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Real world efficacy of dolutegravir plus lamivudine in PLWH with undetectable viral load after previous failures

Roberta Gagliardini¹, Patrizia Lorenzini ¹, Alessandro Cozzi-Lepri ², Alessandro Tavelli³, Vanni Borghi⁴, Laura Galli ⁵, Gianmarco Tagliaferri⁶, Franco Maggiolo⁷, Cristina Mussini⁴, Antonella Castagna⁵, Antonella d'Arminio Monforte⁶, Andrea Antinori¹, for the Icona Foundation Study Group

1-IRCCS Lazzaro Spallanzani, Rome, Italy;  
2-University College London, London, UK;  
3- Icona Foundation, Milan;  
4- Azienda Ospedaliera Universitaria Policlinico di Modena, Modena, Italy;  
5- Infectious Diseases Clinic, IRCCS San Raffaele, Milan, Italy;  
6- ASST Santi Paolo e Carlo, Department of Health Sciences, University of Milan, Milan, Italy;  
7- Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy;  
8- San Raffaele Vita-Salute University, Milan, Italy.

Correspondence  
Corresponding author:  
Roberta Gagliardini  
UOC Immunodeficienze Virali  
INMI Lazzaro Spallanzani, IRCCS  
via Portuense 292 - 00149 Rome  
Tel: +39 0655170368  
Fax: +39 06 55170477  
email: roberta.gagliardini@inmi.it

Keywords  
HIV-1, antiretroviral therapy, switch therapy, two-drug regimens, integrase inhibitors.
Highlights

- In this large multi-cohort Italian studies, 20% of maintenance therapy with dolutegravir + lamivudine was prescribed in patients with previous history of virological failure.
- The overall incidence rate of virological failure dolutegravir + lamivudine was 1.5 per 100 PYFU (95% CI 1.0-2.3).
- Despite the low absolute 1-year risk in both groups, real-world data confirmed that PLWH with a previous failure have an increased risk of viral rebound.

Abstract

Background
Dolutegravir (DTG) + lamivudine (3TC) combination has shown to be as effective as triple therapy as maintenance therapy and has been extensively prescribed in clinical practice. We aimed to investigate the impact of previous virological failures (VF) on virological efficacy.

Methods
The analysis included data of PLWH with HIV-RNA ≤ 50 copies/mL enrolled in an Italian retrospective multi-cohort study, switching to DTG+3TC. Primary endpoint was viral rebound (VR, confirmed HIV-RNA ≥ 50 copies/mL or a single HIV-RNA ≥ 50 copies/mL followed by change of ART). Kaplan-Meier curves were used to estimate probabilities of VR according to history of previous VF (single HIV-RNA >=1000 or confirmed HIV-RNA >=50 copies/mL). A weighted Cox regression model was fitted to estimate the causal hazard ratio (HR) of history of failure on the risk of VR.

Results
A total of 966 PLWH were included, 20.1% of them with history of previous VF. VR was detected in 23 PLWH. The 1-year probability was 1.2% (95% CI 0.2%-2.2%) in PLWH without previous VF and 3.3% (95% CI 0.4%-6.2%) in those with >= 1 VF (log-rank p=0.042). By multivariate analysis adjusted for CD4+ cells count at nadir, duration of virological suppression and mode of HIV transmission, PLWH with >= 1 previous VF had a higher risk of virological rebound than those without previous VF (adjusted HR 3.06 [95% CI 1.00-9.44], p=0.051).

