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Author

Han, Win Min, Broom, Jennifer, Bopage, Rohan, Templeton, David J, Edmiston, Natalie, Petoumenos, Kathy

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RESEARCH ARTICLE

Investigating rates and predictors of viral blips, low-level viraemia and virological failure in the Australian HIV observational database

Win Min Han[1] | **Jennifer Broom**[2,3] | **Rohan Bopage**[4] | **David J. Templeton**[1,5,6] | **Natalie Edmiston**[7] | **Kathy Petoumenos**[1] | **on behalf of the Australian HIV Observational Database**

[1]Kirby Institute, UNSW Sydney, Sydney, New South Wales, Australia

[2]Infectious Diseases Research Network, Sunshine Coast University Hospital, Birtinya, Queensland, Australia

[3]Faculty of Medicine, The University of Queensland, Herston, Queensland, Australia

[4]Western Sydney Sexual Health Centre and Westmead Clinical School, University of Sydney, Sydney, New South Wales, Australia

[5]Department of Sexual Health Medicine and Sexual Assault Medical Service, Sydney Local Health District, Camperdown, New South Wales, Australia

[6]Discipline of Medicine, Central Clinical School, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia

[7]School of Medicine, Western Sydney University, Sydney, New South Wales, Australia

Correspondence
Win Min Han, Kirby Institute, UNSW Sydney, Sydney, Cnr High St & Botany St, UNSW, Kensington NSW 2052, Australia.
Email: wmhan@kirby.unsw.edu.au

Abstract

Objectives: Australia has made significant progress towards achieving the UNAIDS's 95-95-95 cascade targets including HIV viral suppression. To investigate the burden of HIV viraemia, we assessed viral blips, low-level viraemia (LLV) and virologic failure (VF) in an Australian cohort.

Methods: We studied the proportion of people with viral suppression, viral blips, LLV and VF in the Australian HIV observational database (AHOD) between 2010 and 2021. The association between blips or LLV, and VF was investigated using Cox regression, and predictors of viral blips and LLV were assessed using repeated-measured logistic regression.

Results: Among 2544 AHOD participants who were in follow-up and on antiretroviral therapy (ART) from 1 January 2010 (88.7% male), 444 had experienced VF (incidence rate: 2.45 [95% CI: 2.23–2.69] per 100 person-years [PY]) during 18,125 PY of follow-up (a median of 7.6 years). The proportion of people with VF decreased over time, whereas rates of blips and LLV remained stable. Participants with blips (hazard ratio, 2.89; 95% CI: 2.31–3.61) and LLV (4.46; 95% CI: 3.38–5.89) were at increased risk of VF. Hepatitis B co-infection, longer documented treatment interruption duration, younger age and lower CD4 at ART initiation, and protease inhibitors-based initial regimen were associated with an increased risk of VF. Common predictors of blips and LLV such as higher HIV-1 RNA and lower CD4 at ART initiation, longer treatment interruption, more VL testing and types of care settings (hospitals vs. sexual health services) were identified.

Conclusions: Blips and LLV predict subsequent VF development. We identified important predictors of HIV viraemia including VF among individuals on INSTI-based regimens to help direct HIV management plans.

KEYWORDS
HIV, low-level viraemia, treatment failure, viral blip, virological failure

BACKGROUND

HIV treatment and viral suppression prevent HIV-related illness, avert AIDS-related deaths, prevent onwards HIV transmission and prevent the development of drug resistance [1–3]. In recent years, Australia has made significant progresses towards achieving the UNAIDS's 95-95-95 targets [4, 5]. A high proportion of people living with HIV have achieved virological suppression [5–8], with a nearly 98% suppression rate by the end of 2021 [5]. Despite these efforts, in Australia, a small percentage of people with HIV on treatment still experience viraemia [5, 6, 8].

Detectable HIV viraemia may be due to viral load blips, which are transient and small increases in VL, low-level

viraemia (LLV), which is persistent but low levels of viraemia between the detection limits of the assay used and 200 copies/mL, or virologic failure (VF) with confirmed levels of viraemia >200 copies/mL. Even with highly efficacious antiretroviral treatment (ART) options, VF has implications for disease progression, transmission and the need for treatment change [9, 10]. Data are conflicting regarding whether blips and LLV increase the risk of subsequent VF [10–15]. A recent study from a large European Multicenter Cohort, which grouped viraemia level experienced by people with HIV on ART as suppression, blips and LLV categories, found that both blips and LLV were associated with increased risks of subsequent VF [10]. However, others have demonstrated inconsistent findings on the associations of either blip or LLV with VF, especially when different VL cut-offs were used to define the viraemia groups [9, 12, 13].

A comprehensive understanding of the factors associated with HIV viraemia can inform clinician responses to virological blips and LLV in clinical HIV care and, therefore, to assist Australia in meeting the UNAIDS's target of virological suppression. In this study, we investigate the proportions of individuals with VF, detectable viral loads due to blips and LLV in the Australian HIV observational database (AHOD) cohort between 2010 and 2021. Further, we investigate whether blips and LLV are associated with the development of subsequent VF and individual factors associated with people with HIV experiencing blips, LLV and VF.

METHODS

Study population

AHOD cohort was established since 1999, and its primary goals are to evaluate the trends in ART use and HIV disease and treatment outcomes among people with HIV in Australia. Since its inception, a total of 31 clinical sites around Australia, including general practice clinicals, hospitals and sexual health clinics, have contributed data to AHOD. A detailed description of the cohort had previously been published [16, 17]. All 31 AHOD sites contributed data in this analysis and all AHOD participants on ART and in follow-up from 1 January 2010 were included. Data from sites that are no longer contributing data were administratively censored at their last data transfer date. Additional criteria for inclusion were having had at least 6 months of treatment resulting in virological suppression based on a VL carried out between 6 and 12 months after initiation of treatment, followed by at least 1 further year of follow-up and at least one VL every year during ART.

Outcomes

We aimed to estimate the rates of HIV viraemia and to describe factors associated with viral blips, LLV and VF among participants on at least three-drug combination ART or national guideline-endorsed dual therapy since 2010. For each year between 2010 and 2021, we described the proportion of participants who have VF, detectable VLs due to blips and LLV. Second, we investigated factors associated with VF, viral blip and LLV.

