Clinical Infectious Diseases

MAJOR ARTICLE

Plasma Human Immunodeficiency Virus 1 RNA and CD4$^+$ T-Cell Counts Are Determinants of Virological Nonsuppression Outcomes With Initial Integrase Inhibitor-Based Regimens: A Prospective RESPOND Cohort Study

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Background. There are conflicting data regarding baseline determinants of virological nonsuppression outcomes in persons with human immunodeficiency virus (HIV) starting antiretroviral treatment (ART). We evaluated the impact of different baseline variables in the RESPOND cohort.

Methods. We included treatment-naive participants aged ≥18 who initiated 3-drug ART, in 2014–2020. We assessed the odds of virological suppression (VS) at weeks 48 and 96 using logistic regression. Viral blips, low-level viremia (LLV), residual viremia (RV), and virological failure (VF) rates were assessed using Cox regression.

Results. Of 4310 eligible participants, 72% started integrase strand transfer inhibitor (INSTI)-based regimens. At 48 and 96 weeks, 91.0% and 93.3% achieved VS, respectively. At 48 weeks, Kaplan-Meier estimates of rates were 9.6% for viral blips, 2.1% for LLV, 22.2% for RV, and 2.1% for VF. Baseline HIV-1 RNA levels >100 000 copies/mL and CD4$^+$ T-cell counts ≤200/μL were negatively associated with VS at weeks 48 (adjusted odds ratio, 0.51 [95% confidence interval, .39–.68] and .40 [.27–.58], respectively) and 96 and with significantly higher rates of blips, LLV, and RV. CD4$^+$ T-cell counts ≤200/μL were associated with higher risk of VF (adjusted hazard ratio, 3.12 [95% confidence interval, 2.02–4.83]). Results were consistent in those starting INSTIs versus other regimens and those starting dolutegravir versus other INSTIs.

Conclusions. Initial high HIV-1 RNA and low CD4$^+$ T-cell counts are associated with lower rates of VS at 48 and 96 weeks and higher rates of viral blips, LLV, and RV. Low baseline CD4$^+$ T-cell counts are associated with higher VF rates. These associations remain with INSTI-based and specifically with dolutegravir-based regimens. These findings suggest that the impact of these baseline determinants is independent of the ART regimen initiated.

Keywords. blip; low-level viremia; residual viremia; virological failure; integrase inhibitors.

Received 17 December 2022; editorial decision 06 April 2023; published online 13 April 2023

Presented in part: HIV Glasgow Drug Therapy Congress, Glasgow, United Kingdom, 23–26 October 2022; abstract 228.

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Clinical Infectious Diseases® 2023;77(4):593–605

https://doi.org/10.1093/cid/ciad219

Antiretroviral treatment (ART) durably suppresses plasma human immunodeficiency virus (HIV) type 1 RNA to <50 copies/mL [1]. Virological nonsuppression outcomes including viral blips, persistent low-level viremia (LLV), residual viremia (RV), and virological failure (VF) hamper ART efficacy and may enable the selection of antiretroviral resistance and allow its transmission [2].

The lack of standardized definitions for LLV, VF [2–11], and RV [12, 13] has hindered the identification of baseline surrogate markers, with discordant results. The US Department of Health and Human Services guidelines define LLV as confirmed detectable HIV-1 RNA <200 copies/mL, VF as a confirmed viral load ≥200 copies/mL, and a viral blip as an isolated quantifiable HIV-1 RNA preceded and followed by virological suppression (VS) [14].

Virions can still be produced during ART-mediated suppression, with plasma HIV-1 RNA levels <20–50 copies/mL [15]. It is unclear whether this RV results from a combined or separated process of virus production by latently or long-lived HIV-infected cells and/or from virus replication in lymphoid tissue sanctuary sites. Some studies point to a relationship between pre-ART HIV-1 RNA, the size of established HIV-DNA reservoirs and the subsequent release of this detectable and persistent HIV-1 RNA in plasma during ART [16–20]. Viral blips could reflect the size of the reservoir [18, 21] and could predict LLV [18]. In addition, RV has been associated with viral blips and LLV [12]. Intriguingly, in some cohort studies, LLV with HIV-1 RNA 200–499 copies/mL was associated with increased risk of VF [5, 6, 9], whereas in those with LLVs of 50–199 copies/mL, this association was inconsistent [2–6, 11]. There is also discordance in the association between blips and VF [2, 13, 22–24].

Using data from a prospective multinational cohort consortium, we aimed to examine baseline factors associated with virological nonsuppression outcomes (blips, LLV, RV, and VF) in treatment-naive persons with HIV (PWH) who started a 3-drug ART regimen in the integrase strand transfer inhibitor (INSTI) era.

METHODS

Study Design and Data Sources

The International Cohort Consortium of Infectious Diseases (RESPOND) is a collaboration among 19 cohorts from Europe and Australia, using the HIV Cohorts Data Exchange Protocol for data collection (details at https://hicdep.org/) [25]. Clinical and demographic data were collected retrospectively back to 2012 at RESPOND enrollment and prospectively since 2017.

Study Population

Participants consented to share data according to local requirements. All cohorts had approval to share data with RESPOND according to national requirements. We included all ART-naive adults aged ≥18 years who started ART between 1 January 2014 and 31 December 2020, from 17 of 19 cohorts. Participants had a $CD4^+$ T-cell count measured and a detectable plasma HIV-1 RNA value at ART initiation and a minimum follow-up time of 36 weeks.

Virological Outcome Definitions

VS was defined as HIV-1 RNA levels <50 copies/mL at weeks 48 and 96, with a 12-week window on either side; LLV, as the first of ≥ 2 consecutive plasma HIV-1 RNA measurements of 50–199 copies/mL, following VS; viral blip, as an isolated plasma HIV-1 RNA level of 50–199 copies/mL with previous and subsequent HIV-1 RNA levels <50 copies/mL, following VS; RV, as any detectable and quantifiable plasma HIV-1 RNA between 20 and 49 copies/mL, among participants with a HIV-1 RNA measurement with a limit of detection of 20 copies/mL, following VS; and VF, as the first of 2 consecutive plasma HIV-1 RNA measurements ≥50 copies/mL, with 1 measurement ≥200 copies/mL, following VS.

Statistical Methods

A descriptive analysis of participants' demographic and immunovirological characteristics at ART initiation was carried out using frequency tables for categorical variables and median and interquartile range (IQR) for continuous variables. The outcomes were assessed in an intention-to-treat-exposed analysis including all participants starting their first ART regimen regardless of subsequent discontinuations and/or switches.

We used a logistic regression model to assess the impact of multiple baseline predictor variables on VS at weeks 48 and 96, expressed as adjusted odds ratios and 95% confidence intervals (CIs). Kaplan-Meier curves were used to estimate the time to viral blips, LLV, RV and VF, stratified by the third drug, and the comparison among curves was performed using log-rank tests. We performed a survival analysis using Cox regression to assess the impact of baseline variables on virological nonsuppression outcomes (ie, viral blips, LLV, RV, and VF). Associations were expressed as adjusted hazard ratios and 95% CIs.

Baseline variables were defined a priori. Models were adjusted for sex, age, year of ART initiation, race, hepatitis C (hepatitis C virus antibodies), European Australian region, prior AIDS-defining illness, HIV-1 RNA, $CD4^+$ T-cell count and initial ART classes. The latter included: a 2–nucleos(t)ide reverse-transcriptase inhibitor (NRTI) backbone (abacavir-lamivudine, tenofovir disoproxil fumarate [TDF]–emtricitabine, tenofovir alafenamide [TAF]–emtricitabine) plus 1 of the following third agents: cobicistat- or ritonavir-boosted darunavir (protease inhibitor [PI]), rilpivirine (nonnucleoside reverse-transcriptase inhibitor [NNRTI]), and cobicistat-boosted elvitegravir, dolutegravir, or raltegravir (INSTI).