Conclusions
Despite the low absolute 1 year risk in both groups, real-world data confirmed that PLWH with a previous failure have an increased risk of viral rebound.
Introduction

As HIV has become a chronic condition, there is a growing interest in simpler, more tolerated antiretroviral therapies (ART). In this context, two-drug regimens (2DR) for maintenance therapy in people living with HIV (PLWH) have been developed and are increasingly used in clinical practice. 2DR with dolutegravir (DTG) plus lamivudine (3TC) resulted effective as maintenance therapy in randomized trials [1,2] in a selected population of PLWH virologically suppressed, with no prior virological failures and no documented nucleos(t)ide reverse-transcriptase inhibitors (NRTI) or integrase inhibitors (INSTI) resistance mutations at pre-treatment genotype. Many cohort studies conducted mainly in Europe confirmed the high virological efficacy for dolutegravir plus lamivudine combination in different real-life settings [3–9]. Different co-factors such as quantitative HIV-DNA, CD4+ T cells count at nadir, duration of virological suppression, specific previous resistance mutations and previous failures could contribute to a possible different risk of virological failure with 2DR [10]. Interestingly, real-life data revealed that a relevant proportion of all 2DR prescriptions are in PLWH with a history of virological failures (VF), up to 14% considering dolutegravir plus lamivudine combination [11]. However, limited data about the prevalence of use and virological potency of DTG+3TC in target populations with a history of previous virological failures and/or previous detection of resistance mutations are available to date. Relevant data came from the Dolulam study, a small prospective study of dolutegravir +lamivudine as switch strategy, where the detection of NRTI mutations at least once in RNA/DNA genotypes in more than half of the patients did not alter the probability of maintaining virological suppression [12]. More recently, a prospective pilot study assessed the switch strategy to DTG+3TC in patients with and without previously acquired lamivudine resistance. This regimen resulted to be effective in maintaining virological suppression despite the presence of lamivudine resistance mutations
in cumulative genotype and the presence of archived mutations assessed by next-generation sequencing [13]. In two retrospective studies, M184V/I lamivudine resistance mutation was found in the historical genotype in 9-17% of virologically suppressed PLWH switched to DTG+3TC and no clear impact on risk of virological failure was found, even though some concerns for viral blips and for viral efficacy in the context of short time of viral suppression were raised [6,14,15]. The purpose of this study was to explore the virological potency of DTG+3TC in patients with and without prior virological failures, estimating the risk of viral rebound and evaluating whether there was an association between this risk and history of previous failure.

Methods

We conducted a retrospective cohort study including patients enrolled in Icona Foundation Study or in five Italian monocentric clinical databases (National Institute for Infectious Diseases L. Spallanzani of Rome, Azienda Ospedaliera San Paolo of Milan, Azienda Ospedaliera Universitaria Policlinico of Modena, San Raffaele Hospital in Milan, Azienda Ospedaliera Papa Giovanni XXIII of Bergamo) satisfying a common sets of inclusion criteria. ICONA Foundation Study is a multi-centre prospective observational study of HIV-1-infected patients. The ICONA Foundation study has been approved by Institutional Review Boards of all the participating centres; sensitive data from patients are seen only in aggregate form. Demographic, clinical and laboratory data and information on therapy are collected for all participants and recorded using electronic data collection [www.icona.org].

All patients signed a consent form to participate in the cohorts, in accordance with the ethical standards of the committee on human experimentation and the Helsinki Declaration (last amendment October 2013). All information, including virological and therapeutic data, was recorded and merged in an anonymized database.

Patients were included in this analysis if the following inclusion criteria were satisfied: >=18 years of age, currently receiving ART (regardless of the type of regimen), starting for the first time DTG 50 mg plus 3TC 300 mg as two-pills or single-pill regimen, with a current HIV-1 RNA < 50 copies/mL, with known history of ART regimens use and with at least one virological follow-up visit within 6 months thereafter.