In the primary analysis, the proportion of people with detectable VLs for each year between 2010 and 2021 was identified and classified as follows: (a) 'VF' defined as two consecutive VLs of ≥200 copies/mL or a single VL of ≥1000 copies/mL while on ART and (b) a single 'blip' defined as a single/isolated VL of between 51 copies/mL and 999 copies/mL immediately preceded and followed by a VL ≤50 copies/mL and (c) 'LLV' defined as ≥2 consecutive VLs of 51–200 copies/mL ≥30 days apart. Readings within 30 days of each other were considered a single blip. Blips that occurred within 6 months of a treatment switch due to treatment failure or during periods of loss to follow-up were excluded. Additionally, if a participant had one VL episode of 51–200 copies/mL with one VL episode of 201–1000 copies/mL, followed by <200 copies/mL, they were categorised as LLV in a sensitivity analysis since these episodes did not meet the definition for VF.

Statistical analysis

Outcomes for VF, blips and LLV are presented by key participant characteristics (demographics, clinical and HIV-related). Data are presented using medians with interquartile ranges (IQRs) for continuous data and frequencies and percentages for categorical data.

In calculating the proportions of viraemia episodes (VF, blips and LLV) per calendar year between 2010 and 2021, the episodes that spanned December and January were categorised into the respective calendar years by applying appropriate weighting to account for the proportionate representation of each episode across the years.

For the VF outcome analysis, a univariable Cox proportional hazard regression was carried out to investigate the associations between VF and the following variables: age group, sex, HIV exposure (male to male sex [MSM], heterosexual sex and injection drug use), duration of known HIV infection, Australian versus overseas born, duration of ART, CD4 cell count and VL at ART initiation, initial ART regimen (NNRTI, PI, INSTI and Other), HBV/HCV coinfection status, patient care setting (general practice [GP], hospital, sexual health clinics [SHC]), number of VL measurements, duration of documented treatment interruption. The duration of treatment interruption of participants was determined based on the number of days during which they did not have a documented history of being dispensed for ART from clinics. The documented treatment interruption was modelled as time-varying variable in the regression models. In the analysis using VF as an outcome, we investigated whether individuals with or without viral blips and LLV subsequently predict VF.

Viraemia groups (blip, LLV and VF) were also separately modelled as time-varying variables and we allowed the

reclassification only to a higher viraemia group (i.e., viral suppression < blip < LLV < VF). Therefore, the viraemia category included in the analyses was the highest historical VL result for each participant post-ART initiation [10]. Kaplan–Meier methods were also used to estimate the incidence of VF depending on viraemia category (viral suppression, blip or LLV). All potential confounding variables were included in multivariable Cox proportional hazard regression regardless of their significance in the univariable analysis results. All statistical tests were two-sided, and statistical significance was set at p <0.05.

For the analyses of viral blip and LLV outcomes, only participants who had four or more VL measurements were included in these analyses since at least three VLs are needed to define blips and LLVs. Univariable and multivariable random-effects repeated-measure logistic regression was used to investigate the individual factors associated with viral blips and LLV. We censored follow-up at the last visit or at the time of VF if that occurred. All analyses were adjusted by site to account for the heterogeneity of healthcare systems. SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for data management, and Stata software version 16.1 (StataCorp, College Station, TX, USA) was used to perform all analyses.

Sensitivity analysis

Sensitivity analyses for viral blips were conducted using VL cut-offs of 51–200 copies/mL to define blips. In the analyses that further explored whether individuals with viral blips or LLV subsequently developed VF, we conducted a sensitivity analysis using a single VL of ≥500 copies/mL as cut-off for virological failure (instead of ≥1000 copies/mL used in the primary analysis). Additional sensitivity analyses limiting only to participants who started ART after 1 January 2010 for all the outcomes mentioned above, analyses excluding those experienced treatment interruption and analyses limited to individuals started with only INSTI-based ART were conducted.

Ethics statement

Written informed consent was obtained from participating individuals. Ethics approval for the AHOD study was granted by St Vincent's Human Research Ethics Committee, Sydney (IRB 00002019), and all other relevant institutional review boards.

RESULTS

A total of 2544 people living with HIV who were on ART and in follow-up from 1 January 2010 in AHOD were included in the analysis. Of them, 88.7% were male and 28.7% were born outside Australia/New Zealand. The median CD4 count at ART initiation was 320 (IQR: 200–489) cells/mm^3, and the median age at ART initiation was 39 (IQR: 32–47) years. Hepatitis B and C co-infection was reported in 80 (3.1%) and 215 (8.5%) of AHOD participants, respectively. The median duration of known HIV infection and ART was 14.7 (8.5–21.6) and 11.3 years (6.6–17.5), respectively. Table 1 shows the detailed demographic characteristics of participants included.

Virological failure

During 18,125 person-years of follow-up (PYFU) (median, 7.6 [3.7–10.9] years), 444 participants experienced VF (incidence rate: 2.45 [95% CI: 2.23–2.69] per 100 PYFU). As shown in Table 1, those who had VF were younger and had lower CD4 count at ART initiation (23.7% with VF and 18.7% without VF had CD4 count ≤200 cells/mm^3). The proportion of people with viral suppression, blip, LLV and VF during the years 2010–2021 is shown in Figure 1. Overall, the proportion of people with VF was lower in recent years, with a decrease from 9% in 2010 to 3% in 2021.

Using Kaplan–Meier methods, the estimated probability of VF up to 12 years of ART initiation was 21% (95% CI: 19.2–22.9). Figure 2 shows the probability of virological failure by viraemia group which was higher in participants with LLV and blip than in those with viral suppression, log-rank p < 0.001), respectively.

In multivariable analysis, hepatitis B co-infection (adjusted hazard ratio [aHR]: 1.75; 95% CI: 1.11–2.78), longer treatment interruption duration: 14 days to 3 months (2.42; 95% CI: 1.58–3.6), 3 months to 6 months (6.90; 95% CI: 4.47–10.64) and >6 months (6.23; 95% CI: 4.82–8.05) versus no treatment interruption, higher number of VL measurements (per 5-times increase, 1.09; 95% CI: 1.03–1.16), NRTI+PI as initial ART regimen (1.34; 95% CI: 1.08–1.67; vs. NRTI + NNRTI), viral blip (2.78; 95% CI: 2.23–3.46) and LLV (1.69; 95% CI: 1.32–2.17) were associated with increased VF risk. Older participants, those with higher CD4 count at ART initiation and those who had a longer duration of ART had reduced risk of VF (multivariable model I, Table 2). The association between hepatitis B co-infection and VF remained significant in a multivariable model additionally adjusted for time-varying exposure to ARVs with anti-HBV activity (i.e., TDF- or TAF-containing regimen).

In addition, when viraemia group was included as a time-varying variable in the model which allowed the viraemia reclassification only to a higher group, viral blip and LLV had significantly higher risk of VF compared with those with viral suppression (multivariable model II, Table 2). The association of blips and LLV with increased VF risk was consistent in a multivariable Cox regression adjusting for time-varying ART regimens (aHR for blips: 2.94, 95% CI: 2.30–3.76; aHR for LLV: 4.50, 95% CI: 3.32–6.11 vs. viral suppression).

