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MAJOR ARTICLE

Plasma HIV-1 RNA and CD4+ T-cell counts are determinants of virological non-suppression 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 non-suppression outcomes in persons with HIV who initiate antiretroviral treatment (ART). We evaluated the impact of different baseline variables in the RESPOND cohort.

Methods: We included treatment-naïve 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: Out of 4,310 eligible participants, 72% initiated 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 of viral blips were 9·6%, LLV 2·1%, RV 22·2% and VF 2·1%. Baseline HIV-1 RNA >100,000 copies/mL and CD4+ count ≤200 cells/μL were negatively associated with VS at weeks 48 (aOR 0·51;95%CI:0·39-0·68 and 0·40;95%CI:0·27-0·58, respectively) and 96, and with significantly higher rates of blips, LLV and RV. CD4+ counts ≤200 cells/μL were associated with higher risk of VF (aHR 3·12;95%CI:2·02-4·83).

Results were consistent in those starting INSTIs versus other regimens and those initiating dolutegravir versus other INSTIs.

Conclusions: Initial high HIV-1 RNA and low CD4+ 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+ counts are associated with higher VF rates.These associations remain with INSTI- and specifically 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; dolutegravir.

PREVIOUS PRESENTATION OF PARTIAL DATA

Partial data of the manuscript have been previously publicly presented at the HIV Glasgow Drug The-rapy Congress, 23-26 October, 2022 [Abstract number 228].

BACKGROUND

Antiretroviral treatment (ART) durably suppresses plasma HIV-1 RNA to less than 50 copies/mL [1]. Virological non-suppression 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 of 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 VL ≥200 copies/mL and a viral blip as an isolated quantifiable HIV-1 RNA preceded and followed by virological suppression [14].

Virions can still be produced during ART-mediated suppression, with plasma HIV-1 RNA levels below 20-50 copies/mL [15]. It is unclear if 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 esta-blished 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 LLV within 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].

We aimed to examine baseline factors associated with virological non-suppression outcomes (blips, LLV, RV and VF) in treatment-naïve persons with HIV (PWH) who started a three-drug ART regimen in the INSTI era using a prospective multinational cohort consortium.

MATERIAL AND 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 (HICDEP) 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-naïve adults aged ≥18 years who initiated ART between January 1, 2014 and December 31, 2020, from 17 out of 19 cohorts. Participants had a CD4+ count measured and detectable plasma HIV-1 RNA value at ART initiation and a minimum follow-up time of 36 weeks.

Virological outcome definitions

VS: HIV-1 RNA <50 copies/mL at weeks 48 and 96, with a 12-week window on either side.

LLV: the first of at least two consecutive plasma HIV-1 RNA measurements of 50-199 copies/mL, fol-lowing VS.

Viral blip: an isolated plasma HIV-1 RNA of 50-199 copies/mL with a previous and a subsequent HIV-1 RNA <50 copies/mL, following VS.

RV: any detectable and quantifiable plasma HIV-1 RNA between 20 and 49 copies/mL, among participants with HIV-1 RNA measurement with a limit of detection of 20 copies/mL, following VS.

VF: the first of two consecutive plasma HIV-1 RNA ≥50 copies/mL, one of them ≥200 copies/mL, following VS.

Statistical methods

A descriptive analysis of participants' demographic and immuno-virological 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 on an intention-to-treat-exposed (ITT-e) 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 week 48 and 96, expressed as adjusted odds ratios (aORs) and 95% confidence intervals (CIs).

Kaplan-Meier curves estimated the time-to-viral blips, LLV, RV and VF, stratified by the third drug and comparison among curves was performed using log-rank test.

We used a survival analysis using Cox regression to assess the impact of baseline variables on virological non-suppression outcomes (i.e., viral blips, LLV, RV and VF). Associations were expressed as adjusted hazard ratios (aHRs) and 95% CIs.

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

Sensitivity analyses were performed for viral blips, LLV, RV and VF, restricted first to only 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 (Statistical Analysis Software, Cary, NC, US), version 9.4. All tests were two-tailed, and a significance level α was set at 0·05.

