clinical implications of this finding are not clear but could represent a higher prevalence of comorbidities, more frequent use of public insurance or underinsurance, and/or more episodic engagement in care among Black PWH compared with other groups [34–36]. While several studies have identified factors associated with poor retention in care among Black PWH, including mistrust of medical providers [37], lower health literacy [38],

poorer quality of health care [37], substance use, and HIV-related stigma [39], identifying reasons for viral rebound among those successfully retained in care and whether this viral rebound had any negative health consequences deserves further investigation.

Multiple studies have examined whether smoking is a risk factor for poor ART adherence and HIV viremia, with mixed results. A recent systematic review and meta-analysis that examined the relationship between smoking and ART adherence globally found that smoking was associated with suboptimal ART adherence [40]. Studies conducted in the United States have found an association between current smoking status and suboptimal ART adherence and/or HIV viremia and suggested that other factors including low socioeconomic status, substance and alcohol use, and depression are intertwined into this relationship [41–43]. Furthermore, a study conducted by Moreno et al. did not demonstrate an association between smoking and poor ART adherence [44]. Additional research is needed to better understand the association between smoking and risk for viral rebound among persons with viral suppression. For example, the CNICS data set did not include information about social determinants of health, for example, housing stability, that, if more common among smokers, might suggest that concomitant structural adversities are playing a role.

Persons who had been treated with ART for at least 5 years had somewhat increased risk of any and sustained viral rebound compared with persons on HIV treatment for only 2–4 years (the difference in risk among participants on ART for 5–9 years was significant when compared with that of those on treatment for 2–4 years). We suspect that this finding is due to simplification of ART regimens over time, with single-pill once-daily regimens becoming the standard of care. Persons on ART for longer periods of time likely had to use multiple pills and more complex ART regimens early in their treatment compared with persons started on ART more recently and could have accumulated HIV resistance mutations as a consequence. Previous studies have demonstrated that single-pill regimens in comparison with multiple-pill regimens lead to improved retention in care and viral suppression [45–47].

Consistent with our work, prior studies have identified higher risk of viral rebound among younger compared with older patients [31, 33]. Other risk factors noted in prior studies but not independently associated with viral rebound in this study include lower education level [33], being non-MSM [33], history of incarceration [33], history of injection drug use [31], higher CD4 count [31], and year of ART initiation [33]. Of note, InSTI use was independently associated with viral rebound in our study. We specifically examined InSTI use given a previous study conducted by Nance et al. that examined viral suppression over time among CNICS patients; it found that InSTI use was associated with lower odds of having a detectable viral load [20]. Our study differed given that it was limited to patients with established viral suppression. While the use of InSTIs increased between 2010 and 2016 as InSTI-based ART regimens became the first-line preferred regimens, first-generation InSTIs (raltegravir, boosted elvitegravir) were initially used and had lower genetic barrier to resistance compared with second-generation InSTIs (dolutegravir, bictegravir), which later became the preferred InSTIs. In addition, only 19% of patients were on an InSTI at study entry. Therefore, this finding may be attributed to early use of first-generation InSTIs among a small proportion of patients and/or could represent previous suboptimal adherence or history of ART treatment failure, which could account for higher rates of subsequent viral rebound.

Our study was strengthened by the use of the multisite CNICS, which provided a large and diverse sample of PWH in longitudinal care in the United States. However, it also had limitations. Our definitions of viral rebound and sustained viral rebound were intended to use clinically meaningful cutoffs and timeframes; however, the proportion of persons with sustained viral rebound may have been slightly underestimated given that 27% of persons classified as having any viral rebound did not have a second viral load within 6 months to confirm this classification. Additionally, our analysis was limited to PWH engaged in care at clinics that participated in CNICS; the results may not be generalizable to other patient populations and care centers.

In conclusion, among PWH who have achieved viral suppression for a period of 2 years, ~1 in 10 will experience any viral rebound and ~1 in 25 will experience sustained viral rebound in the subsequent 2 years, suggesting that treatment as prevention could be a viable primary HIV prevention strategy for many patients given the durability of viral suppression. Some patients, including younger patients, may benefit from additional supports to ensure persistence of viral suppression, such as more intensive adherence counseling, interventions to ensure retention in care, and more frequent VL monitoring. Although research to identify evidence-based implementation approaches to improve the HIV care continuum among young PWH and Black PWH is ongoing [48–50], more needs to be done, particularly to address key systemic, structural, and social factors [51].

Supplementary Data

Supplementary materials are available at *Open Forum 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.

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Author contributions. Drs. Liu, Hansen, and Beckwith conceptualized and designed the study, designed the data collection instruments, analyzed the data, and reviewed and revised the manuscript. Dr. Chambers analyzed the data and reviewed and revised the manuscript. Ms. Bazerman reviewed and revised the manuscript. Drs. Cachay, Christopoulos, Drainoni, Gillani, Mayer, Moore, and Rana reviewed and revised the manuscript.

Patient consent. The design of the work has been approved by local ethical committees.

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