Primary study endpoint was defined as the composite outcome of a confirmed HIV-RNA ≥ 50 copies/mL on DTG+3TC (with or without ART change) or a single HIV-RNA ≥ 50 copies/mL on DTG+3TC followed by change of ART.
Secondary endpoint was the cumulative probability of viral blips (VB, a single HIV-RNA ≥ 50 copies/mL followed by a value ≤50 without a change of ART).
We also considered an alternative endpoint in which viral rebound was defined as the first confirmed HIV-RNA ≥ 50 copies/mL.
The follow-up accrued from baseline (BL, time of switch to DTG+3TC) to the occurrence of the outcome or last observation or DTG+3TC discontinuation, whichever comes first.
Two different definitions of past virological failure were applied, defined as having experienced a single HIV-RNA ≥ 1000 copies/mL or confirmed HIV-RNA ≥ 50 copies/mL on any ART previous to BL (I) or on a NRTI or INSTI-containing regimen (II).
A sensitivity analysis excluding PLWH with incomplete history of viral load data, defined as one year or more gap in HIV-RNA measurements, was also performed.
For the statistical analysis, differences between groups in characteristics at baseline were assessed by means of Chi-square or Wilcoxon rank sum (Mann-Whitney) test, as appropriate. Kaplan Meier survival method was used to estimate the cumulative proportion of patients experiencing the study endpoints, with corresponding 95% confidence interval (CI); differences between groups were evaluated by the log-rank test.
We used a Cox proportional hazard models with censoring weights and with exposure (past virological failure) weights to estimate the hazard ratios (HRs) for each outcome. To reduce the potential confounding effect of the different distribution of characteristics in exposed and not exposed to past virological failure and of the distribution of censoring on the outcome, we calculated inverse probability of weights and of censoring weights using two separate logistic regression models. We fitted a pooled logistic regression model weighted for inverse probability of both stabilized weights. Confounding variables analysed were CD4+ cells count at nadir (equal/higher or lower than 350 cells/mmc), duration of virological suppression and mode of HIV transmission.
All statistical analyses were performed with STATA, version 15.1, College Station, Texas USA.

Results
A total of 966 PLWH were included in the analysis and their baseline characteristics are shown in Table 1. Of them, 248 (25.7%) were females, median age was 51 years (interquartile range, IQR 44-57), 150 (15%) were CDC-C stage, their median CD4+ cells count at nadir was 247 cells/mmc (IQR 98-372), median time of HIV-RNA suppression before switching to DTG+3TC was 7 years (IQR 3-12).
Seven hundred and seventy-two (79.9%) of them had no previous VF to any ART and 194 (20.1%) had at least one previous VF (12% had 1 previous VF, 4% had 2 VF, 3% had 3 VF and 1% had 4 VF or more).

Significant differences between history of previous failure to any ART groups at baseline were observed with respect to age, mode of HIV transmission, CDC-C stage (13.9% in PLWH without previous VF versus 22.2% in PLWH with at least one previous VF, p=0.017), co-infections, CD4+ cells count at nadir (268 cells/mm in PLWH without previous VF versus 165 cells/mm in PLWH with at least one previous VF, p<0.001), duration of HIV infection, of ART exposure and of HIV-RNA suppression (all longer in PLWH with at least one previous VF), number of therapeutic lines (higher in PLWH with at least one previous VF) and last ART regimens pre-switch (Table1). Median observation time was 15 months (IQR 6-32).

Seven hundred and eighty (80.1%) participants had no previous VF to NRTI or INSTI and 186 (19.2%) had at least one previous VF to these classes of antiretrovirals.

The study population included in the sensitivity analysis (excluding PLWH with incomplete history of viral load data) consisted of 667 PLWH, with baseline characteristics similar to those described above (Table 1 in Supplementary material).

Virological rebound

Virological rebounds defined as confirmed HIV-RNA ≥ 50 copies/mL or a single HIV-RNA ≥ 50 copies/mL followed by change of ART occurred in 23 patients (14 in PLWH without previous VF and 9 in PLWH with at least one previous VF), over 1504 person-year follow-up (PYFU), for an overall incidence rate (IR) of 1.5 per 100 PYFU (95% CI 1.0-2.3). This rate was 1.2 x 100 PYFU (95% CI 0.7-2.0) in PLWH without previous VF and 2.4 x 100 PYFU (95% CI 1.2-4.9) in PLWH with at least one previous VF.

As median, VF occurred after 245 days (IQR 203-404) from the switch to DTG+3TC and with 74 copies/ml (IQR 58-92). All but one VF occurred with HIV-RNA < 1000 copies/ml.