Sensitivity analyses were performed for viral blips, LLV, RV, and VF, restricted first only to participants who started treatment with INSTIs and further restricted to those who started dolutegravir versus other INSTIs. A category was included for missing data for confounders where required. Statistical analysis was performed using SAS software (Statistical Analysis Software), version 9.4. All tests were 2 tailed, and the significance level α was set at .05.

RESULTS

Baseline Characteristics

We included 4310 eligible ART-naive participants (Figure 1). Of these, 84% were male, 69.2% were white, 61.2% were men who had sex with men, 42.6% were from Central Europe, 89.8% were without prior AIDS, and 43.3% started ART in year 2014–2015. Their median age (IQR) was 38 (30–47) years, and 812 (18.8%) were >50 years old (Table 1). The median follow-up time (IQR) since starting ART was 3.8 (2.4–5.1) years, with 16 106 person-years of follow-up, with a median (IQR) of 8 (5–12) $CD4^+$ T-cell counts and 10 (6–14) HIV-1 RNA measurements.

The median (IQR) $CD4^+$ T-cell count was 378/μL (199–560/μL). Overall, 1971 participants (45.7%) had $CD4^+$ T-cell counts ≤350/μL at presentation, and 1092 (25.3%) had severe immunosuppression ($CD4^+$ T-cell count, ≤200/μL); 36.1% had HIV-1 RNA levels ≥100 000 copies/mL. Overall, 72.3% of participants initiated an INSTI-based regimen, of whom 1970 (63.3%) started dolutegravir (Table 1).

Virological Outcomes

VS at weeks 48 and 96 was achieved in 3306 of 3638 (90.9% [95% CI, 89.9%–91.8%) and 2908 of 3118 (93.3% [92.4%–94.1%]) participants, respectively. At 48 weeks, Kaplan-Meier estimates of the proportions were 9.6% (95%, CI, 8.7%–10.5%) for viral blips, 2.1% (1.6%–2.5%) for LLV, 22.2% (20.0%–24.3%) for RV, and 2.1% (1.7%–2.6%) for VF.

Virological Suppression

In multivariate analysis, darunavir (vs dolutegravir), baseline HIV-1 RNA levels >100 000 copies/mL and $CD4^+$ T-cell counts ≤350/μL at ART initiation were associated with significantly lower VS rates at week 48 (Table 2). At week 96, abacavir-lamivudine (vs TDF-emtricitabine), raltegravir (vs dolutegravir), HIV-1-RNA levels >100 000 copies/mL, and $CD4^+$ T-cell counts ≤350/μL were associated with significantly lower VS rates (Table 2).

Viral Blips Analysis

In the time-to-blip analysis (Figure 2*A*), differences among third drugs favored rilpivirine ($P < .001$) with a time to blip longer than raltegravir ($P < .001$). Darunavir and dolutegravir had similar times to blip ($P = .16$).

Female sex was associated with a lower blip incidence in multivariate analysis. Factors associated with a higher rate of blips were age 41–50 years, Central European region, prior AIDS, and $CD4^+$ T-cell count ≤350/μL. Baseline HIV-1 RNA levels paralleled blip incidence, with values ≤10 000 copies/mL associated with lower rates, whereas those >100 000 copies/mL had the highest blip risk. We found no association between NRTIs or the third drug and blip incidence (Figure 3*A*).

Within the subset initiating any INSTI-based regimen, female sex, age 41–50 years, Central European region, HIV-1 RNA level >100 000 copies/mL and $CD4^+$ T-cell count ≤350/μL remained associated with blips. The same analysis restricted to dolutegravir-based regimens showed an association between HIV-1 RNA levels and $CD4^+$ T-cell counts and blips (Supplementary Tables 1 and 2).

LLV Analysis

In the time-to-LLV analysis (Figure 2*B*), differences among all third drugs favored rilpivirine ($P = .004$) overall, with a longer time than raltegravir ($P = .001$) or dolutegravir ($P < .001$) and similar results as for darunavir and dolutegravir ($P = .90$).

Female sex and Eastern European region were associated with lower LLV rates in multivariate analysis. Baseline HIV-1 RNA levels ≤10 000 copies/mL were associated with lower LLV rates and levels >100 000 copies/mL with the highest rates. $CD4^+$ T-cell counts ≤500/μL were associated with a higher LLV risk. We found no association between NRTIs or the third drugs and LLV (Figure 3*B*).

These associations remained in the subset receiving INSTI-based regimens (female sex, Eastern European region, HIV-1 RNA level >100 000 copies/mL, $CD4^+$ T-cell count ≤350/μL). In the dolutegravir subset, HIV-1 RNA levels >100 000 copies/mL and $CD4^+$ T-cell counts ≤500/μL remained associated with LLV (Supplementary Tables 1 and 2).

RV Analysis

The time-to-RV analysis across third drugs favored rilpivirine ($P < .001$) (Figure 2*C*). Darunavir showed a similar time to RV as rilpivirine ($P = .28$) and a longer time than dolutegravir ($P = .01$). Eastern European region was associated with lower RV rates in multivariate analysis. TAF-emtricitabine (vs TDF-emtricitabine) was associated with a higher RV incidence. Baseline HIV-1 RNA levels ≤10 000 copies/mL were associated with a lower RV rate, whereas those >100 000 copies/mL and $CD4^+$ T-cell counts ≤200/μL were associated with the highest RV rates (Figure 4*A*). Within the subset treated with INSTI and specifically dolutegravir, Eastern European region and HIV-1 RNA levels, but not $CD4^+$ T-cell counts, remained associated with RV (Supplementary Tables 1 and 2).

VF Analysis

In the time-to-VF analysis (Figure 2*D*), differences among third drugs again favored rilpivirine ($P < .001$). Raltegravir had a shorter time to VF than rilpivirine ($P < .001$),