TABLE 1 Participant characteristics.

	Total ($N = 2544$, 100%)		No VF ($N = 2100$, 82.5%)		VF ($N = 444$, 17.5%)	
Number (%) or median (IQR)	**Frequency or median**	**Percentage or IQR**	**Frequency or median**	**Percentage or IQR**	**Frequency or median**	**Percentage or IQR**
Age at ART initiation	39	32, 47	40	33, 48	37	30, 44
≤30	449	17.7	338	16.1	111	25.0
31–40	907	35.7	739	35.2	168	37.8
41–50	717	28.2	598	28.5	119	26.8
>50	471	18.5	425	20.2	46	10.4
Sex						
Male	2257	88.7	1857	88.4	400	90.1
Female	287	11.3	243	11.6	44	9.9
Country of birth						
Australia and New Zealand	1532	60.2	1245	59.3	287	64.6
Overseas	729	28.7	619	29.5	110	24.8
Unknown	283	11.1	236	11.2	47	10.6
HIV mode of acquisition						
MSM	1808	71.1	1500	71.4	308	69.4
Injecting drug use	134	5.3	96	4.6	38	8.6
Heterosexual	516	20.3	435	20.7	81	18.2
Other/Unknown	86	3.4	69	3.3	17	3.8
CD4 at ART initiation, cells/mm^3	320	200, 489	320	203, 490	290	168, 451
≤200	497	19.5	392	18.7	105	23.7
201–350	564	22.2	480	22.9	84	18.9
351–500	402	15.8	349	16.6	53	11.9
500+	433	17.0	366	17.4	67	15.1
Missing	648	25.5	513	24.4	135	30.4
HIV RNA at ART initiation, copies/mL						
≤100,000	1183	46.5	994	47.3	189	42.6
>100,000	564	22.2	449	21.4	115	25.9
Missing	797	31.3	657	31.3	140	31.5
Treatment interruption duration						
No interruption	1568	61.6	1420	67.6	148	33.3
1–14 days	267	10.5	238	11.3	29	6.5
14 days–3 months	128	5.0	101	4.8	27	6.1
3 months–6 months	62	2.4	33	1.6	29	6.5
>6 months	519	20.4	308	14.7	211	47.5
HBV surface antigen positivity						
Negative	2055	80.8	1676	79.8	379	85.4
Positive	80	3.1	60	2.9	20	4.5
Unknown	409	16.1	364	17.3	45	10.1
HCV antibody positivity						
Negative	2087	82.0	1732	82.5	355	80.0
Positive	215	8.5	165	7.9	50	11.3
Unknown	242	9.5	203	9.7	39	8.8
Number of VL measurement, median (IQR)	14	(8–23)	13	(7–22)	18	(10–26)
ART type commenced						
NRTI+NNRTI	1251	49.2	1058	50.4	193	43.5
NRTI+PI	691	27.2	522	24.9	169	38.1
NRTI+INSTI	436	17.1	396	18.9	40	9.0

(Continues)

TABLE 1 (Continued)

Number (%) or median (IQR)	Total ($N = 2544$, 100%)		No VF ($N = 2100$, 82.5%)		VF ($N = 444$, 17.5%)	
	Frequency or median	Percentage or IQR	Frequency or median	Percentage or IQR	Frequency or median	Percentage or IQR
Other	166	6.5	124	5.9	42	9.5
Year of ART initiation						
≤2005	955	37.5	733	34.9	222	50.0
2006–2010	696	27.4	567	27.0	129	29.1
2011–2015	701	27.6	619	29.5	82	18.5
2016–2022	192	7.6	181	8.6	11	2.5
Participant care setting						
Sexual health services	1229	48.3	1003	47.8	226	50.9
Genera practice	863	33.9	729	34.7	134	30.2
Hospital/Tertiary referral settings	452	17.8	368	17.5	84	18.9
Duration of HIV (years), median (IQR)	14.7	8.5–21.6	13.9	8.1–20.8	17.2	11.8–23.6
Duration of ART (years), median (IQR)	11.3	6.6–17.5	10.6	6.3–17.1	13.4	8.9–19.5

Abbreviations: ART, antiretroviral therapy; MSM, male to male sex; VL, viral load, IQR, interquartile range; NRTI, nucleoside/nucleotide reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor.

