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1 **Characterization of Viral Rebounds on Dual Etravirine/Raltegravir Maintenance Therapy (ANRS-163 ETRAL Trial)**

2 Short title: Etravirine/Raltegravir therapy in HIV-infected middle aged patients.

3

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29

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33

34

35 **ABSTRACT**

36 **Background:** ANRS-163 ETRAL trial, a switch study to etravirine 200 mg/raltegravir 400 mg twice daily regimen in 165 patients with HIV-1
37 infection, showed durable efficacy until week 96. The aim of this work was to investigate in details the virological rebounds (VR) defined as at
38 least by one plasma HIV viral load (VL) > 50 copies/mL.

39 **Methods:** Quantification of HIV-DNA level was assessed at baseline, weeks 48 and 96 (n=157). VLs were measured in seminal plasma at week
40 48 (n=26). Genotypic resistance testing by ultradeep sequencing (UDS) for reverse transcriptase (RT) and integrase regions were performed at
41 baseline and at time of VR.

42 **Results:** In this study, 19 patients experienced VR with 2 patients with virological failure (2 consecutive VL>50 copies/mL). For the first patient
43 with VF, UDS detected minority resistant variants only on RT (K103N: 9.6%; Y181C: 4.9%) at baseline. Some RT variants became dominant at
44 VF (K101E: 86.3%; Y181C: 100.0%; G190A: 100.0%) and others emerged on integrase (Y143C: 2.4%; Q148R: 6.2%; N155H: 18.8%). For the
45 second patient with VF, neither NNRTI nor INI mutations were detected at baseline and VF. Median HIV-DNA level was similar at baseline,
46 weeks 48 and 96 (2.17, 2.06 and 2.11 log₁₀ copies/10⁶ cells, respectively). Only one patient had a detectable seminal HIV VL (505 copies/mL).

47 **Conclusions:** The dual regimen etravirine/raltegravir as maintenance therapy was effective and the emergence of mutations in case of VF was
48 similar to that seen in other dual regimen studies. No HIV-DNA level modification was evidenced through week 96.

49

50 **BACKGROUND**

51 During long life therapy, alternative strategies are needed, particularly in HIV middle-aged patients to better manage comorbidities and
52 polypharmacy. In the context of antiretroviral (ARV) toxicity, particularly NRTIs and PIs associated with long-term toxicity, a dual combination
53 of etravirine/raltegravir (200/400 mg twice daily) was evaluated. The ANRS-163 ETRAL is a non-comparative study, aimed to evaluate over 96
54 weeks of treatment the capacity to maintain virological success of a dual raltegravir/etravirine twice a day regimen in HIV-1 infected patients, older
55 than 45 years of age, with suppressed plasma viremia switching from a boosted PI-containing regimen (ClinicalTrial.gov: NCT02212379). The
56 dual therapy raltegravir plus etravirine showed durable efficacy in the 165 virologically-suppressed patients, with benefits in metabolic and
57 inflammatory parameters over 48 and 96 weeks, respectively. Only two patients had a virological failure (VF).¹ Furthermore, there was no clinically
58 significant pharmacokinetic interaction between etravirine and raltegravir and both etravirine and raltegravir plasma concentrations were adequate
59 in most patients of this study.²

60

61 The aim of this analysis was to describe in details the virological rebounds (VR) defined as at least one plasma viral load (pVL) > 50
62 copies/mL in terms of : 1) resistance by Ultra Deep Sequencing (UDS), 2) HIV cell-associated HIV DNA changes and 3) seminal VL in the ETRAL
63 ANRS-163 study. Furthermore, the potential factors associated with the VR were evaluated.

64

65 **PATIENTS AND METHODS**

66

67 **Study participants**

68 The study population consisted in 165 HIV-1-infected adults enrolled and followed as previously described.¹ The VF was defined as 2
69 consecutive measurements of HIV-1 pVL > 50 copies/mL (n=2) and VR as at least one VL >50 copies/mL (n=19). A seminal sub-study was
70 conducted in this trial in one center and semen samples were collected at week 48 (n=26). Furthermore, 17 patients without VR but with etravirine
71 resistance mutations or K103N (etravirine sensitive) on the screening genotype were also studied as control for the HIV resistance analysis.

72

73 **Procedures**

74 The reverse transcriptase (RT) and integrase fragments were PCR-amplified with the « Agence Nationale de Recherche sur le Sida et les
75 hépatites virales » protocols and Sanger sequencing was performed at screening (DNA) and in case of VF or viral blip (RNA). The resistance
76 mutations were interpreted with the last version of ANRS algorithm (<http://www.hivfrenchresistance.org/>).