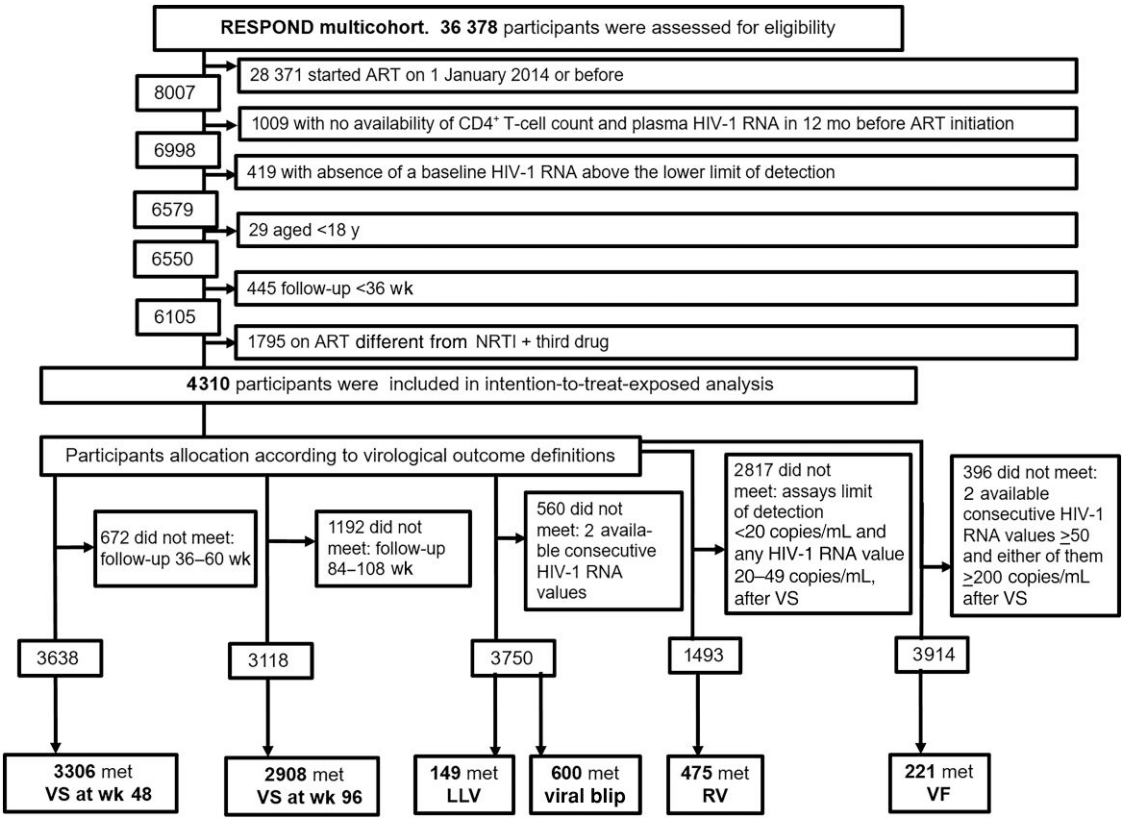


Figure 1. International Cohort Consortium of Infectious Diseases (RESPOND) flow chart. Abbreviations: ART, antiretroviral treatment; HIV-1, human immunodeficiency virus type 1; LLV, low-level viremia; NRTI, nucleos(t)ide reverse-transcriptase inhibitor; RV, residual viremia; VF, virological failure; VS, virological suppression.

dolutegravir ($P = .002$), and darunavir (borderline significance, $P = .056$).

In multivariate analysis, factors associated with higher VF rates (Figure 4*B*) were female sex, nonwhite race, chronic hepatitis C virus, prior AIDS, and Central European region, whereas age 31–50 years was associated with lower VF rates. Low baseline $CD4^+$ T-cell counts (≤200/μL or 351–500/μL) were associated with higher VF rates (Figure 4*B*), but, intriguingly, HIV-1 RNA levels were not. Raltegravir use was associated with higher VF rates in multivariate analysis compared to dolutegravir, whereas rilpivirine was not. TAF-emtricitabine (vs TDF-emtricitabine) was associated with lower rates of VF.

The subset of any INSTI- and dolutegravir-based regimen showed an increased risk of VF associated with lower $CD4^+$ T-cell count. No association was found with HIV-1 RNA levels or TAF-emtricitabine (Supplementary Tables 1 and 2).

DISCUSSION

PWH who initiated ART beyond 2014 in the multinational prospective RESPOND cohort, with 72% of participants receiving INSTI-based regimens, had high VS rates at weeks 48 and 96 (91.0% and 93.3%, respectively). Using stringent definitions for virological nonsuppression outcomes, at 48 weeks the proportions with viral blips, LLV, RV, and VF were 9.6%, 2.1%, 22.2%, and 2.1%, respectively.

High baseline HIV-1-RNA and low CD4+ counts were strongly associated with lower rates of VS at 48 and 96 weeks. The use of darunavir (vs dolutegravir) was associated with a significantly lower probability of VS at week 48, but this association was lost at week 96. PIs have slower initial viral load decay kinetics compared with INSTIs, particularly with high baseline HIV-1 RNA levels, as shown in randomized clinical trials [26, 27] and cohort studies [28]. In our study, abacavir-lamivudine, higher HIV-1 RNA and lower $CD4^+$ T-cell counts were associated with lower rates of VS at 96 weeks. Abacavir-lamivudine was associated with a significantly shorter time to VF than TDF-emtricitabine combined with either boosted atazanavir or efavirenz in the AIDS Clinical Trials Group A5202, in strata of HIV-1 RNA levels ≥100 000 copies/mL and $CD4^+$ T-cell counts <200/μL [29]. However, this has not been reproduced in pivotal dolutegravir studies in initial treatment [26, 30].

We found a significant association between high baseline plasma HIV-1 RNA level or low $CD4^+$ T-cell count and the blip incidence in the overall cohort and in participants starting

Table 1. Baseline Characteristics of Participants in the Intention-to-Treat Exposed Population

Characteristic	Participants, No. (%) by ART Regimen[a]					
	Overall (n = 4310)	DRV Based (n = 641)	RPV Based (n = 555)	EVG/c Based (n = 771)	DTG Based (n = 1970)	RAL Based (n = 373)
Sex						
Male	3614 (83.9)	503 (78.5)	465 (83.8)	692 (89.8)	1678 (85.2)	276 (74.0)
Female	696 (16.1)	138 (21.5)	90 (16.2)	79 (10.2)	292 (14.8)	97 (26.0)
HIV transmission route						
MSM	2636 (61.2)	327 (51.0)	354 (63.8)	543 (70.4)	1223 (62.1)	189 (50.7)
Heterosexual	1206 (28.0)	221 (34.5)	161 (29.0)	159 (20.6)	543 (27.6)	122 (32.7)
IDU	208 (4.8)	49 (7.6)	22 (4.0)	23 (3.0)	94 (4.8)	20 (5.4)
Other	260 (6.0)	44 (6.9)	18 (3.2)	46 (6.0)	110 (5.6)	42 (11.3)
Race						
White	2982 (69.2)	419 (65.4)	416 (75.0)	481 (62.4)	1423 (72.2)	243 (65.1)
Other	555 (12.9)	82 (12.8)	66 (11.9)	63 (8.2)	260 (13.2)	84 (22.5)
Unknown	773 (17.9)	140 (21.8)	73 (13.2)	227 (29.4)	287 (14.6)	46 (12.3)
HBV (HBsAg) result						
Negative	3257 (75.6)	457 (71.3)	429 (77.3)	569 (73.8)	1579 (80.2)	223 (59.8)
Positive	113 (2.6)	19 (3.0)	17 (3.1)	19 (2.5)	45 (2.3)	13 (3.5)
Unknown	940 (21.8)	165 (25.7)	109 (19.6)	183 (23.7)	346 (17.6)	137 (36.7)
HCV (antibody) result						
Negative	3077 (71.4)	424 (66.1)	429 (77.3)	516 (66.9)	1492 (75.7)	216 (57.9)
Positive	344 (8.0)	66 (10.3)	36 (6.5)	52 (6.7)	154 (7.8)	36 (9.7)
Unknown	889 (20.6)	151 (23.6)	90 (16.2)	203 (26.3)	324 (16.4)	121 (32.4)
Region						
Southern Europe	1461 (33.9)	209 (32.6)	302 (54.4)	309 (40.1)	561 (28.5)	80 (21.4)
Central Europe	1835 (42.6)	268 (41.8)	201 (36.2)	246 (31.9)	1009 (51.2)	111 (29.8)
Northern Europe or Australia	609 (14.1)	91 (14.2)	32 (5.8)	128 (16.6)	210 (10.7)	148 (39.7)
Eastern Europe	405 (9.4)	73 (11.4)	20 (3.6)	88 (11.4)	190 (9.6)	34 (9.1)
BMI[b]						
≤18	117 (2.7)	19 (3.0)	6 (1.1)	20 (2.6)	60 (3.0)	12 (3.2)
18.1–25	1693 (39.3)	251 (39.2)	233 (42.0)	314 (40.7)	824 (41.8)	71 (19.0)
25.1–30	598 (13.9)	68 (10.6)	74 (13.3)	121 (15.7)	305 (15.5)	30 (8.0)
>30	184 (4.3)	24 (3.7)	32 (5.8)	30 (3.9)	89 (4.5)	9 (2.4)
Smoking status						
Never	1173 (27.2)	173 (27.0)	135 (24.3)	240 (31.1)	562 (28.5)	63 (16.9)
Current	1416 (32.9)	168 (26.2)	188 (33.9)	242 (31.4)	759 (38.5)	59 (15.8)
Previous	178 (4.1)	26 (4.1)	25 (4.5)	46 (6.0)	77 (3.9)	4 (1.1)
Unknown	1543 (35.8)	274 (42.7)	207 (37.3)	243 (31.5)	572 (29.0)	247 (66.2)
Prior AIDS						
No	3872 (89.8)	562 (87.7)	544 (98.0)	721 (93.5)	1751 (88.9)	294 (78.8)
Yes	438 (10.2)	79 (12.3)	11 (2.0)	50 (6.5)	219 (11.1)	79 (21.2)
Age at ART initiation						
≤30 y	1029 (23.9)	142 (22.2)	118 (21.3)	184 (23.9)	500 (25.4)	85 (22.8)
31–40 y	1388 (32.2)	211 (32.9)	206 (37.1)	251 (32.6)	612 (31.1)	108 (29.0)
41–50 y	1081 (25.1)	171 (26.7)	151 (27.2)	192 (24.9)	483 (24.5)	84 (22.5)
>50 y	812 (18.8)	117 (18.3)	80 (14.4)	144 (18.7)	375 (19.0)	96 (25.7)
Age at ART initiation, median (IQR), y	38 (30–47)	38 (31–48)	38 (31–46)	38 (30–47)	38 (30–47)	39 (31–50)
Year of ART initiation						
2014–2015	1866 (43.3)	407 (63.5)	371 (66.8)	350 (45.4)	556 (28.2)	182 (48.8)
2016–2017	1627 (37.7)	142 (22.2)	140 (25.2)	318 (41.2)	899 (45.6)	128 (34.3)
2018–2019	817 (19.0)	92 (14.4)	44 (7.9)	103 (13.4)	515 (26.1)	63 (16.9)
Baseline HIV viral load (HIV-1 RNA copies/mL)[c]						
≤10 000	971 (22.5)	105 (16.4)	234 (42.2)	152 (19.7)	403 (20.5)	77 (20.6)
10 001–99 999	1782 (41.3)	241 (37.6)	302 (54.4)	349 (45.3)	760 (38.6)	130 (34.9)
100 000–500 000	986 (22.9)	181 (28.2)	14 (2.5)	198 (25.7)	503 (25.5)	90 (24.1)
>500 000	571 (13.2)	114 (17.8)	5 (0.9)	72 (9.3)	304 (15.4)	76 (20.4)
HIV-1 RNA $\log_{10}$, median (IQR), copies/mL	4.7 (4.1–5.3)	4.9 (4.3–5.4)	4.1 (3.6–4.5)	4.7 (4.1–5.1)	4.8 (4.1–5.3)	4.9 (4.2–5.5)