The cumulative estimated probability of virological rebound according to the presence or not of ≥1 previous virological failure to any ART was 1.2% (95% CI 0.2%-2.2%) in PLWH without previous VF versus 3.3% (95% CI 0.4%-6.2%) in PLWH with at least one previous VF at one year and 3.3% (95% CI 1.5%-5.1%) versus 5.2% (95% CI 1.2%-9.1%) at two years (p=0.042).

For the alternative endpoint in which viral rebound was defined as confirmed HIV-RNA ≥ 50 copies/mL, 15 events over 1504 PYFU were detected, with an IR of 1.0 x 100 PYFU (95% CI 0.6-1.6).
In this context, the cumulative estimated probability of virological rebound was 0.6% (95% CI 0.1%-1.2%) in PLWH without previous VF versus 2.1% (95% CI 0.0%-4.5%) in PLWH with at least one previous VF to any ART at one year (p=0.094). Risks of viral rebound from fitting a separate Cox regression model according to previous VF are also shown in Table 2. After controlling for potential confounding factors, participants with at least one previous VF showed a tendency for a higher risk of virological rebound than those without previous VF to any ART, even if not statistically significant (adjusted HR, aHR of 3.06 [95% CI 1.00-9.44], p=0.051) (Table 2). Participants with exactly one previous VF had aHR 4.20 (95% CI 1.36-12.94). Similar risks were observed throughout the other analyses, including the sensitivity ones and with different definition of VF that include only VF to NRTI or INSTI, and aHR was 3.52 (95% CI 0.75-16.53) for the alternative endpoint in which viral rebound was defined as confirmed HIV-RNA ≥ 50 copies/mL (Table 2).

**Viral blips**

Viral blips occurred in 59 PLWH, with an IR of 4.0 x 100 PYFU (95% CI 3.1-5.2). One-year cumulative estimated probability of viral blips was 3.9% (95% CI 2.3%-5.5%) in PLWH without previous VF versus 3.5% (95% CI 0.6%-6.4%) in PLWH with at least one previous VF to any ART (p=0.486). Again, results were similar in the sensitivity analysis restricted to people with more complete virological monitoring before the date of switch.

By multivariable analysis, after controlling for the same set of potential confounding factors, PLWH with at least one previous VF to any ART had a higher risk of having viral blips than those without previous VF (aHR of 1.81 [95% CI 0.95-3.42], p=0.069) (Table 2). Similarly, restricting the analysis to those with complete history of viral load data (sensitivity analysis), PLWH with at least one previous VF to any ART confirmed to have a higher risk of viral blips, aHR 2.64 (95% CI 1.18-5.90) (p=0.018). Moreover, PLWH with at least one previous VF to NRTI or INSTI had a statistically significant higher risk of having viral blips than those without previous VF in the sensitivity analysis analysis (aHR 2.70 [95% CI 1.22-6.15], p=0.014), not confirmed in the analysis in the overall population (aHR 1.68 [95% CI 0.87-3.22], p=0.121).

The risk of viral blips from fitting a separate Cox regression model according to the exact number of previous VF to any ART (1 VF versus 0 and ≥2 versus 0), suggest too a greater risk for patients with one or two previous virological failure, but the results were not statistically significant.

**Discussion**
Herein we report a multi-cohort study aiming to evaluate the virological potency of 2DR with dolutegravir plus lamivudine in virologically suppressed patients in the real-life setting, in an ad hoc collaboration constructed for this specific query.

We found that one-year probability of viral rebound was low regardless of the chosen definition of viral rebound and comparable to the estimate provided in two meta-analysis of studies including dolutegravir-based 2DR (0.7%, 95% CI 0.4-1.3 and 1.3% 95% CI 0.6-2.1)[3,16]. It needs to be noted that the first meta-analysis included 2DR regimens based on DTG but with also other companion drugs besides lamivudine, such as rilpivirine, atazanavir or darunavir.