RESULTS

Baseline characteristics

We included 4,310 eligible ART-naïve participants (Figure 1). Eighty-four percent were male, 69·2% white race, 61·2% men who had sex with men, 42·6% from Central Europe, 89·8%

without prior AIDS, and 43·3% initiated ART in year 2014-15. The median age was 38 (IQR 30-47) years and 812 (18·8%) were >50 years old (Table 1).

The median follow-up from starting ART was 3·8 (IQR 2·4-5·1) years, with 16,106 person-years of follow-up, with a median of 8 (IQR 5-12) CD4+ count and 10 (IQR 6-14) HIV-1 RNA measurements.

The median CD4+ count was 378 (IQR 199-560) cells/μL. Overall, 1,971 participants (45·7%) had CD4+ counts ≤350 cells/μL at presentation and 1,092 (25·3%) had severe immunosuppression (CD4+ ≤200 cells/μL); 36·1% had HIV-1 RNA ≥100,000 copies/mL. Overall, 72·3% of participants initiated an INSTI-based regimen, of whom 1,970 (63·3%) initiated dolutegravir (Table 1).

Virological outcomes

VS at weeks 48 and 96 was achieved in 3,306/3,638 (90·9%, 95%CI: 89·9-91·8) and 2,908/3,118 (93·3%, 95%CI: 92·4-94·1) participants, respectively. At 48 weeks, Kaplan-Meier estimates of the proportion with viral blips were 9·6% (95%CI: 8·7-10·5), LLV 2·1% (95%CI: 1·6-2·5), RV 22·2% (95%CI: 20·0-24·3) and VF 2·1% (95%CI: 1·7-2·6).

Virological suppression

In multivariate analysis, darunavir (versus dolutegravir), baseline HIV-1 RNA >100,000 copies/mL and CD4+ ≤350cells/μL at ART initiation were associated with significantly lower VS rates at week 48 (Table 2).

At week 96, abacavir/ lamivudine (versus TDF/emtricitabine), raltegravir (versus dolutegravir), HIV-1-RNA >100,000 copies/mL and CD4+ ≤350cells/μL were associated with significantly lower VS rates (Table 2).

Viral blips

In time-to-blip analysis (Figure 2A), differences among third drugs favoured rilpivirine (p<0·0001) with a time-to-blip longer than raltegravir (p<0·0001). Darunavir and dolutegravir had similar time-to-blip (p=0·16).

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+ ≤350cells/μL. Baseline HIV-1 RNA levels paralleled blip incidence, with ≤10,000 copies/mL associated with lower rates whereas >100,000 copies/mL had the highest blip risk. We found no association between NRTIs or third drug and blip incidence (Figure 3A).

Within the subset initiating any INSTI-based regimen, female sex, age 41-50 years, Central European region, HIV-1 RNA >100,000 copies/mL and CD4+ ≤350cells/μL, remained

associated with blips. The same analysis restricted to dolutegravir-based regimens showed an association between HIV-1 RNA and CD4+ and blips (Tables S1/S2).

Low-level viremia

In time-to-LLV analysis (Figure 2B), differences among all third drugs favoured rilpivirine (p=0·0035) overall, with a longer time than raltegravir (p=0·0012) or dolutegravir (p=0·0007), and similar results for darunavir and dolutegravir (p=0·90).

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

These associations remained in the subset receiving INSTI-based regimens (female sex, Eastern European region, HIV-1 RNA >100,000 copies/mL, CD4+ ≤350 cells/μL). In the dolutegravir subset, HIV-1 RNA >100,000 copies/mL and CD4+ ≤500 cells/μL remained associated with LLV (Tables S1/S2).

Residual viremia

Time-to-RV analysis across third drugs favoured rilpivirine (p=0·0009) (Figure 2C). Darunavir showed a similar time-to-RV to rilpivirine (p=0·28) and longer than dolutegravir (p=0·012).

Eastern European region was associated with lower RV rates in multivariate analysis. TAF/emtricitabine (versus TDF/emtricitabine) was associated with higher RV incidence. Baseline HIV-1 RNA ≤10,000 copies/mL was associated with a lower RV rate, whereas >100,000 copies/mL and CD4+ ≤200 cells/μL were associated with the highest RV rates (Figure 4A).