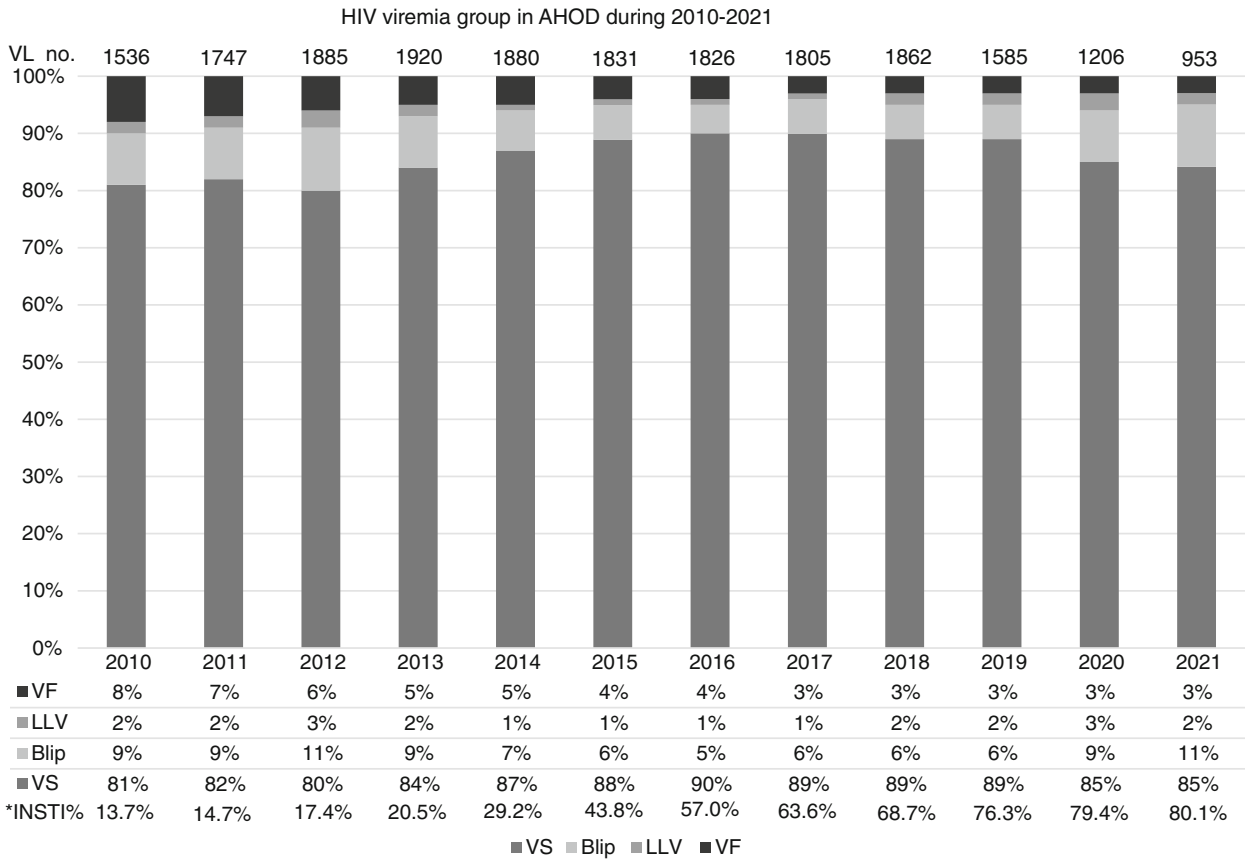

FIGURE 1 HIV viraemia group (viral suppression, blip, low-level viraemia and virological failure) in AHOD. The proportion of VS, blip, LLV and VF are presented for each year between 2010 and 2021 in AHOD. The definitions of the viraemia group are included in Methods. *The proportion of integrase strand transfer inhibitors (INSTI) use over time is presented for each year. LLV, low-level viraemia; VF, virological failure, VS, viral suppression.

Sensitivity analyses

The sensitivity analysis using a VF cut-off of 500 copies/mL, instead of 1000 copies/mL, is shown in Table S1. Overall, 475 VF events were included (VF rate of 2.64 [95% CI: 2.42–2.89 per 100 PYFU], and results were consistent, including factors associated with VF. A total of 1078 participants were included in the second sensitivity analysis that

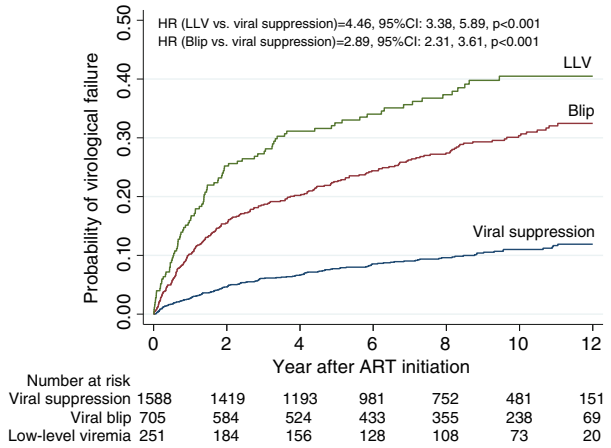

FIGURE 2 Probability of virological failure by viraemia group.

was limited to participants who started ART in 2010. There were 128 VF events, resulting in an incidence rate of 1.98 (95% CI: 1.67–2.36) per 100 PYFU. The proportion of people with VF over the study period (2010–2021) was lower (ranging from 3% to 5%) than the proportion in the primary analysis (Table S2). The factors associated with VF in this sensitivity analysis are presented in Table S3. Viral blip and LLV were associated with VF in the multivariable Cox regression models.

In the sensitivity analysis where VL cut-off defining a blip was 51–200 copies/mL, the number of blips was reduced from 290 in the main analysis to 246 in the sensitivity analysis. Multivariable analysis shows that a viral blip remained a significant predictor for VF, although the magnitude of association was moderately reduced (aHR: 2.19; 95% CI: 1.76–2.73).

There were 68 VF events, which occurred during treatment interruption periods in the primary analysis. We conducted a sensitivity analysis excluding those who experienced treatment interruption, and blips and LLV remained associated with increased risks of VF (Table S4). Finally, when we limited the analysis only to participants who started with an INSTI regimen, blips and LLV still remained associated with higher subsequent VF risk (aHR for blip: 6.02; 95% CI: 2.29–15.87, and for LLV: 11.05, 95% CI: 3.06–43.21) (Table S5).

Viral blips

The proportion of people with a viral blip was stable at 6%–11% during the years 2010–2021 (Figure 1). Using multivariable repeated measured logistic regression, factors associated with viral blips were age ≥ 50 years at ART initiation (adjusted odds ratio [aOR]: 0.75, 95% CI: 0.6–0.93; vs. ≤30 years), heterosexual (1.24, 95% CI: 1.02–1.51; vs. MSM), higher CD4 cell count ART initiation (201–350 cells/mm^3: 0.68, 95% CI: 0.56–0.82, 351–500 cells/mm^3: 0.57, 95% CI: 0.46–0.70, and >500 cells/mm^3: 0.52, 95% CI: 0.41–0.65; vs. ≤200 cells/mm^3), longer duration of treatment interruption (3–6 months: 1.53, 95% CI: 1.07–2.18 and >6 months: 1.62, 95% CI: 1.35–1.93), higher frequency of VL measurement (per 5-unit increase: 1.1, 95% CI: 1.06–1.15), longer duration of ART (per 5-year increase: 0.78, 95% CI: 0.69–0.88) and participants from hospitals 0.82, 95% CI: 0.68–0.98; vs. sexual health services (Table 3).

In the sensitivity analysis, which we limited to participants who started ART in 2010, the proportion of viral blip over the study period was comparable to the primary analysis (Table S2). We also found that higher HIV-1 RNA at ART initiation (≥100,000 copies/mL, aOR: 1.3, 95% CI: 1.03–1.63; vs. <100,000 copies/mL) was found to be associated with increased risk of viral blip in addition to the predictors in the primary analysis (i.e., lower CD4 cell count, treatment interruption duration >6 months, number of VL measurements and duration of ART). Among participants who started ART after 2010 in the sensitivity analysis (Table S4), GP clinic attendees were more likely to have viral blips compared with sexual health service attendees.

Similar factors were identified when the cut-off of 51–200 copies/mL was used to define blips in the sensitivity analysis. Higher HIV-1 RNA (≥100,000 copies/mL) at ART initiation remained associated with blips.