In our analysis, notwithstanding the optimal virological potency demonstrated, the risk of viral rebound appeared to be increased in PLWH with previous virological failures, especially in those with one VF in comparison to those without previous VF. In a lesser extent, even the risk of viral blips appeared to be increased in PLWH with previous VF.

It is possible that PLWH with a history of previous virological failures are also those having lower adherence to ART. Indeed it has been previously shown that patients experiencing ART treatment failure remain at higher risk of failing subsequent regimens and poor adherence is a major determinant of this outcome [17,18].

Previous virological failure was shown to predict future virological outcome in another large retrospective study including any ART [19] and in one study including dolutegravir plus rilpivirine [20], but not in another study of patients switching to triple therapy with 2NRTI plus DTG [21].

It has to be highlighted that in our dataset, DTG+3TC regimen has been prescribed also in patients with history of previous VF (about 20% of this population), in a proportion higher than elsewhere reported [11,22]. Although this is somewhat surprising giving the current guidelines, having a larger prevalence facilitated the success of this analysis. In contrast, other retrospective studies, with smaller sample size, reported that DTG+3TC was prescribed in an even greater proportion of patients with previous VF (44%-51%)[5,23] but this was not associated with a higher risk of treatment failure [5]. Of note, these switches are made in clinical practice beyond commercial label therapeutic indications which recommend the switch only patients with no known or suspected resistance to the INSTI class or to lamivudine [24,25].

Our study presents some limitations. First of all, because it is retrospective and observational, we cannot rule out unmeasured confounding. In particular, neither a measure of patients’ adherence nor genotype resistance tests (GRT) results were available in our dataset. Missing of adherence data is a common issue for many large cohort databases, but Icona Foundation Cohort is putting an effort to fill the gap by implementing an app developed for evaluation of Patients’ Reported Outcomes (PROs) in PLWH (E-qol app). Moreover, our study does not allow the evaluation of the impact of
archived resistance mutations, in particular of M184V, on the risk of virological failure, because cumulative GRTs were not available. We were unable to evaluate whether the switch to 2DR was guided by GRT and if patients with previous VF had or not archived resistance mutations at time of switch to control for these likely confounding factors.

Furtherly, despite the large sample size of the cohort including most of people treated with this combination in Italy who are included in epidemiological studies, the number of rebounds events was extremely small to allow a comprehensive evaluation of confounding. Considering the exact number of previous VF, having exactly one previous VF is a predictor of viral rebound but not of viral blip, thus larger sample could be helpful to better categorize the impact of number of previous virological failure and to show if a dose-response relationship exists. Moreover, a comparison with 3-drug regimens (3DR) dolutegravir-based was not performed. Consequently, we cannot exclude that PLWH with a previous failure may also have an increased risk of viral rebound under a 3DR, but recent Canadian observational data failed to demonstrate this association when switching to dolutegravir plus 2 NRTIs [21].

On the other hand, key strengths of this work are that past history of virological failures were accurately defined and the results of the secondary and sensitivity analysis were largely consistent with those of the main analysis.

To conclude, DTG+3TC demonstrated high virological efficacy but should be cautiously used in PLWH with a history of virological failure. In fact, previous history of failure was associated with higher risk of viral rebound and viral blips.

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Ethical approval: All patients signed a consent form to participate in the cohorts, in accordance with the ethical standards of the committee on human experimentation and the Helsinki Declaration (last amendment October 2013).
Authorship: RG, PL, ADM and AA design the study; PL interpretated the data; AT acquired data; RG, ACL, AT, VB, AC, FM, LG, GT and CM drafted and revised the article. All authors have approved the final article