Within the subset treated with INSTI- and specifically dolutegravir, Eastern European region and HIV-1 RNA but not CD4+, remained associated with RV (Tables S1/S2).

Virological failure.

In time-to-VF analysis (Figure 2D), differences among third drugs again favoured rilpivirine (p <0·0001). Raltegravir had a shorter time to VF than rilpivirine (p <0·0001), dolutegravir (p=0·0017) and darunavir (borderline significance, p=0·056).

In multivariate analysis, factors associated with higher VF rates (Figure 4B) were female sex, non-white race, chronic HCV, prior AIDS and Central European region, whereas age 31-50 years was associated with lower VF rates. A low baseline CD4+ (≤200 and 351-500 cells/μL) was associated with higher VF rates (Figure 4B), but intriguingly, HIV-1 RNA was not. Raltegravir use was associated with higher VF rates in multivariate analysis compared to dolutegravir,

whereas rilpivirine was not. TAF/emtricitabine (versus 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+. No association was found with HIV-1 RNA nor TAF/emtricitabine (Tables S1/S2).

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 non-suppression 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 (versus dolutegravir) was associated with a significantly lower pro-bability of VS at week 48, but this association was lost at week 96. PIs have slower initial viral load decay kinetics as compared with INSTIs, particularly with high baseline HIV-1 RNA, as shown in randomized clinical trials [26,27] and cohort studies [28]. In our study, abacavir/lamivudine, higher HIV-1 RNA and lower CD4+ were associated with lower rates of VS at 96 weeks. Abacavir/lamivudine was associated with a significantly shorter time-to-VF versus TDF/emtricitabine combined with either boosted atazanavir or efavirenz in the ACTG A5202, in strata of HIV-1 RNA $\geq$100,000 copies/mL and CD4+ <200 cells/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 or low CD4+ count and blip incidence in the overall cohort and in participants initiating an INSTI- and dolutegravir-based regimen. This is consistent with previous cohorts [23,24]. In turn, blip rates were higher with PI-based ART and lower with INSTI-based ART. However, there could have been a channelling prescription bias of PIs to higher-risk PWH based on their perceived higher barrier to resistance [24]. We found no asso-ciation 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 and low CD4+ count was also seen with LLV overall, with any INSTI- or dolutegravir-based regimens. These findings are in agreement with a Spanish cohort [31] showing that plasma HIV-1 RNA >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 and low CD4+ were also associated with increased rates of RV. In our analysis, the association with HIV-1 RNA remained in participants receiving any INSTI and dolutegravir in parti-cular, consistent with a previous French cohort [32].

Interestingly, while low CD4+ counts were significantly associated with VF, high baseline HIV-1 RNA was not. This finding is consistent with a French cohort [11], with no relationship between baseline HIV-1 RNA and VF. In addition, HIV-1 RNA >100,000 copies/mL did not impact 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 $\geq$100,000 copies/mL on INSTI-based regimens. However, both cohorts used 50copies/mL thresholds for VF, therefore many VFs could have been LLV. Other recent analysis has found an association between baseline HIV-1 RNA and VF (HR 1·1;95%CI:1·0-1·2) [2], but using a broader definition of VF.

In our analysis,TAF (compared to TDF) was associated with higher rates of RV, but a lower risk of VF. TAF showed superior virological efficacy compared to 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 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+ counts, but we did not have access to dosing data for raltegravir in RESPOND [36,37]. In a recent European cohort analysis, INSTI- or NNRTI-based ART had similar rates of VF, whereas PI-based ART was associated with increased risk of VF [2].However, every single drug within a class was not assessed due to the limited number of virological outcome events.

Results were consistent regarding HIV-1 RNA and CD4+ count in those starting INSTIs versus other ART classes or those initiating dolutegravir (compared to other individual INSTIs), for every virological non-suppression outcome. These findings strongly suggest that HIV-1 RNA and CD4+ 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 only associated with a low baseline CD4+ count. All these findings support that the interaction between the HIV reservoir established before ART initiation and the rates of viral blips, LLV and RV seem to be closely related to baseline HIV-1 RNA but not with the type of ART administered, including the second generation INSTIs [18, 38-40]. HIV-1 integrated into silent chromosomal sites in deep latency of clonally expanded infected T cells can harbour defective proviruses and less likely intact (replication-competent) viruses, which are not affected by ART [41,42]. Non-suppressible residual viremia has been associated with large HIV reservoir size [43,44]. In addition, nadir CD4+ count was inversely correlated with levels of both

cell associated-DNA and cell associated-RNA in a pooled analysis of ACTG treatment interruption studies [38].