Table 1. Continued

Characteristic	Participants, No. (%) by ART Regimen[a]					
	Overall (n = 4310)	DRV Based (n = 641)	RPV Based (n = 555)	EVG/c Based (n = 771)	DTG Based (n = 1970)	RAL Based (n = 373)
Baseline CD4⁺ T-cell count[c]						
≤100/μL	633 (14.7)	148 (23.1)	4 (0.7)	75 (9.7)	323 (16.4)	83 (22.3)
101–200/μL	459 (10.6)	81 (12.6)	18 (3.2)	70 (9.1)	231 (11.7)	59 (15.8)
201–350/μL	879 (20.4)	147 (22.9)	108 (19.5)	164 (21.3)	393 (19.9)	67 (18.0)
351–500/μL	988 (22.9)	122 (19.0)	183 (33.0)	205 (26.6)	418 (21.2)	60 (16.1)
>500/μL	1351 (31.3)	143 (22.3)	242 (43.6)	257 (33.3)	605 (30.7)	104 (27.9)
CD4⁺ T-cell count, median (IQR), cells/μL	378 (199–560)	293 (109–473)	480 (359–633)	404 (250–587)	366 (175–554)	300 (121–530)
Comorbid conditions						
Hypertension	740 (17.2)	87 (13.6)	87 (15.7)	147 (19.1)	392 (19.9)	27 (7.2)
Diabetes mellitus	105 (2.4)	9 (1.4)	12 (2.2)	20 (2.6)	49 (2.5)	15 (4.0)
Prior CVD	21 (0.5)	4 (0.6)	2 (0.4)	2 (0.3)	12 (0.6)	1 (0.3)
Prior NADC	38 (0.9)	4 (0.6)	5 (0.9)	3 (0.4)	21 (1.1)	5 (1.3)
Prior ESLD	6 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	4 (0.2)	1 (0.3)
Prior CKD	8 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	7 (0.4)	0 (0.0)
Initial ART						
NRTI						
ABC-3TC	908 (21.1)	111 (17.3)	0 (0.0)	0 (0.0)	797 (40.5)	0 (0.0)
TDF-FTC	2417 (56.1)	463 (72.2)	418 (75.3)	462 (59.9)	728 (37.0)	346 (92.8)
TAF-FTC	985 (22.9)	67 (10.5)	137 (24.7)	309 (40.1)	445 (22.6)	27 (7.2)
Third drug						
DRV	641 (14.9)	…	…	…	…	…
RPV	555 (12.9)	…	…	…	…	…
EVG/c	771 (17.9)	…	…	…	…	…
DTG	1970 (45.7)	…	…	…	…	…
RAL	373 (8.7)	…	…	…	…	…
Booster						
None	2898 (67.2)	0 (0.0)	555 (100.0)	0 (0.0)	1970 (100.0)	373 (100.0)
Cobicistat	899 (20.9)	128 (20.0)	0 (0.0)	771 (100.0)	0 (0.0)	0 (0.0)
Ritonavir	513 (11.9)	513 (80.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: 3TC, lamivudine; ABC, abacavir; AIDS, acquired immunodeficiency syndrome, referred as AIDS-defining illness; ART, antiretroviral treatment; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; DRV, darunavir; DTG, dolutegravir; ESLD, end-stage liver disease; EVG/c, cobicistat-boosted elvitegravir; FTC, emtricitabine; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug user; IQR, interquartile range; MSM, men who have sex with men; NADC, non–AIDS-defining cancer; NRTI, nucleos(t)ide reverse-transcriptase inhibitor; RAL, raltegravir RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a]Data represent no. (%) of participants unless otherwise specified.

[b]BMI calculated as weight in kilograms divided by height in meters squared.

[c]Baseline CD4⁺ T-cell count and HIV-1 RNA level were defined as the last measurement in the 12 months preceding the ART initiation date, and, where this was not available, the first measurement up to 14 days after ART initiation.

an INSTI- and dolutegravir-based regimen. This is consistent with findings in previous cohorts [23, 24]. In turn, blip rates were higher with PI-based and lower with INSTI-based ART. However, there could have been a channeling prescription bias of PIs to higher-risk PWH based on their perceived higher barrier to resistance [24]. We found no association between viral blips and NRTI or third drug types in our analysis. These data are consistent with results from a randomized trial comparing dolutegravir with ritonavir-boosted darunavir [26].

A significant association between high baseline plasma HIV-1 RNA level and low CD4⁺ T-cell count was also seen with LLV overall, with any INSTI- and dolutegravir-based regimens. These findings are in agreement with those in a Spanish cohort [31] showing that a plasma HIV-1 RNA level >100 000 copies/mL was an independent predictor of LLV, an association that remained for participants starting any INSTI-based regimen. Conversely, other cohorts have reported a higher risk of LLV with PI-based than with NNRTI- and INSTI-based regimens [6]. However, these analyses had a low proportion of darunavir use among PIs (most participants received atazanavir or lopinavir) [6]. It is likely that the risk of LLV could be different for darunavir versus other PIs. In our study the only PI included was darunavir, the only currently recommended PI [1, 14].