77 The Illumina sequencing technology (MiSeq) was used to study HIV DNA RT and integrase resistance. The RT and integrase mutations
78 were analyzed with Smartgene® according to the latest ANRS mutation list (cut-off 1%) (<http://www.hivfrenchresistance.org/>) and by Genious
79 (version 10.3.2; <http://www.geneious.com>).³

80 Quantification of pVL and seminal VL was performed using the AmpliPrep/COBAS TaqMan HIV-1 Test v2 or CAP/CTM TaqMan 48
81 HIV-1 V.2 (Roche Diagnostics, Basel, Switzerland), and the Abbot Realtime HIV-1 M2000rt (Abbott laboratories, Illinois, USA). Whole blood
82 was collected at baseline, weeks 48 and 96, and cell associated HIV DNA was quantified as previously described (n=157).⁴

83 Plasma concentrations of etravirine and raltegravir, were determined by ultra-high performance liquid chromatography coupled with tandem
84 mass spectrometry (UPLC-MS/MS; Waters Acquity UPLC-TQD, Milford, MA).⁵ The limit of quantification was < 5 ng/ml for all assays, and
85 interpretation was based on the corresponding *in vitro* protein-adjusted 95% inhibitory concentration (PBIC95) for wild-type (WT) HIV1: 116
86 ng/ml for etravirine and 15 ng/ml for raltegravir.⁶

87

88 **Statistical analysis**

89 Variables were summarized with numbers and percentage for categorical variables and with median and range or interquartile range (IQR)
90 for continuous variables. Kaplan-Meier estimator was used to estimate the proportion of participants with VR. Univariable and multivariable Cox
91 regression model was used to identify factors associated with VR: age (≤ 60 y and > 60 y), gender, ethnicity, CDC stage, transmission group, previous

92 antiretroviral treatment (ART) intake (twice or once daily), previous ART (mono, dual or triple therapies), presence of tenofovir in the previous
93 ART, duration of ART, baseline CD4 and CD8 cell counts, CD4/CD8 ratio, nadir CD4 cell count, time since HIV diagnosis, duration of suppressed
94 viraemia, pre-ART pVL, baseline HIV cell-associated DNA, HIV-1 subtype, ETR resistance mutation, K103N mutation evidenced in historical or
95 screening genotypes, presence of G to A mutation in DNA RT, tobacco consumption, alcohol consumption (≥ 2 glasses/day), and presence of
96 comorbidities. Variables with univariable P-value < 0.2 were retained in the multivariable analysis. Changes in cell associated HIV-DNA were
97 compared between baseline and week 48 and 96 using paired Wilcoxon test and the Mann-Whitney test was used for comparison of continuous
98 variables between participants with and without VR. All reported P values are two-tailed, with significance set at 0.05. Analyses were performed
99 with SPSS statistics version 22.0 for Windows.

100

101 **RESULTS**

102

103 **Description of HIV resistance for patients with virological rebound by UDS**

104 For the first patient with VF (patient 1), minority HIV-1 variants on RT associated with etravirine resistance were detected (K103N: 9.6%,
105 Y181C: 4.9%) at baseline with an increase of some variants at time of VF (K101E: 86.3%, K103N: 12.5%, K103S: 2.2%, Y181C: 100.0%,
106 G190A:100.0%). In addition, integrase resistant variants not detected at baseline emerged at VF (T66I: 65.4%, Y143C: 2.4%, Q148R: 6.2%,

107 N155H: 18.8%), leading to raltegravir resistance. The presence of these resistant variants was associated with HIV resistance to all NNRTIs and
108 integrase inhibitors. The raltegravir (132 ng/mL) and etravirine (547 ng/mL) plasma concentrations 12 hours after the last drug intakes were
109 adequate at the time of failure (table 1).

110 With regards to the second patient with VF (patient 2), there was no detection at baseline of resistant variants in the RT and integrase genes
111 using UDS DNA genotype despite past etravirine associated resistance mutations (K103N, E138A and V106I) that were missed at screening. At
112 time of VF, no mutation to NNRTIs and integrase inhibitors was detected by Sanger and UDS (table 1). The raltegravir (1,418 ng/ml) and etravirine
113 (505 ng/mL) plasma concentrations were also adequate (table 1).

114 Along the study duration, 17 patients experienced at least one VL >50 copies/mL: 10 occurred between week 4 and week 48, and 8 between
115 week 64 and 96 (median 106 copies/mL; range 57-543) (table 1). The raltegravir and etravirine concentrations were in median for these 17 patients
116 331 and 488 ng/mL, respectively. Due to the low level of pVL, only 5 RT and 6 integrase genes (7 patients) were successfully amplified by Sanger
117 sequencing with no mutation leading to etravirine or raltegravir resistance. The E138K mutation was detected on integrase gene leading to
118 elvitegravir resistance in one patient with a pVL at 163 copies/mL (patient 14). The pVL were so low at VL rebound that only 1 RT (patient 8) and
119 2 integrase (patient 3 and 8) genes could be amplified for UDS with no resistance mutations for NNRTIs and a S147G in integrase gene (1.1% for
120 the patient 8) (table 1). To better understand the potential implications of minority variants in the viral blips in the ETRAL trial, the RT and
121 integrase genes were also evaluated at baseline for these 17 patients by UDS in DNA. At baseline, 6 RT (patients 3, 4, 7, 10, 11 and 14) and 8
122 integrase genes (patients 3, 4, 6, 7, 8, 10, 11 and 14) could be amplified. Considering etravirine resistance associated mutations, two minority

123 variants are reported: E138K (8.6%, patient 7), E138G (1.5%, patient 11). Only the patient 4 exhibits a resistance variant associated with raltegravir
124 resistance (G118R: 1.4%) (table 1).