References


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Table 1: Characteristics of the overall population and of the two groups at baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall population N=966</th>
<th>No previous virological failure to any ART N=772</th>
<th>≥1 previous virological failure to any ART N=194</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender, n(%)</td>
<td>248 (25.7%)</td>
<td>189 (24.5%)</td>
<td>59 (30.4%)</td>
<td>0.091</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>51 (44-57)</td>
<td>50 (42-57)</td>
<td>53 (49-58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mode of HIV transmission, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>heterosexual</td>
<td>340 (35.2%)</td>
<td>274 (35.5%)</td>
<td>66 (34.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVDU</td>
<td>146 (15.1%)</td>
<td>94 (12.2%)</td>
<td>52 (26.8%)</td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>356 (36.9%)</td>
<td>307 (39.8%)</td>
<td>49 (25.3%)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>124 (12.8%)</td>
<td>97 (12.5%)</td>
<td>27 (13.9%)</td>
<td></td>
</tr>
<tr>
<td>CDC stage C, n(%)</td>
<td>150 (15.5%)</td>
<td>107 (13.9%)</td>
<td>43 (22.2%)</td>
<td>0.017</td>
</tr>
<tr>
<td>HCV Ab, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>753 (78.0%)</td>
<td>623 (80.7%)</td>
<td>130 (67.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>positive</td>
<td>172 (17.8%)</td>
<td>111 (14.4%)</td>
<td>61 (31.4%)</td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>41 (4.2%)</td>
<td>38 (4.9%)</td>
<td>3 (1.6%)</td>
<td></td>
</tr>
<tr>
<td>HBsAg, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>834 (87.7%)</td>
<td>653 (86.3%)</td>
<td>181 (93.3%)</td>
<td>0.008</td>
</tr>
<tr>
<td>positive</td>
<td>15 (1.6%)</td>
<td>11 (1.4%)</td>
<td>4 (2.1%)</td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>102 (10.7%)</td>
<td>93 (12.3%)</td>
<td>9 (4.6%)</td>
<td></td>
</tr>
<tr>
<td>Nadir CD4, cell/mm, median (IQR)</td>
<td>247 (98-372)</td>
<td>268 (126-400)</td>
<td>165 (44-270)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4 at switch, cell/mm, median (IQR)</td>
<td>699 (541-888)</td>
<td>695 (545-898)</td>
<td>714 (525-864)</td>
<td>0.870</td>
</tr>
<tr>
<td>Years of HIV infection, median (IQR)</td>
<td>12 (6-21)</td>
<td>9 (5-17)</td>
<td>22 (19-27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Years of ART, median (IQR)</td>
<td>8.4 (4.0-17.5)</td>
<td>6.6 (3.3-12.1)</td>
<td>18.9 (16.5-20.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Years of viral suppression, median (IQR)</td>
<td>7.0 (3.4-12.0)</td>
<td>5.9 (2.9-10.6)</td>
<td>12.0 (8.4-14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Therapeutic lines, median (IQR)</td>
<td>5 (3-9)</td>
<td>4 (3-6)</td>
<td>11 (7-15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ART pre-BL, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 NRTI + PI</td>
<td>102 (10.6%)</td>
<td>73 (9.5%)</td>
<td>29 (15.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 NRTI + INSTI</td>
<td>214 (22.2%)</td>
<td>177 (22.9%)</td>
<td>37 (19.1%)</td>
<td></td>
</tr>
<tr>
<td>2NRTI + NNRTI</td>
<td>178 (18.4%)</td>
<td>158 (20.5%)</td>
<td>2.0 (10.3%)</td>
<td></td>
</tr>
<tr>
<td>2DR</td>
<td>205 (21.2%)</td>
<td>144 (18.6%)</td>
<td>61 (31.4%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>267 (27.6%)</td>
<td>220 (28.5%)</td>
<td>47 (24.2%)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2: Crude and adjusted hazard ratios (95%CI) of the risk of viral rebound (A) and viral blips (B) from fitting a weighted Cox regression model by standard definition (confirmed HIV-RNA ≥ 50 copies/mL or a single HIV-RNA ≥ 50 copies/mL followed by change of ART) and modified definition (confirmed HIV-RNA ≥ 50 copies/mL).