In our study, the time-to virological non-suppression 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. Rilpivirine plus 2 NRTIs has been approved only for PWH with HIV-1 RNA <100,000 copies/mL and is not recommended with CD4+ <200 cells/μL, supporting a likely channelling prescription bias as it is preferentially prescribed in PWH with characteristics associated with better virological outcomes [14,45]. The Italian ICONA cohort compared rilpivirine- and INSTI-based first-line regimens in participants with HIV-1 RNA <100,000 copies/mL and CD4+ >200cells/μL and found no differences in virological rebound rates [46].

We identified higher rates of VF in PHW with non-white race. This is probably associated with higher rates of immigration, socio-economic 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 two-drug regimen dolutegravir/lamivudine and the new NNRTI doravirine were not included due 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 this 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 non-suppression outcomes not explored in randomized trials, using strict definitions.

In conclusion, baseline plasma HIV-1 RNA >100,000copies/mL and CD4+ ≤350cells/μL were associated with lower rates of VS at 48 and 96 weeks, and higher rates of viral blips, RV and LLV. CD4+ ≤200cells/μL was associated with a higher risk of VF. Importantly, the association between HIV-1 RNA or CD4+ count with these virological outcomes persisted in participants initiating INSTI- and specifically dolutegravir-based regimens. These data suggest that baseline HIV-1 RNA and CD4+ count are determinants associated with virological non-suppression outcomes regardless of the antiretroviral regimen initiated and point to underlying mechanisms established prior to the initiation of ART, likely focused on the HIV reservoir size.

Further research is warranted to explore the impact of bictegravir/emtricitabine/TAF, doravirine and INSTI-based two-drug regimens on long-term virological non-suppression outcomes.

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6.

FIGURE LEGENDS:

Figure 1: Flow Chart

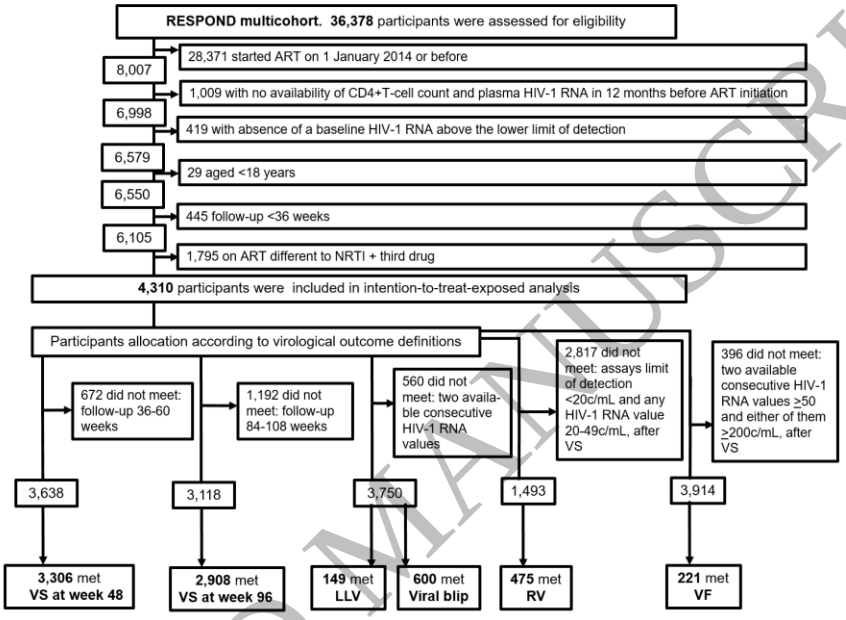


Figure 2: Time-to-Blip Analysis

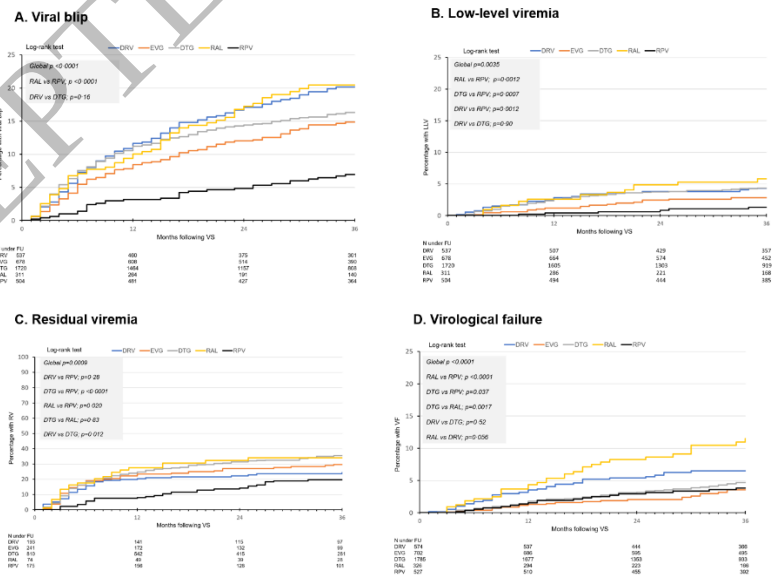


Figure 3: Blip Incidence

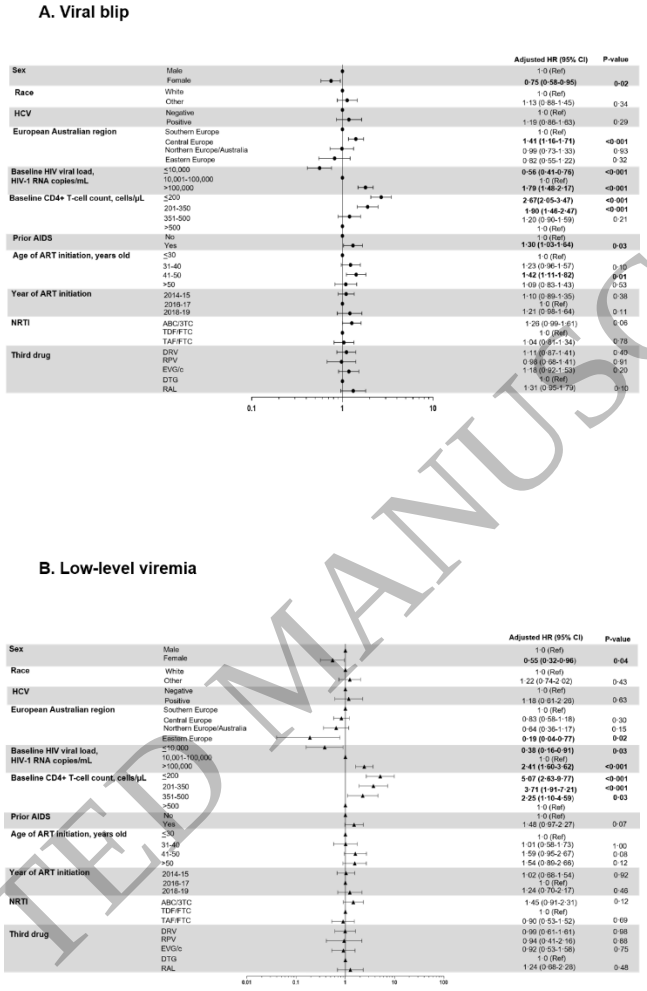
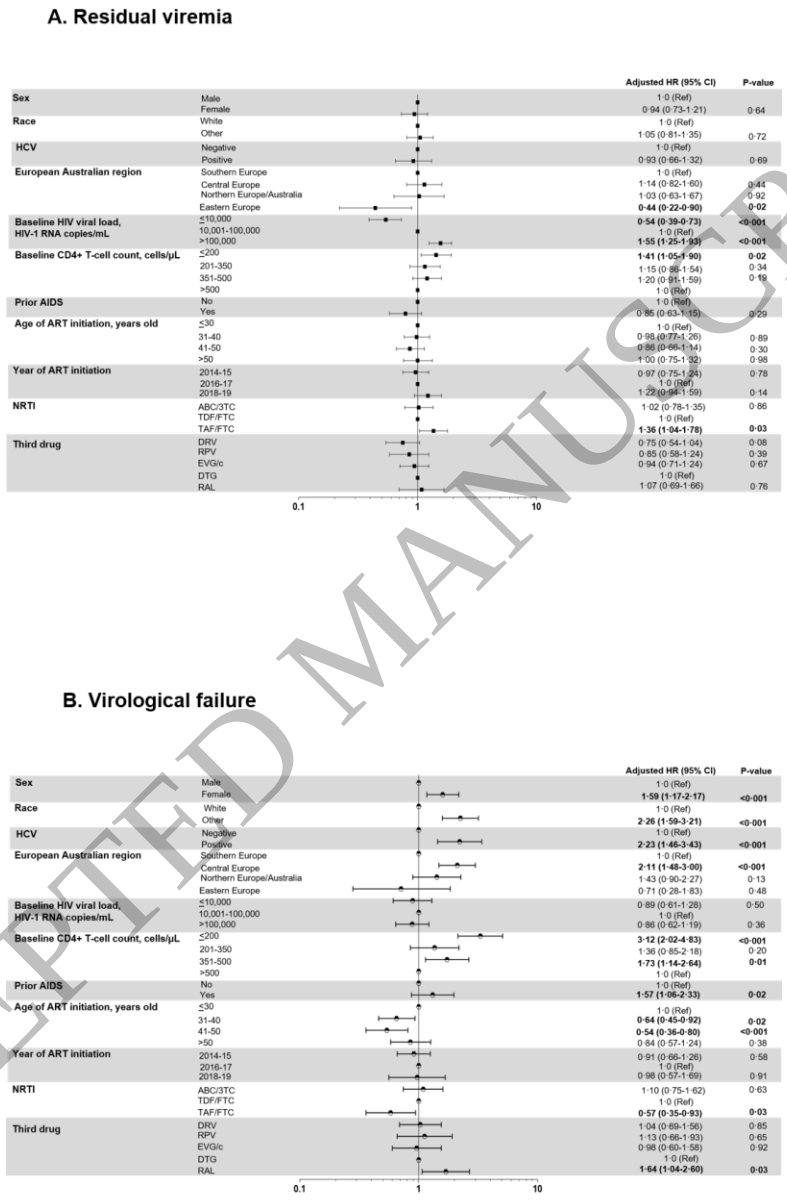