Low-level viraemia

The proportion of people with LLV was lower than those with viral blips and stable at 1%–4% during the years 2010–2021 (Figure 1). In multivariable analysis, factors associated with LLV were lower CD4 cell count, longer duration of treatment interruption, longer duration on ART, higher number of VL measurements and those who were clients of hospitals compared to sexual health services (Table 4). When we limited the analysis to participants starting ART after 1 January 2010, treatment interruption duration and patient care setting were no longer associated with LLV compared with the results from the primary analysis. However, a high level of HIV-1 RNA at ART initiation was associated with LLV among those who started ART after 2010 (Table S4).

DISCUSSION

Among AHOD participants who were on treatment and in follow-up from 1 January 2010, VF was frequent, yet steadily declined over the years 2010–2021. In this study, we found that participants with viral blips, as well as those with LLV, had increased risks of subsequent VF. Our study has also identified important factors associated with VF development, blips and LLV. Younger age at ART initiation, longer duration of treatment interruption, hepatitis B co-infection, lower CD4 count and those who started ART in the earlier

TABLE 2 Factors associated with virological failure in AHOD using Cox regression.

	Person-years of follow-up (PYFU)	Virological failure (*n*)	IR per 100 PYFU (95% CI)	Univariable		Multivariable model I		Multivariable model II	
				Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
Overall ($N = 2544$)	18125.26	444	2.45 (2.23, 2.69)						
Age at ART initiation					<0.001		**<0.001**		**<0.001**
≤30	2655.35	111	4.18 (3.47, 5.03)	Ref		Ref		Ref	
31–40	6441.68	168	2.61 (2.24, 3.03)	0.67 (0.53, 0.86)		0.67 (0.53, 0.86)		0.67 (0.52, 0.85)	
41–50	5366.04	119	2.22 (1.85, 2.65)	0.58 (0.45, 0.75)		0.59 (0.45, 0.77)		0.58 (0.44, 0.76)	
>50	3662.19	46	1.26 (0.94, 1.68)	0.33 (0.24, 0.47)		0.33 (0.23, 0.47)		0.33 (0.23, 0.47)	
Sex									
Male	16144.74	400	2.48 (2.25, 2.73)	Ref		Ref		Ref	
Female	1980.51	44	2.22 (1.65, 2.99)	0.88 (0.64, 1.20)	0.408	0.73 (0.49, 1.1)	0.13	0.72 (0.48, 1.08)	0.11
Country of birth					0.298		0.46		0.46
Australia and New Zealand	11304.32	287	2.54 (2.26, 2.85)	Ref		Ref		Ref	
Overseas	4847.12	110	2.27 (1.88, 2.85)	0.84 (0.68, 1.05)		0.89 (0.69, 1.13)		0.9 (0.71, 1.15)	
Unknown	1973.82	47	2.38 (1.79, 3.17)	0.92 (0.67, 1.25)		0.83 (0.59, 1.18)		0.83 (0.59, 1.17)	
HIV mode of acquisition					0.008		0.88		0.88
MSM	13090.20	308	2.35 (2.10, 2.63)	Ref		Ref		Ref	
Injecting drug use	842.44	38	4.51 (3.28, 6.2)	1.84 (1.31, 2.57)		1.18 (0.81, 1.71)		1.13 (0.78, 1.64)	
Heterosexual	3567.87	81	2.27 (1.83, 2.82)	0.94 (0.73, 1.20)		1.08 (0.78, 1.48)		1.09 (0.79, 1.5)	
Other/Unknown	624.74	17	2.72 (1.69, 4.38)	1.16 (0.71, 1.89)		0.97 (0.59, 1.62)		0.97 (0.59, 1.62)	
CD4 at ART initiation, cells/mm^3					0.001		**0.005**		**0.005**
≤200	3617.00	105	2.90 (2.40, 3.51)	Ref		Ref		Ref	
201–350	4277.51	84	1.96 (1.59, 2.43)	0.68 (0.51, 0.91)		0.74 (0.55, 0.99)		0.74 (0.55, 0.99)	
351–500	2997.37	53	1.77 (1.35, 2.31)	0.61 (0.44, 0.84)		0.63 (0.44, 0.88)		0.63 (0.44, 0.88)	
500+	2796.21	67	2.40 (1.89, 3.04)	0.78 (0.57, 1.06)		0.83 (0.6, 1.15)		0.84 (0.6, 1.17)	
Missing	4437.17	135	3.04 (2.57, 3.6)	1.02 (0.79, 1.31)		1.16 (0.84, 1.62)		1.18 (0.85, 1.63)	
HIV RNA at ART initiation, copies/mL					0.596		0.24		0.24
≤100,000	8446.14	189	2.24 (1.94, 2.58)	Ref		Ref		Ref	
>100,000	4010.69	115	2.87 (2.39, 3.44)	1.29 (1.02, 1.62)		1.08 (0.85, 1.38)		1.1 (0.87, 1.4)	
Missing	5668.43	140	2.47 (2.09, 2.91)	1.11 (0.89, 1.38)		0.85 (0.63, 1.15)		0.84 (0.62, 1.12)	
Documented treatment interruption duration[a]					<0.001		**<0.001**		**<0.001**
No interruption	11065.04	148	1.34 (1.14, 1.57)	Ref		Ref		Ref	
1–<14 days	2327.51	29	1.25 (0.87, 1.79)	1.03 (0.69, 1.53)		1.10 (0.73, 1.66)		0.74 (1.67, 1.66)	

TABLE 2 (Continued)