The rate of RV in our study (22.2%) was similar to that described in a Dutch cohort (24.7%) [12]. High baseline HIV-1 RNA level and low CD4⁺ T-cell count were also associated with increased rates of RV. In our analysis, the association with HIV-1 RNA level

Table 2. Multivariate Logistic Regression Analysis of Variables Associated With Virological Suppression at Weeks 48 and 96, for All Participants

	Virological Suppression wk 48		Virological Suppression at wk 96	
Variable	Adjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Sex				
Male	1.0 (Reference)	…	1.0 (Reference)	…
Female	1.16 (.83–1.61)	.40	.81 (.56–1.18)	.27
Race				
White	1.0 (Reference)	…	1.0 (Reference)	…
Other	.80 (.55–1.16)	.23	.80 (.51–1.26)	.34
HCV				
Negative	1.0 (Reference)	…	1.0 (Reference)	…
Positive	.46 (.32–.68)	<.001[a]	.64 (.38–1.05)	.08
Region				
Southern Europe	1.0 (Reference)	…	1.0 (Reference)	…
Central Europe	.87 (.65–1.15)	.32	1.00 (.71–1.41)	.99
Northern Europe or Australia	.90 (.60–1.34)	.60	1.30 (.80–2.12)	.29
Eastern Europe	.74 (.45–1.21)	.23	.88 (.44–1.75)	.72
Baseline HIV viral load (HIV-1 RNA copies/mL)[b]				
≤10 000	1.19 (.80–1.76)	.39	1.41 (.87–2.27)	.16
10 001–100 000	1.0 (Reference)	…	1.0 (Reference)	…
>100 000	.51 (.39–.68)	<.001[a]	.69 (.49–.97)	.03[a]
Baseline CD4$^+$ T-cell count[b]				
≤200/μL	.40 (.27–.58)	<.001[a]	.35 (.22–.55)	<.001[a]
201–350/μL	.58 (.39–.84)	<.001[a]	.48 (.30–.76)	<.001[a]
351–500/μL	.91 (.60–1.38)	.66	1.13 (.67–1.93)	.64
>500/μL	1.0 (Reference)	…	1.0 (Reference)	…
Prior AIDS				
No	1.0 (Reference)	…	1.0 (Reference)	…
Yes	.72 (.52–1.00)	.05	.73 (.48–1.12)	.15
Age at ART initiation				
≤30 y	1.0 (Reference)	…	1.0 (Reference)	…
31–40 y	.95 (.68–1.34)	.78	1.04 (.68–1.58)	.85
41–50 y	1.17 (.81–1.67)	.40	1.40 (.88–2.21)	.15
>50 y	.87 (.60–1.25)	.44	.77 (.50–1.20)	.26
Year of ART initiation				
2014–2015	1.17 (.87–1.58)	.30	.93 (.65–1.34)	.70
2016–2017	1.0 (Reference)	…	1.0 (Reference)	…
2018–2019	.74 (.55–1.11)	.14	.68 (.42–1.08)	.10
NRTI				
ABC-3TC	.85 (.60–1.19)	.34	.46 (.30–.69)	<.001[a]
TDF-FTC	1.0 (Reference)	…	1.0 (Reference)	…
TAF-FTC	1.19 (.84–1.69)	.33	.97 (.61–1.53)	.88
Third drug				
DRV	.63 (.45–.87)	.01[a]	.65 (.43–1.00)	.05
RPV	.99 (.57–1.71)	.96	.66 (.34–1.26)	.20
EVG/c	1.08 (.72–1.62)	.70	.66 (.41–1.07)	.09
DTG	1.0 (Reference)	…	1.0 (Reference)	…
RAL	.79 (.51–1.23)	.29	.52 (.29–.90)	.02[a]

Abbreviations: 3TC, lamivudine; ABC, abacavir; AIDS, acquired immunodeficiency syndrome, referred as AIDS-defining illness; ART, antiretroviral treatment; CI, confidence interval; DRV, darunavir; DTG, dolutegravir; EVG/c, cobicistat-boosted elvitegravir; FTC, emtricitabine; HCV, hepatitis C virus infection; HIV, human immunodeficiency virus; NRTI, nucleos(t)ide reverse-transcriptase inhibitor; OR, odds ratio;

RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a]Significant at P < .05.

[b]Baseline CD4$^+$ T-cell count and HIV-1 RNA level were defined as the last measurement in the 12 months preceding ART initiation date and, where this was not available, the first measurement up to 14 days after ART initiation.

remained in participants receiving any INSTI and dolutegravir in particular, consistent with findings in a previous French cohort [32].

Interestingly, while low CD4$^+$ T-cell counts were significantly associated with VF, high baseline HIV-1 RNA levels were not. This finding is consistent with findings in a