Figure 4: Multivariate Analysis



	Overall (n=4,310)	DRV-based (n=641)	RPV-based (n=555)	EVG/c-based (n=771)	DTG-based (n=1,970)	RAL-based (n=373)
Sex· n (%)						
Male	3,614 (83·9)	503 (78·5)	465 (83·8)	692 (89·8)	1,678 (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 · n (%)						
MSM	2,636 (61·2)	327 (51·0)	354 (63·8)	543 (70·4)	1,223 (62·1)	189 (50·7)
Heterosexual	1,206 (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· n (%)						
White	2,982 (69·2)	419 (65·4)	416 (75·0)	481 (62·4)	1,423 (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)· n (%)						
Negative	3,257 (75·6)	457 (71·3)	429 (77·3)	569 (73·8)	1,579 (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 (antibodies)· n (%)						
Negative	3,077 (71·4)	424 (66·1)	429 (77·3)	516 (66·9)	1,492 (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)
European Australian region· n (%)						
Southern Europe	1,461 (33·9)	209 (32·6)	302 (54·4)	309 (40·1)	561 (28·5)	80 (21·4)
Central Europe	1,835 (42·6)	268 (41·8)	201 (36·2)	246 (31·9)	1,009 (51·2)	111 (29·8)
Northern Europe/ 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 (kg/m^2)· n (%)						
≤18	117 (2·7)	19 (3·0)	6 (1·1)	20 (2·6)	60 (3·0)	12 (3·2)
18·1-25	1,693 (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· n (%)						
Never	1,173 (27·2)	173 (27·0)	135 (24·3)	240 (31·1)	562 (28·5)	63 (16·9)
Current	1,416 (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	1,543 (35·8)	274 (42·7)	207 (37·3)	243 (31·5)	572 (29·0)	247 (66·2)
Prior AIDS· n (%)						
No	3,872 (89·8)	562 (87·7)	544 (98·0)	721 (93·5)	1,751 (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 (years old)· n (%)						
≤30	1,029 (23·9)	142 (22·2)	118 (21·3)	184 (23·9)	500 (25·4)	85 (22·8)
31-40	1,388 (32·2)	211 (32·9)	206 (37·1)	251 (32·6)	612 (31·1)	108 (29·0)
41-50	1,081 (25·1)	171 (26·7)	151 (27·2)	192 (24·9)	483 (24·5)	84 (22·5)
>50	812 (18·8)	117 (18·3)	80 (14·4)	144 (18·7)	375 (19·0)	96 (25·7)
Median age at ART initiation, years old (IQR)	38 (30-47)	38 (31-48)	38 (31-46)	38 (30-47)	38 (30-47)	39 (31-50)