	Person-years of follow-up (PYFU)	Virological failure (*n*)	IR per 100 PYFU (95% CI)	Univariable		Multivariable model I		Multivariable model II	
				Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
14 days–3 months	926.15	27	2.92 (2.00, 4.25)	2.29 (1.52, 3.45)		2.42 (1.58, 3.69)		1.61 (3.76, 3.69)	
3 months–6 months	398.22	29	7.28 (5.06, 10.48)	5.64 (3.79, 8.39)		6.9 (4.47, 10.64)		4.19 (9.98, 10.64)	
>6 months	3408.34	211	6.19 (5.41, 7.08)	4.88 (3.95, 6.03)		6.23 (4.82, 8.05)		4.81 (8.05, 8.05)	
HBV surface antigen positivity					0.013		**0.001**		**0.001**
Negative	14841.18	379	2.55 (2.31, 2.82)	Ref		Ref		Ref	
Positive	517.79	20	3.86 (2.49, 5.99)	1.45 (1.02, 2.27)		1.75 (1.11, 2.78)		1.80 (1.13, 2.85)	
Unknown	2766.28	45	1.63 (1.21, 2.18)	0.61 (0.45, 0.83)		0.60 (0.4, 0.88)		0.62 (0.42, 0.91)	
HCV antibody positivity					0.03		0.06		0.054
Negative	15035.41	355	2.36 (2.13, 2.62)	Ref		Ref		Ref	
Positive	1497.29	50	3.34 (2.53, 4.41)	1.41 (1.05, 1.89)		0.99 (0.72, 1.37)		1.02 (0.74, 1.41)	
Unknown	1592.56	39	2.45 (1.79, 3.35)	0.98 (0.71, 1.37)		1.73 (1.14, 2.62)		1.66 (1.1, 2.51)	
Number of VL measurement (per 5-unit increase)				1.11 (1.06, 1.16)	<0.001	1.09 (1.03, 1.16)	**0.004**	1.1 (1.03, 1.17)	**0.004**
ART type commenced					<0.001		**0.03**		**0.03**
NRTI+NNRTI	9658.96	193	2 (1.74, 2.3)	Ref		Ref		Ref	
NRTI+PI	5028.11	169	3.36 (2.89, 3.91)	1.67 (1.36, 2.06)		1.34 (1.08, 1.67)		1.35 (1.08, 1.68)	
NRTI+INSTI	2267.34	40	1.76 (1.29, 2.41)	0.71 (0.50, 1.00)		1.21 (0.8, 1.84)		1.21 (0.80, 1.83)	
Other	1170.85	42	3.59 (2.65, 4.85)	1.75 (1.25, 2.44)		1.38 (0.97, 1.97)		1.42 (1, 2.02)	
Year of ART initiation					<0.001		**<0.001**		**<0.001**
≤2005	7509.33	222	2.96 (2.59, 3.37)	Ref		Ref		Ref	
2006–2010	5663.17	129	2.28 (1.92, 2.71)	0.76 (0.61, 0.95)		0.54 (0.37, 0.77)		0.56 (0.38, 0.8)	
2011–2015	4229.26	82	1.94 (1.56, 2.41)	0.54 (0.42, 0.70)		0.31 (0.19, 0.49)		0.32 (0.2, 0.51)	
2016–2022	723.5	11	1.52 (0.84, 2.75)	0.33 (0.18, 0.60)		0.19 (0.08, 0.44)		0.20 (0.09, 0.46)	
Duration of ART (per 5-year increase)				0.53 (0.43, 0.60)	<0.001	0.50 (0.42, 0.59)	**<0.001**	0.50 (0.43, 0.59)	**<0.001**
Participant care setting					0.08		**0.014**		**0.013**
Sexual health services	8395.00	226	2.69 (2.36, 3.07)	Ref		Ref		Ref	
GP	6526.71	134	2.05 (1.73, 2.43)	0.79 (0.64, 0.98)		0.71 (0.56, 0.89)		0.71 (0.56, 0.90)	
Hospital	3203.55	84	2.62 (2.12, 3.25)	0.99 (0.77, 1.27)		0.98 (0.74, 1.29)		0.98 (0.74, 1.29)	
Viral blip[a]									
No	11590.68	154	1.33 (1.13, 1.56)	Ref		Ref			
Yes	6534.58	290	4.45 (3.97, 4.99)	3.39 (2.79, 4.12)	<0.001	2.78 (2.23, 3.46)	**<0.001**		

(Continues)

TABLE 2 (Continued)

	Person-years of follow-up (PYFU)	Virological failure (*n*)	IR per 100 PYFU (95% CI)	Univariable		Multivariable model I		Multivariable model II	
				Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
Low level viraemia[a]									
No	16543.37	350	2.12 (1.91, 2.35)	Ref		Ref			
Yes	1581.89	94	6.02 (4.92, 7.37)	2.78 (2.21, 3.49)	<0.001	1.69 (1.32, 2.17)	**<0.001**		
Viraemia group[b]									
Viral suppression	11511.2	147	1.28 (1.09, 1.5)	Ref				Ref	
Blip	5052.08	203	4.02 (3.5, 4.61)	3.20 (2.59, 3.95)	<0.001			2.89 (2.31, 3.61)	**<0.001**
LLV	1561.98	94	6.02 (4.92, 7.37)	4.61 (3.56, 5.98)				4.46 (3.38, 5.89)	

Note: All analyses were adjusted by site to account for the heterogeneity of healthcare systems. Global *p*-values are tested for heterogeneity excluding missing values. Bold values represent significant *p*-values from multivariable models.

Abbreviations: ART, antiretroviral therapy; HR, hazard ratio; INSTI, integrase strand transfer inhibitor; IR, incidence rate; MSM, male to male sex; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitors; PI, protease inhibitor; PYS, person-years follow up; VL, viral load.

[a]Time-updated variables.

[b]Viraemia group was included as a time-updated covariate and reclassification was allowed only for a higher VL group.

years of the study were associated with increased risk of VF. Although the rates of VF in our cohort were lower than those from other settings, such as in low to middle-income settings [18–20], it is still essential to continue to monitor those with low-level viraemia or those who are at risk of VF to navigate the path to the UNAIDS's 95-95-95 targets and for the benefits of 'Undetectable = Untransmittable'.

Our study results are robust to different VL cut-offs for the definitions of VF, blips or LLV. Previous studies, which used different definitions of VF such as VL ≥500 or ≥1000 copies/mL, did not find an association of LLV with increased risk of VF [12, 13]. In line with a recent study from a large European cohort of people living with HIV [10], our study, which also defined VF as two consecutive VLs of ≥200 copies/mL or a single VL of ≥1000 copies/mL while on ART, found that both viral blips and LLV predicted VF development. In the sensitivity analysis, in which we defined VF using two consecutive VLs of ≥200 copies/mL or a single VL of ≥500 copies/mL, blips and LLV remained associated with increased risks of VF. Moreover, similar to several recent studies [9, 10, 21] in which a VL cut-off of <200 copies/mL was used to define blips, as in our sensitivity analysis, we found that individuals with blips had significantly elevated risks of subsequent VF. We also confirmed the findings from recent studies, which were conducted among individuals starting with INSTI regimens [9, 21], that there are associations between viral blips and LLV and subsequent VF, despite the very high potency of new generation INSTI regimens. This suggests that viral blips and LLV are important risk factors to monitor regardless of the ART regimen used.

Interestingly, compared with participants with viral suppression, those with LLV had a higher risk of VF than those with viral blips. This suggests that blips, which are more transient in nature than LLV, may have less impact on VF. LLV is more likely to reflect the residual HIV viraemia that could be the result of several mechanisms such as ongoing viral replication, suboptimal drug adherence, treatment resistance and other underlying causes. In the analysis which was limited to individuals who started ART after 2010, lower CD4 counts and VL >100,000 copies/mL at ART initiation were associated with higher risks of LLV development. This finding suggests that those who initiated ART with more advanced HIV disease and/or possibly with a large viral reservoir were at higher risk of LLV and subsequently, higher VF risk. The association of younger age with elevated risks for VF development has also been reported in other studies [19, 22]. The finding suggests that younger individuals may face greater challenges for ART adherence compared with older participants. Several social and environmental factors, such as stigma and fear of disclosure, may contribute to poorer ART adherence among younger individuals [23]. In addition, PI-based ART, but not INSTI-based ART, has been shown to be associated with an increased risk of VF in a recent large multi-cohort study [10], also shown in our study.