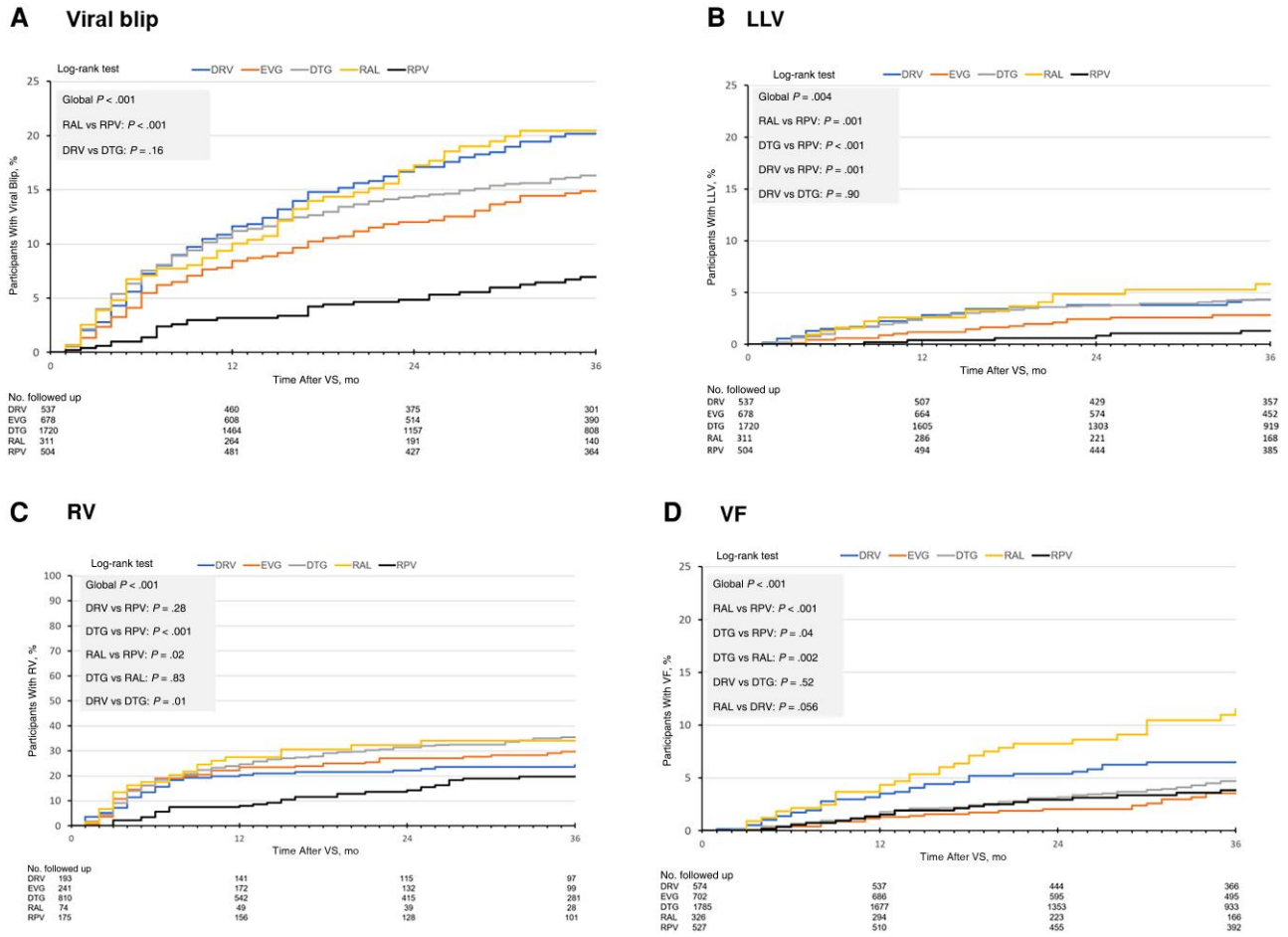


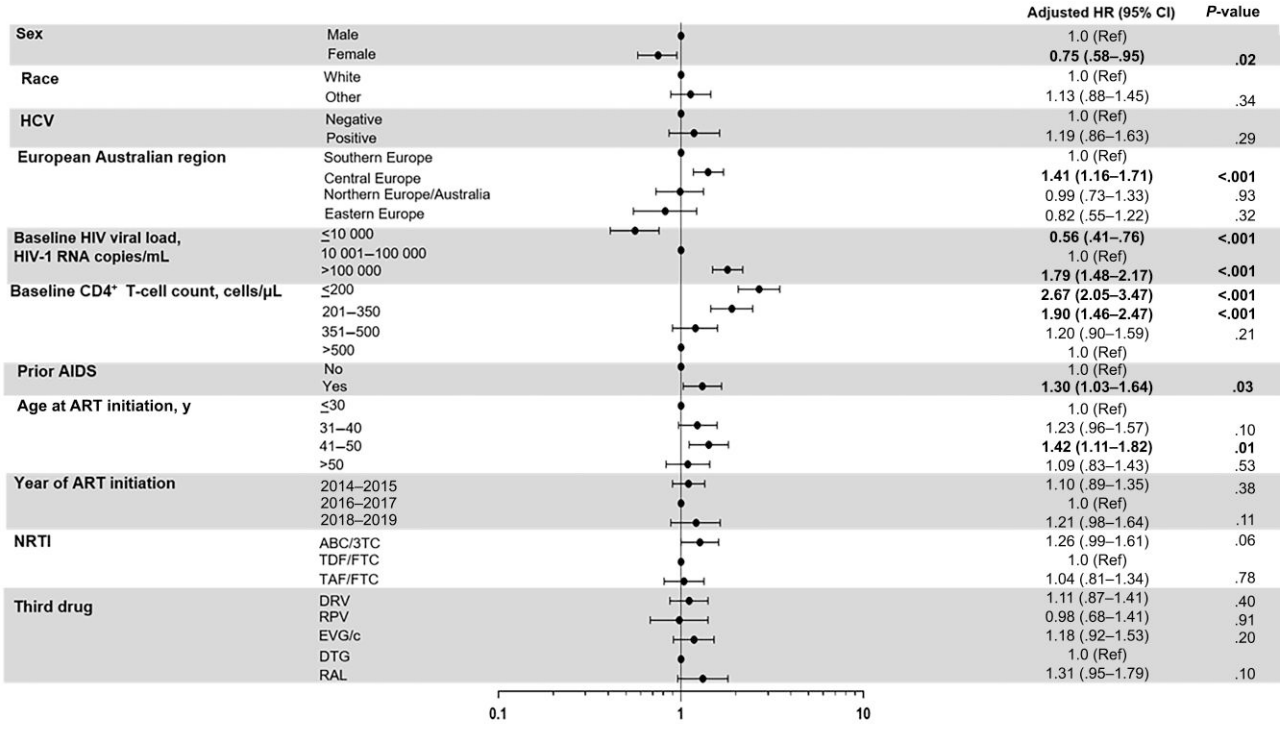
Figure 2. Time-to-virological outcomes estimated by Kaplan-Meier curves. A. Time-to-viral blip following virological suppression. B. Time-to-low-level viremia following virological suppression. C. Time-to-residual viremia following virological suppression. D. Time-to-virological failure following virological suppression. Abbreviations: DTG, dolutegravir; DRV, darunavir; EVG, elvitegravir; FU, follow-up; LLV, low-level viremia; RAL, raltegravir; RPV, rilpivirine; RV, residual viremia; VF, virological failure; VS, virological suppression.

French cohort [11], with no relationship between baseline HIV-1 RNA level and VF. In addition, HIV-1 RNA >100 000 copies/mL did not affect risk of VF in a European cohort [28]. These results differ from those observed in a Spanish cohort [31] in which a HIV-1 RNA >100 000 copies/mL was a consistent predictor of VF. Different definitions of VF and time points for HIV-1 RNA measurements could lead to non-comparable results. Similarly, other cohorts [33, 34] found a higher risk of VF with HIV-1 RNA levels ≥100 000 copies/mL on INSTI-based regimens. However, because both cohorts used thresholds of 50 copies/mL for VF, many VFs could have been LLV. Another recent analysis has found an association between baseline HIV-1 RNA level and VF (hazard ratio, 1.1 [95% CI, 1.0–1.2]) [2], but for a broader definition of VF.

In our analysis, compared to TDF, TAF was associated with higher rates of RV but a lower risk of VF. TAF showed superior virological efficacy compared with TDF in a clinical trial [35]; however, there were no data on its impact on RV.

Raltegravir had a significantly shorter time to VF than rilpivirine, darunavir, or dolutegravir. This association remained significant in multivariate analysis. This is consistent with findings of the SPRING-2 trial, showing fewer participants who met protocol-defined VF with dolutegravir versus raltegravir [30]. Indeed, raltegravir showed lower VS rates at week 96 in our multivariate analysis. Unmeasured residual confounding could exist regarding raltegravir dosing notwithstanding. Raltegravir once daily is associated with higher rates of VF, particularly with high HIV-1 RNA and low $CD4^+$ T-cell counts, but we did not have access to dosing data for raltegravir in RESPOND [36, 37]. In a recent European cohort analysis, INSTI- and NNRTI-based ART had similar rates of VF, whereas PI-based ART was associated with an increased risk of VF [2]. However, not every drug within a class was