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Year of ART initiation · n (%)						
2014-15	1,866 (43·3)	407 (63·5)	371 (66·8)	350 (45·4)	556 (28·2)	182 (48·8)
2016-17	1,627 (37·7)	142 (22·2)	140 (25·2)	318 (41·2)	899 (45·6)	128 (34·3)
2018-19	817 (19·0)	92 (14·4)	44 (7·9)	103 (13·4)	515 (26·1)	63 (16·9)
	Overall (n=4,310)	DRV-based (n=641)	RPV-based (n=555)	EVG/c-based (n=771)	DTG-based (n=1,970)	RAL-based (n=373)
Baseline HIV viral load (HIV-1 RNA copies/mL)[a] · n (%)						
≤ 10,000	971 (22·5)	105 (16·4)	234 (42·2)	152 (19·7)	403 (20·5)	77 (20·6)
10,001- 99,999	1,782 (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)
Median HIV-1 RNA $\log_{10}$ copies/mL (IQR)	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)
Baseline CD4 + T-cell count (cells/μL)[a]· n (%)						
≤100	633 (14·7)	148 (23·1)	4 (0·7)	75 (9·7)	323 (16·4)	83 (22·3)
101-200	459 (10·6)	81 (12·6)	18 (3·2)	70 (9·1)	231 (11·7)	59 (15·8)
201-350	879 (20·4)	147 (22·9)	108 (19·5)	164 (21·3)	393 (19·9)	67 (18·0)
351-500	988 (22·9)	122 (19·0)	183 (33·0)	205 (26·6)	418 (21·2)	60 (16·1)
>500	1,351 (31·3)	143 (22·3)	242 (43·6)	257 (33·3)	605 (30·7)	104 (27·9)
Median CD4+ T-cell count, cells/μL (IQR)	378 (199-560)	293 (109-473)	480 (359-633)	404 (250-587)	366 (175-554)	300 (121-530)
Comorbidities· n (%)						
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 NADM	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 · n (%)						
NRTI						
ABC/3TC	908 (21·1)	111 (17·3)	0 (0·0)	0 (0·0)	797 (40·5)	0 (0·0)
TDF/FTC	2,417 (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	1,970 (45·7)	-	-	-	-	-
RAL	373 (8·7)	-	-	-	-	-
Booster						
None	2,898 (67·2)	0 (0·0)	555 (100·0)	0 (0·0)	1,970 (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: MSM, men who have sex with men; IDU, injection drug user; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; BMI, body mass index; AIDS, acquired immunodeficiency syndrome, referred as AIDS-defining illness; CVD, cardiovascular disease; NADM, non-AIDS-defining malignancies; ESLD, end-stage liver disease; CKD, chronic kidney disease; ART, antiretroviral treatment; NRTI, nucleos(t)ide reverse transcriptase inhibitor; ABC, abacavir; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; TAF, tenofovir alafenamide; DRV, darunavir; RPV, rilpivirine; EVG/c, elvitegravir/cobicistat; DTG, dolutegravir; RAL, raltegravir

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

Table 1. Baseline characteristics of participants in the Intention-to-treat exposed population.

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Table 2. Logistic regression analysis (multivariate) of factors associated with virological suppression at week 48 and 96, for all participants included.