TABLE 3 Factors associated with viral blip in AHOD using repeated measured logistic regression.

	Univariable model		Multivariable model	
	OR (95% CI)	***p*-value**	**Adjusted OR (95% CI)**	***p*-value**
Age at ART initiation		0.12		**0.049**
≤30	Ref		Ref	
31–40	0.85 (0.71, 1.03)		0.88 (0.73, 1.06)	
41–50	0.89 (0.74, 1.08)		0.93 (0.77, 1.13)	
>50	0.77 (0.62, 0.96)		0.75 (0.6, 0.93)	
Sex				
Male	Ref		Ref	
Female	1.02 (0.83, 1.26)	0.85	0.82 (0.64, 1.06)	0.14
Country of birth		0.07		0.08
Australia and New Zealand	Ref		Ref	
Overseas	1 (0.86, 1.15)		0.91 (0.78, 1.06)	
Unknown	0.78 (0.63, 0.97)		0.7 (0.56, 0.88)	
HIV mode of acquisition		0.018		0.07
MSM	Ref		Ref	
Injecting drug use	1.41 (1.07, 1.86)		1.31 (0.98, 1.75)	
Heterosexual	1.2 (1.03, 1.41)		1.24 (1.02, 1.51)	
Other/Unknown	1.12 (0.8, 1.56)		1.1 (0.78, 1.54)	
CD4 at ART initiation, cells/mm^3		<0.001		**<0.001**
≤200	Ref		Ref	
201–350	0.68 (0.56, 0.82)		0.68 (0.56, 0.82)	
351–500	0.59 (0.48, 0.74)		0.57 (0.46, 0.7)	
500+	0.59 (0.47, 0.73)		0.52 (0.41, 0.65)	
Missing	0.78 (0.65, 0.93)		0.82 (0.66, 1.03)	
HIV RNA at ART initiation, copies/mL		0.03		0.37
≤100,000	Ref		Ref	
>100,000	1.24 (1.05, 1.45)		1.09 (0.93, 1.28)	
Missing	1.03 (0.89, 1.2)		0.94 (0.78, 1.14)	
Documented treatment interruption duration[a]		<0.001		**<0.001**
No interruption	Ref		Ref	
1–<14 days	0.93 (0.75, 1.15)		0.98 (0.79, 1.22)	
14 days–3 months	1.06 (0.8, 1.42)		1.13 (0.85, 1.51)	
3 months–6 months	1.45 (1.02, 2.07)		1.53 (1.07, 2.18)	
>6 months	1.36 (1.17, 1.59)		1.62 (1.35, 1.93)	
HBV surface antigen positivity		0.77		0.94
Negative	Ref		Ref	
Positive	1.08 (0.76, 1.54)		1.01 (0.71, 1.44)	
Unknown	0.95 (0.79, 1.14)		0.96 (0.77, 1.2)	
HCV antibody positivity		0.38		0.98
Negative	Ref		Ref	
Positive	1.11 (0.88, 1.38)		1.02 (0.8, 1.3)	
Unknown	1.03 (0.81, 1.3)		1.02 (0.78, 1.35)	
Number of VL measurement (per 5-unit increase)	1.03 (1, 1.07)	0.05	1.1 (1.06, 1.15)	**<0.001**
ART type commenced		0.30		0.57
NRTI+NNRTI	Ref		Ref	
NRTI+PI	1.09 (0.94, 1.26)		1.06 (0.91, 1.23)	
NRTI+INSTI	1.12 (0.92, 1.38)		1.02 (0.79, 1.32)	

(Continues)

TABLE 3 (Continued)

	Univariable model		Multivariable model	
	OR (95% CI)	***p*-value**	**Adjusted OR (95% CI)**	***p*-value**
Other	0.88 (0.68, 1.15)		0.87 (0.67, 1.14)	
Year of ART initiation		0.011		**<0.001**
<2005	Ref		Ref	
2006–2010	0.87 (0.75, 1.02)		0.68 (0.52, 0.88)	
2011–2015	1.03 (0.87, 1.21)		0.84 (0.6, 1.16)	
2016–2022	1.45 (1.07, 1.98)		1.2 (0.73, 1.96)	
Duration of ART (per 5-year increase)	0.97 (0.93, 1.02)	0.28	0.78 (0.69, 0.88)	**<0.001**
Participant care setting		0.36		**0.015**
Sexual health services	Ref		Ref	
GP	1.02 (0.88, 1.18)		1.09 (0.94, 1.27)	
Hospital	0.89 (0.75, 1.07)		0.82 (0.68, 0.98)	

Note: Global *p*-values are tested for heterogeneity excluding missing values. Bold values represent significant *p*-values from multivariable models.
Abbreviations: ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor; MSM, male to male sex; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitors; OR, odds ratio; PI, protease inhibitor; VL, viral load.
[a]Time-updated variables.

The proportion of people with viral blips and LLV remained stable over the study period even in the era of INSTI use despite decreasing proportion of VF. Our study has also identified other important factors associated with blips and LLVs. For example, when the analysis was limited to those who started ART after 2010, high HIV-1 RNA (≥100,000 copies/mL) at ART initiation was associated with later blips and LLV. Consistent with the recent RESPOND analysis [21], higher HIV-1 RNA levels at ART initiation were not associated with VF but lower CD4 cell count was. As reported previously [10, 24], the extent of reservoirs established and CD4+ T-cell depletion before initiation of ART, especially among those with advanced HIV infection, could impact the subsequent treatment outcomes after ART initiation.

Other important factors for VF, blips and LLV identified in the study include hepatitis B co-infection and number of VL measurements. The association of hepatitis B co-infection and VF remains significant in a multivariable model additionally adjusted for time-varying exposure to ARVs with anti-HBV activity (i.e., TDF- or TAF-containing regimen) (data not shown). There is also an ongoing debate on whether the frequency of VL monitoring for people with HIV on long-term ART could be reduced and optimised in HIV care settings [25]. For example, point-of-care VL monitoring may provide additional benefits for VL testing cascade, especially in resource-limited settings [26–28]. Our findings support the recommendation that the frequency of viral load testing could be tailored to individual risk of VF. Individuals with longer duration of treatment interruption could benefit from more frequent VL testing that could identify blips or LLV episodes and offer interventions such as adherence counselling and support. While our study and other recent reports [10, 15] have identified an association between blips or LLV and subsequent VF, it is important to recognise that there is no definitive evidence linking individuals with LLV to HIV sexual transmission [29].