A Viral blip



B Low-level viremia

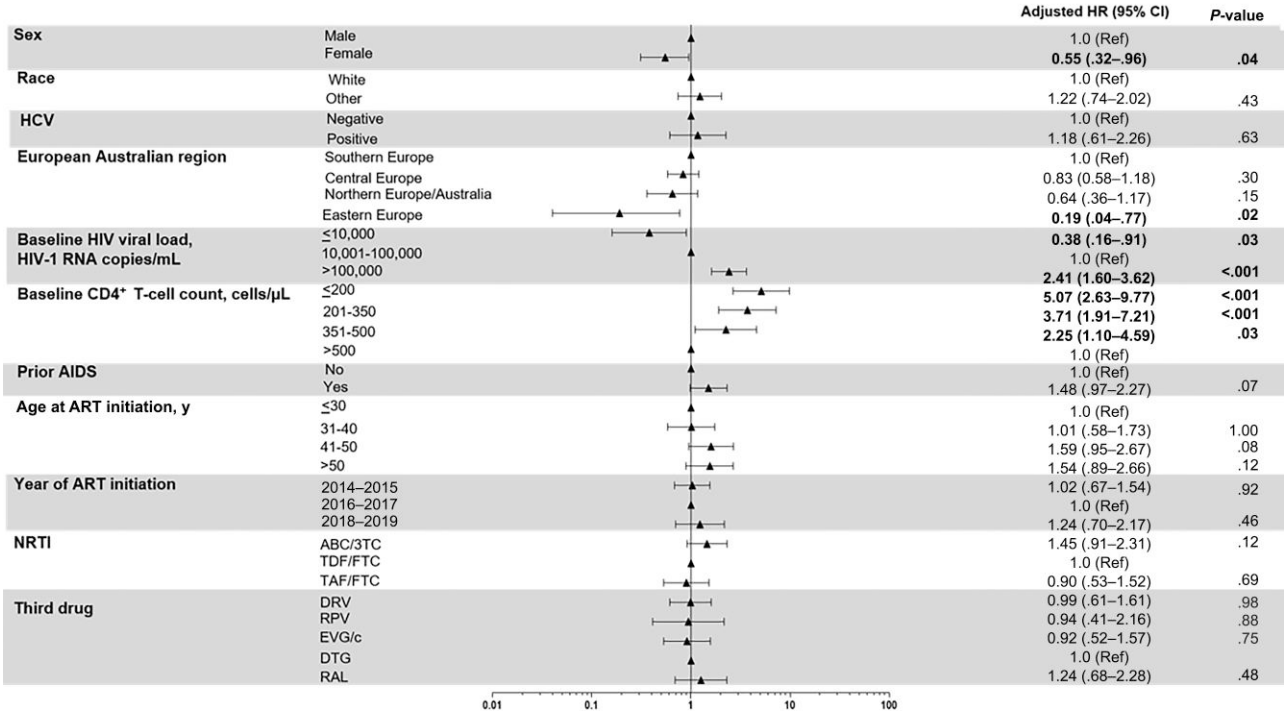


Figure 3. Multivariate analysis of viral blip (*A*) and low-level viremia (*B*) rates. Statistically significant values of variables are highlighted in bold. Abbreviations: 3TC, lamivudine; ABC, abacavir; AIDS, acquired immunodeficiency syndrome, referred as AIDS-defining illness; ART, antiretroviral treatment; CI, confidence interval; DRV, darunavir; DTG, dolutegravir; EVG/c, cobicistat-boosted elvitegravir; FTC, emtricitabine; HCV, hepatitis C virus; HIV, human immunonodeficiency virus; HR, hazard ratio; NRTI, nucleos(t)ide reverse-transcriptase inhibitor; RAL, raltegravir; Ref, reference; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

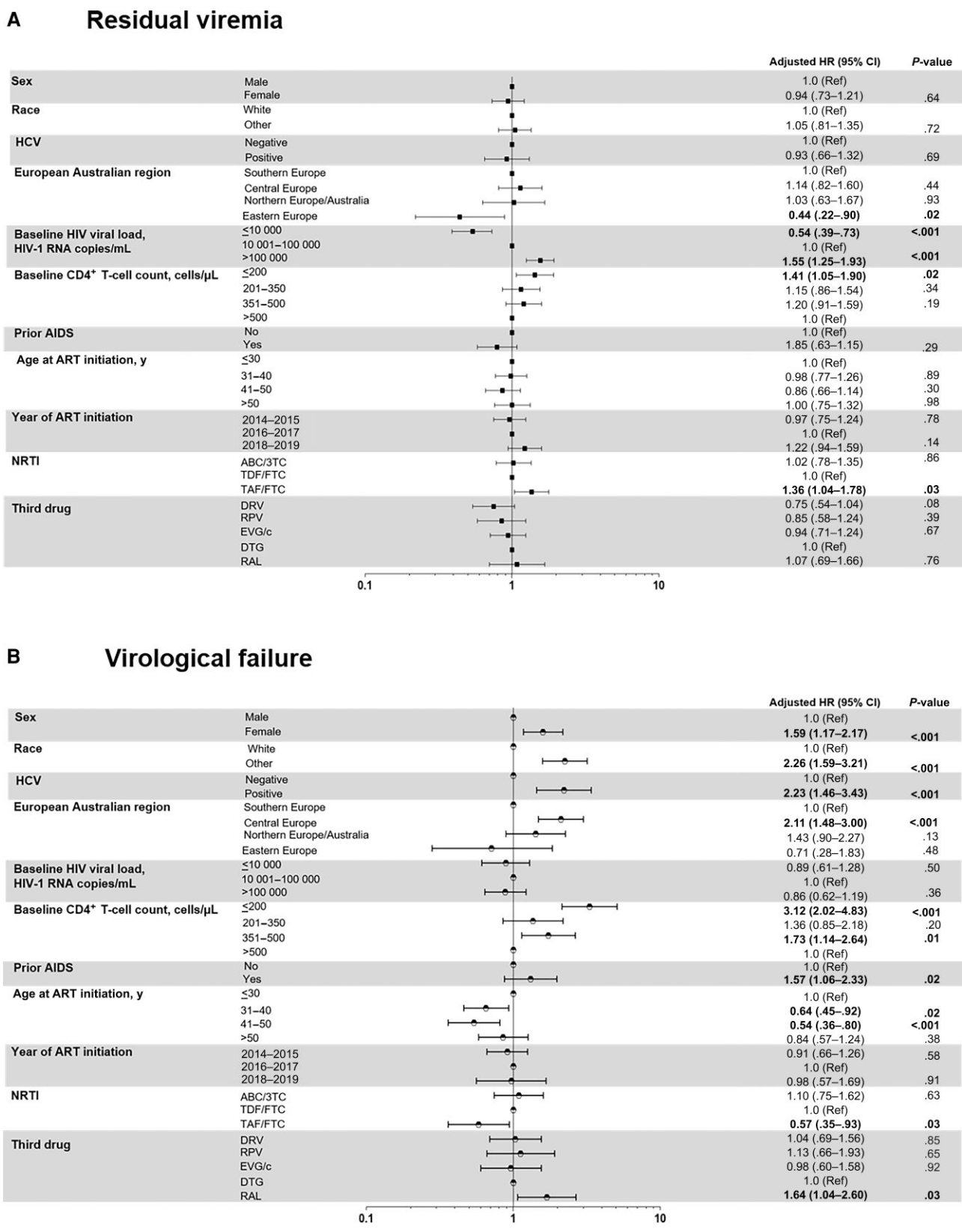


Figure 4. Multivariate analysis of residual viremia (*A*) and virological failure (*B*) rates. Statistically significant values of variables ares highlighted in bold. Abbreviations: 3TC, lamivudine; ABC, abacavir; AIDS, acquired immunodeficiency syndrome, referred as AIDS-defining illness; ART, antiretroviral treatment; CI, confidence interval; DTG, dolutegravir; DRV, darunavir;, dolutegravir; EVG/c, cobicistat-boosted elvitegravir; FTC, emtricitabine; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; NRTI, nucleos(t)ide reverse-transcriptase inhibitor; RAL, raltegravir; Ref, reference; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

assessed owing to the limited number of virological outcome events.

Results were consistent regarding HIV-1 RNA levels and $CD4^+$ T-cell counts in those starting INSTIs versus other ART classes or those starting dolutegravir (compared with other individual INSTIs), for every virological nonsuppression outcome. These findings strongly suggest that HIV-1 RNA level and $CD4^+$ T-cell count are baseline determinants associated with long-term consequences, including higher rates of viral blips, LLV, and RV, independent of the ART regimen initiated. Alternatively, VF was associated only with a low baseline $CD4^+$ T-cell count. All of these findings indicate that the interaction between the HIV reservoir established before ART initiation and the rates of viral blips, LLV, and RV seems to be closely related to baseline HIV-1 RNA level but not to the type of ART administered, including the second-generation INSTIs [18, 38–40]. HIV-1 integrated into silent chromosomal sites in the deep latency of clonally expanded infected T cells can harbor defective proviruses and, less likely, intact (replication-competent) viruses, which are not affected by ART [41, 42]. Nonsuppressible RV has been associated with large HIV reservoir size [43, 44]. In addition, the nadir $CD4^+$ T-cell count was inversely correlated with levels of both cell-associated DNA and cell-associated RNA in a pooled analysis of AIDS Clinical Trials Group treatment interruption studies [38].

In the current study, the time to virological nonsuppression outcomes (viral blips, LLV, RV, and VF) was significantly and consistently longer for rilpivirine. The fact that this association disappeared after adjustment reflects the imbalance in baseline characteristics between the different treatments. The use of rilpivirine plus 2 NRTIs has been approved only for PWH with HIV-1 RNA levels <100 000 copies/mL and is not recommended for those with $CD4^+$ T-cell counts <200/μL, supporting a likely channeling prescription bias, as it is preferentially prescribed in PWH with characteristics associated with better virological outcomes [14, 45]. The Italian Italian cohort naive antiretrovirals cohort compared rilpivirine- and INSTI-based first-line regimens in participants with HIV-1 RNA levels <100 000 copies/mL and $CD4^+$ T-cell counts >200/μL and found no differences in virological rebound rates [46].