<table>
<thead>
<tr>
<th>A)</th>
<th>Viral Rebound [standard definition]</th>
<th>HR 95%CI</th>
<th>p-value</th>
<th>AHR 95%CI</th>
<th>p-value</th>
<th>AHR 95% CI (sensitivity analysis)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VF to any ART ≥ 1 vs 0</td>
<td>2.20 (0.95-5.09)</td>
<td>0.065</td>
<td>3.06 (1.00-9.44)</td>
<td>0.051</td>
<td>6.62 (1.25-35.11)</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>Previous VF to any ART 1 vs 0</td>
<td>3.31 (1.38-7.92)</td>
<td>0.007</td>
<td>4.20 (1.36-12.94)</td>
<td>0.013</td>
<td>7.71 (1.46-40.62)</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>Previous VF to NRTI or INSTI ≥ 1 vs 0</td>
<td>1.90 (0.81-4.48)</td>
<td>0.140</td>
<td>2.15 (0.78-5.92)</td>
<td>0.137</td>
<td>3.25 (0.75-14.04)</td>
<td>0.114</td>
<td></td>
</tr>
<tr>
<td>Previous VF to NRTI or INSTI 1 vs 0</td>
<td>2.75 (1.12-6.75)</td>
<td>0.027</td>
<td>2.86 (1.03-7.92)</td>
<td>0.044</td>
<td>3.46 (0.78-15.27)</td>
<td>0.102</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B)</th>
<th>Viral blips</th>
<th>HR 95%CI</th>
<th>p-value</th>
<th>AHR 95%CI</th>
<th>p-value</th>
<th>AHR 95% CI (sensitivity analysis)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VF to any ART ≥1 vs 0</td>
<td>1.39 (0.79-2.42)</td>
<td>0.251</td>
<td>1.81 (0.95-3.42)</td>
<td>0.069</td>
<td>2.64 (1.18-5.90)</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Previous VF to any ART</td>
<td>1 vs 0</td>
<td>(1.38 \ (0.69-2.74))</td>
<td>0.364</td>
<td>1.74 (0.81-3.73)</td>
<td>0.153</td>
<td>1.98 (0.70-5.60)</td>
<td>0.200</td>
</tr>
<tr>
<td>------------------------</td>
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<td>------------------</td>
<td>------</td>
</tr>
<tr>
<td>Previous VF to any ART</td>
<td>(\geq2) vs 0</td>
<td>(1.39 \ (0.79-2.42))</td>
<td>0.251</td>
<td>1.80 (0.85-3.82)</td>
<td>0.124</td>
<td>2.04 (0.72-5.68)</td>
<td>0.180</td>
</tr>
<tr>
<td>Previous VF to NRTI or INSTI</td>
<td>1 vs 0</td>
<td>(1.32 \ (0.77-2.32))</td>
<td>0.341</td>
<td>1.68 (0.87-3.22)</td>
<td>0.121</td>
<td>2.70 (1.22-6.15)</td>
<td>0.014</td>
</tr>
<tr>
<td>Previous VF to NRTI or INSTI</td>
<td>(\geq1) vs 0</td>
<td>(1.36 \ (0.69-2.7))</td>
<td>0.376</td>
<td>1.61 (0.74-3.51)</td>
<td>0.230</td>
<td>2.28 (0.85-6.10)</td>
<td>0.101</td>
</tr>
<tr>
<td>Previous VF to NRTI or INSTI</td>
<td>(\geq2) vs 0</td>
<td>(1.32 \ (0.75-2.33))</td>
<td>0.341</td>
<td>1.49 (0.76-2.93)</td>
<td>0.247</td>
<td>2.48 (1.10-5.62)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Notes: Sensitivity analysis excluded PLWH with uncomplete data about past viral loads.
AHR are adjusted for CD4+ cells count at nadir (higher or lower than 350 cells/mmc), duration of virological suppression and mode of HIV transmission.
VF, virological failure; aHR, adjusted hazard ratio, NRTI, nucleoside reverse transcriptase inhibitors; INSTI, integrase inhibitors