Virological outcomes All participants	Virological suppression week 48		Virological suppression week 96	
	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Sex				
Male	1·0 (Ref)		1·0 (Ref)	
Female	1·16 (0·83-1·61)	0·40	0·81 (0·56-1·18)	0·27
Race				
White	1·0 (Ref)		1·0 (Ref)	
Other	0·80 (0·55-1·16)	0·23	0·80 (0·51-1·26)	0·34
HCV				
Negative	1·0 (Ref)		1·0 (Ref)	
Positive	**0·46 (0·32-0·68)**	**<0·001**	0·64 (0·38-1·05)	0·08
European Australian region				
Southern Europe	1·0 (Ref)		1·0 (Ref)	
Central Europe	0·87 (0·65-1·15)	0·32	1·00 (0·71-1·41)	0·99
Northern Europe/ Australia	0·90 (0·60-1·34)	0·60	1·30 (0·80-2·12)	0·29
Eastern Europe	0·74 (0·45-1·21)	0·23	0·88 (0·44-1·75)	0·72
Baseline HIV viral load[a], HIV-1 RNA copies/mL				
≤10,000	1·19 (0·80-1·76)	0·39	1·41 (0·87-2·27)	0·16
10,001-100,000	1·0 (Ref)		1·0 (Ref)	
>100,000	**0·51 (0·39-0·68)**	**<0·001**	**0·69 (0·49-0·97)**	**0·03**
Baseline CD4+ T-cell count[a], cells/µL				
≤200	**0·40 (0·27-0·58)**	**<0·001**	**0·35 (0·22-0·55)**	**<0·001**
201-350	**0·58 (0·39-0·84)**	**<0·001**	**0·48 (0·30-0·76)**	**<0·001**
351-500	0·91 (0·60-1·38)	0·66	1·13 (0·67-1·93)	0·64
>500	1·0 (Ref)		1·0 (Ref)	
Prior AIDS				
No	1·0 (Ref)		1·0 (Ref)	
Yes	0·72 (0·52-1·00)	0·05	0·73 (0·48-1·12)	0·15
Age of ART initiation, years old				
≤30	1·0 (Ref)		1·0 (Ref)	
31-40	0·95 (0·68-1·34)	0·78	1·04 (0·68-1·58)	0·85
41-50	1·17 (0·81-1·67)	0·40	1·40 (0·88-2·21)	0·15
>50	0·87 (0·60-1·25)	0·44	0·77 (0·50-1·20)	0·26
Year of ART initiation				
2014-15	1·17 (0·87-1·58)	0·30	0·93 (0·65-1·34)	0·70
2016-17	1·0 (Ref)		1·0 (Ref)	
2018-19	0·74 (0·55-1·11)	0·14	0·68 (0·42-1·08)	0·10
NRTI				
ABC/3TC	0·85 (0·60-1·19)	0·34	**0·46 (0·30-0·69)**	**<0·001**
TDF/FTC	1·0 (Ref)		1·0 (Ref)	
TAF/FTC	1·19 (0·84-1·69)	0·33	0·97 (0·61-1·53)	0·88
Third drug				
DRV	**0·63 (0·45-0·87)**	**0·01**	0·65 (0·43-1·00)	0·05
RPV	0·99 (0·57-1·71)	0·96	0·66 (0·34-1·26)	0·20
EVG/c	1·08 (0·72-1·62)	0·70	0·66 (0·41-1·07)	0·09
DTG	1·0 (Ref)		1·0 (Ref)	
RAL	0·79 (0·51-1·23)	0·29	**0·52 (0·29-0·90)**	**0·02**

Abbreviations: OR, odds ratio; CI, confidence interval; HCV, hepatitis C virus infection; AIDS, acquired immunodeficiency syndrome, referred as AIDS-defining illness; ART, antiretroviral treatment; NRTI, nucleos(t)ide reverse transcriptase inhibitor; ABC, abacavir; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; TAF, tenofovir alafenamide; DRV, darunavir; RPV, rilpivirine; EVG/c, elvitegravir/cobicistat; DTG, dolutegravir; RAL, raltegravir. Statistically significant values of variables are highlighted in bold.

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