We identified higher rates of VF in nonwhite PHW. This association probably reflects higher rates of immigration, socioeconomic deprivation, and lower treatment adherence rates in this group [47].

Our study has limitations. RESPOND does not systematically collect data on HIV subtypes and genotypic resistance analysis, which could affect the choice of initial ART or the virological outcome. The second-generation INSTI bictegravir, the 2-drug regimen dolutegravir-lamivudine and the new NNRTI doravirine were not included owing to an insufficient number of participants or short follow-up. Despite adjustment for a wide range of variables, confounding by indication and residual uncontrolled confounders might still introduce unknown biases in drug comparisons.

A strength of the current study is the inclusion of a large number of INSTI-based participants and the ability to compare individual drugs within ART classes. In addition, we describe virological nonsuppression outcomes not explored in randomized trials, using strict definitions.

In conclusion, baseline plasma HIV-1 RNA levels >100 000 copies/mL and $CD4^+$ T-cell counts ≤350/μL were associated with lower rates of VS at 48 and 96 weeks, and higher rates of viral blips, RV, and LLV. $CD4^+$ T-cell counts ≤200/μL were associated with a higher risk of VF. Importantly, the association between HIV-1 RNA levels or $CD4^+$ T-cell count and these virological outcomes persisted in participants initiating INSTI-based and specifically dolutegravir-based regimens. These data suggest that baseline HIV-1 RNA levels and $CD4^+$ T-cell counts are determinants associated with virological nonsuppression outcomes regardless of the antiretroviral regimen initiated and point to underlying mechanisms established before ART initiation, likely focused on the HIV reservoir size. Further research is warranted to explore the impact of bictegravir-emtricitabine-TAF, doravirine, and INSTI-based 2-drug regimens on long-term virological nonsuppression outcomes.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Author Contributions. H. A. and J. M. L. contributed to the conception and design of the study and drafting of the manuscript. A. M. performed the acquisition of data and statistical analysis. All authors contributed to the collection of data, interpretation of the results, and revision of the manuscript and approved the final version of the manuscript.

Disclaimer. Per International Cohort Consortium of Infectious Disease (RESPOND) governance (https://chip.dk/Portals/0/files/RESPOND/Study%20documents/RESPOND%20governance%20and%20procedures_v6_2020SEP30.pdf?ver=2020-10-20-163958-080), funders of the study were academic collaborators and included as coauthors if they met the ICJME criteria. Funders were not in a position to veto study design, data collection, data analysis, data interpretation, and/or the writing of the manuscript.

Financial support. The International Cohort Consortium of Infectious Disease (RESPOND) is supported by ViiV Healthcare, Gilead Sciences, and Merck Sharp & Dohme. Additional support has been provided by participating cohorts contributing in-kind data and/or statistical support: the Austrian HIV Cohort Study, the Australian HIV Observational Database, CHU Saint-Pierre, University Hospital Cologne, EuroSIDA, the Frankfurt HIV Cohort Study, the Georgian National AIDS Health Information System, the Modena HIV Cohort, the San Raffaele Scientific Institute, the Swiss HIV Cohort Study, the AIDS Therapy Evaluation in the Netherlands Cohort (ATHENA), and the Royal Free HIV Cohort Study. The Australian HIV Observational Database is further supported by the US National Institutes of Health (grant U01-AI069907) and the National Health and Medical Research Council, Australia (grant GNT1050874), and the Swiss HIV Cohort Study is supported by the Swiss National Science Foundation.

Potential conflicts of interest. H. A. has received support for attending meetings from Janssen-Cilag, Gilead Sciences and ViiV Healthcare and honoraria for presentations from Gilead Sciences and ViiV Healthcare, outside the present work. A. M. has received payments or honoraria for lectures, presentations and travel support from ViiV Healthcare and Gilead Sciences and consultancy fees as an expert witness for Eiland and Bonnin, outside the submitted work. H. F. G. has received unrestricted research grants and a travel grant from Gilead Sciences; fees for data and safety monitoring board membership from Merck; consulting/advisory board membership fees from Gilead Sciences, Merck, Johnson & Johnson, Janssen, Novartis, GSK and ViiV Healthcare; and grants from the Swiss National Science Foundation, Yvonne Jacob Foundation, and the National Institutes of Health, outside the present work. C.S. reports payment or honoraria for speaking engagements from Gilead Sciences. F. W. reports membership on the advisory board for ViiV. C. L. reports grants or contracts (paid to the institution) from the German federal ministry of education and research, the Federal Joint Committee (Gemeinsamer Bundesausschuss Innovationsausschuss), the Ministerium für Kultur und Wissenschaft in Nordrhein-Westfalen, and the German Center for Infection Research; payment for speaking engagements from Pfizer, ViiV, Gilead, Novartis, MSD, and Biontech; travel support for the 2023 Conference on Retroviruses and Opportunistic Infections (CROI 2023) from Pfizer; and participation on a data safety monitoring or advisory board for ViiV, Pfizer, and Biontech. C. M. reports a research grant from Gilead (paid to the institution), consulting fees (paid to the author) from ViiV, MSD, Gilead, and Janssen, and participation on a data safety monitoring or advisory board for Corimuno. J. C. W. has received payments or honoraria for lectures from Merck Sharp & Dohme. A. S. reports grants or contracts from Gilead Sciences, participation on data safety monitoring or advisory board for GlaxoSmithKline and Gilead Sciences, and a role on the Swedish Reference Group of Antiviral Therapy. C. Smith Stephan has received grants or contracts from the Robert Koch Institute (ClinSurv Steering committee and grant) abd Gesellschaft für Internationale Zusammenarbeit (Hospital Partnership Developing Project [Esther]); consulting fees from Gilead Sciences (speaker fees and advisory board membership) and from Janssen Cilag, Merck Sharp & Dohme, ViiV Healthcare (advisory board membership); payment for expert testimony for Verwaltungsgericht Berlin; and support for attending meetings form Gilead Sciences (Conference on Retrovirus and Opportunistic Infection [American Retrovirus Conference]), Janssen-Cilag (European AIDS Conference travel grant), and AbbVie (Dagnä-Workshop travel grant), outside the present work. K. P. has received grants or contracts from ViiV Healthcare Australia and Gilead Sciences Australia, outside the present work. V. V. is an employee and shareholder of ViiV Healthcare. J. G. is an employee and shareholder of Gilead Sciences. R. M. I. has received payments for presentations in meetings and symposia as a speaker in HIV Clinical Topics (22–23 September 2022; lecture about late human immunodeficiency virus [HIV] presentation) and from the HIV Nordic Symposium (September 2022; role as chairman in a session about long-acting cabotegravir/rilpivirine [GSK]) and reports participation on an advisory board for GSK (November–December 2022) (personal consulting fee in relation to an advisory board regarding new data on dolutegravir-lamivudine and long-acting treatment with cabotegravir-rilpivirine), outside the present work. L. Y. reports other financial or nonfinancial interests with Merck Sharp & Dohme. J. M. L. has received payments or honoraria for lectures, presentations, or speakers bureau participation from Janssen-Cilag, Gilead Sciences, Thera Technologies, and ViiV Healthcare; consulting fees from and participation on a data safety monitoring or advisory board for Janssen-Cilag, Gilead Sciences, and ViiV Healthcare; and support for attending meetings from Gilead Sciences, outside the present work. A.C. reports grants or contracts (paid to institution) from ViiV

Healthcare, consulting fees, payment for speaking engagements, and participation on data safety monitoring or advisory boards for Janssen Cilag, Gilead, MSD, and ViiV Healthcare (alls support paid to author). All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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