Several limitations of this study need to be acknowledged. First, as an observational study, we cannot account for the unknown biases due to uncontrolled confounders. Second, we did not have genotypic resistance data in our cohort to evaluate the impacts of LLVs and blips on the development of resistant mutations. The emergence of drug-resistant mutations following LLV has previously been reported, although mostly occurs when LLV is categorised above 200 copies/mL [10, 30–32]. Third, the low number of VF events among those who started with INSTI provided wider confidence intervals than for the primary analysis, and thus we lacked power to investigate any effects of different INSTI agents. In addition, we did not undertake a trend analysis to evaluate the statistical significance of the observed viraemia trends. It is also important to note that our results may not be readily generalizable to all settings, particularly in resource-limited settings with limited access to HIV VL testing. Finally, we could not rule out the impact of different VL assays on our results. The potential influence of assay variability on the interpretation of our findings, especially within the LLV range, even when the limit of quantification is set at or above 50 copies/mL should also be considered. Nonetheless, our study has a number of strengths including a long duration of follow-up to investigate VF and consistent findings with various sensitivity analyses using different cut-offs of VF, viral blips and LLV.

In conclusion, we found that viral blips and LLV were strongly associated with increased risk of subsequent VF and that the important predictors such as high HIV-1 RNA and low CD4 counts at ART initiation were associated with elevated risks of blips and LLV. Further studies are needed to explore whether newer ART regimens including new INSTI drugs, dual therapies and long-acting ART could lead to fewer blips and LLV and whether blips and LLV from

TABLE 4 Factors associated with low-level viraemia in AHOD using repeated measured logistic regression.

	Univariable model		Multivariable model	
	OR	***p*-value**	**Adjusted OR**	***p*-value**
Age at ART initiation		0.06		0.21
≤30	Ref		Ref	
31–40	0.65 (0.38, 1.12)		0.66 (0.38, 1.15)	
41–50	1.16 (0.68, 1.99)		1.07 (0.61, 1.87)	
>50	1.15 (0.64, 2.07)		0.98 (0.53, 1.8)	
Sex				
Male	Ref		Ref	
Female	0.9 (0.5, 1.61)	0.72	0.79 (0.38, 1.63)	0.52
Country of birth		0.87		0.22
Australia	Ref		Ref	
Overseas	0.89 (0.59, 1.35)		0.75 (0.48, 1.18)	
Unknown	0.95 (0.54, 1.69)		0.62 (0.33, 1.16)	
HIV mode of acquisition		0.49		0.39
MSM	Ref		Ref	
Injecting drug use	0.98 (0.43, 2.22)		0.9 (0.36, 2.24)	
Heterosexual	1.29 (0.83, 2)		1.32 (0.76, 2.3)	
Other/Unknown	0.6 (0.21, 1.74)		0.5 (0.16, 1.54)	
CD4 at ART initiation, cells/mm^3		0.008		**0.006**
≤200	Ref		Ref	
201–350	0.54 (0.32, 0.92)		0.54 (0.31, 0.93)	
351–500	0.39 (0.21, 0.72)		0.37 (0.19, 0.71)	
500+	0.48 (0.26, 0.87)		0.41 (0.22, 0.79)	
Missing	0.85 (0.51, 1.39)		0.9 (0.48, 1.68)	
HIV RNA at ART initiation, copies/mL		0.07		0.44
≤100,000	Ref		Ref	
>100,000	1.65 (1.05, 2.59)		1.35 (0.85, 2.14)	
Missing	1.41 (0.93, 2.15)		1.14 (0.66, 1.97)	
Document treatment interruption duration[a]		0.76		0.28
No interruption	Ref		Ref	
1–<14 days	1.02 (0.56, 1.84)		1.1 (0.58, 2.06)	
14 days–3 months	1.51 (0.71, 3.25)		1.59 (0.72, 3.5)	
3 months–6 months	1.09 (0.37, 3.28)		1.23 (0.4, 3.74)	
>6 months	1.26 (0.81, 1.96)		1.76 (1.04, 2.98)	
HBV surface antigen positivity		0.62		0.64
Negative	Ref		Ref	
Positive	1.54 (0.6, 3.95)		1.54 (0.6, 3.96)	
Unknown	0.93 (0.55, 1.55)		0.93 (0.49, 1.74)	
HCV antibody positivity		0.96		0.77
Negative	Ref		Ref	
Positive	1.09 (0.58, 2.06)		1.29 (0.65, 2.58)	
Unknown	1 (0.53, 1.9)		1.04 (0.48, 2.28)	
Number of VL measurement (per 5-unit increase)	**1.18 (1.08, 1.29)**	<0.001	1.38 (1.23, 1.56)	**<0.001**
ART type commenced		0.87		0.64
NRTI+NNRTI	Ref		Ref	
NRTI+PI	0.99 (0.65, 1.51)		1.03 (0.66, 1.61)	
NRTI+INSTI	1.2 (0.7, 2.05)		1.33 (0.67, 2.64)	

(Continues)

TABLE 4 (Continued)

	Univariable model		Multivariable model	
	OR	***p*-value**	**Adjusted OR**	***p*-value**
Other	0.87 (0.41, 1.8)		0.7 (0.32, 1.51)	
Year of ART initiation		0.84		0.06
<2005	Ref		Ref	
2006–2010	1.08 (0.7, 1.67)		0.37 (0.18, 0.78)	
2011–2015	1.12 (0.71, 1.77)		0.46 (0.18, 1.15)	
2016–2022	1.44 (0.63, 3.28)		0.49 (0.13, 1.9)	
Duration of ART (per 5-year increase)	**0.93 (0.81, 1.06)**	0.27	0.51 (0.37, 0.72)	**<0.001**
Participant care setting		0.08		**0.013**
Sexual health services	Ref		Ref	
GP	1.32 (0.89, 1.96)		1.32 (0.86, 2.03)	
Hospital	0.73 (0.43, 1.23)		0.55 (0.31, 0.97)	

Note: Global *p*-values are tested for heterogeneity excluding missing values. Bold values represent significant *p*-values from multivariable models.
Abbreviations: ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitors; OR, odds ratio; PI, protease inhibitor; VL, viral load.
[a]Time-updated variables.

these regimens have impact on subsequent virological outcomes.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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