125 To evaluate the impact of the minority resistant variants in a context of VR but also in success, UDS was realized for RT of 17 patients with
126 no VR over the 96 weeks of follow-up, with baseline etravirine resistance mutations detected by Sanger sequencing. Among them, 15 harbored
127 viruses with etravirine resistance mutations at baseline evidenced by UDS confirming the screening Sanger genotypes, and leading to etravirine
128 resistance (R) for 2 patients and to intermediate resistance (I) for 2 others, respectively: V90I (7.2%), K101R (12.1%), V179I (12.6%) [R, n=1];
129 E138K (1.2%) [R, n=1]; A98G (51.6%), K101R (10.3%) [I, n=1]; V90I (76.8%), E138A (2.5%) [I, n=1].

130

131 **Evaluation of HIV-DNA levels**

132 No statistical change of HIV-DNA level was observed between baseline (median 2.17 log₁₀ copies/10⁶ cells), and week 48 (2.06 log₁₀
133 copies/10⁶ cells; p=0.054) or week 96 (2.11 log₁₀ copies/10⁶ cells; p=0.750). Furthermore, there was no impact of HIV-DNA level at baseline on
134 the occurrence of VR defined as at least one pVL > 50 copies/mL (2.29 log₁₀ copies/10⁶ cells versus 2.14 log₁₀ copies/10⁶ cells for patients with
135 or without VR, respectively; p=0.839).

136

137 **Seminal substudy**

138 As the control of HIV VL in compartments in the context of dual therapy was a concern, HIV VL was measured on 26 seminal plasma at
139 week 48. All these VL were <100 copies/mL, except for one patient with a seminal VL at 505 copies/mL (raltegravir concentration: 560 ng/mL;
140 etravirine concentrations: 175 ng/mL) with a corresponding plasma VL < 50 copies/mL. This patient experienced a blip (75 copies/mL) at week
141 96 in plasma (patient 18, table 1). The Sanger genotype revealed no mutation in integrase gene, and unfortunately the RT gene was not successfully
142 amplified. Overall, the raltegravir and etravirine concentrations were 638 and 119 ng/mL in seminal plasma in median, respectively.

143

144 **Factors associated with the virological rebound**

145 Six factors were retained for the multivariable analysis: presence of at least one etravirine resistance mutation in DNA Sanger at baseline
146 or in historical RNA (p=0.117), presence of K103N resistance mutation in DNA Sanger at baseline or in historical RNA (p=0.077), tenofovir
147 disoproxil fumarate in the previous antiretroviral treatment (p=0.018), duration of pVL <50 copies/mL (< or > 4 years, p=0.059), age (< or > 60
148 years, p=0.035) and consumption of alcohol (≥ 2 glasses/day) (p=0.008) (table 2). The multivariable analysis showed that the risk of VR was
149 independently associated with age and alcohol consumption. The risk was 3.7 times higher (95%CI, 1.4-10.1) in patients with >60 years old and
150 11.3 times higher (95%CI, 1.5-85.1) when they consumed ≥ 2 glasses of alcohol per day.

151

152 **DISCUSSION**

153 The dual maintenance therapy with raltegravir/etravirine 400/200 mg twice daily was highly effective in patients over 45 years of age over 96
154 weeks switching from a PI-containing regimen regimen. Only 2 individuals out of 165 experienced virological failure. Seventeen individuals
155 experienced blips with subsequent HIV pVL < 50 copies/mL without treatment changes. The HIV DNA level did not change during the 96 weeks
156 of follow-up.

157 For the first patient with VF, the Sanger sequencing evidenced NNRTI mutations at failure (K101E, Y181C and G190A) and some of them
158 (K103N and Y181C) were already detected at baseline by UDS. All etravirine mutations detected by Sanger sequencing at failure were also shown
159 by UDS as majority variants. To note, the K103N detected at baseline and not associated with etravirine resistance remained as minority variants.
160 Furthermore, some integrase resistance mutations were evidenced by UDS and not previously detected by Sanger sequencing. The use of UDS in
161 this case was informative to explain the VF as the NNRTIs resistance associated mutations were found at baseline and the integrase resistance
162 associated mutations were revealed at failure while they were not evidenced by Sanger sequencing. This result was in line with previous studies
163 showing the input of UDS over Sanger sequencing for detecting resistance for the antiretroviral class of NNRTIs. ^{7,8}

164 For the second patient with VF, some NNRTIs mutations (K103N, E138A and V106I) were retrospectively evidenced in the medical history
165 of the patient after the VF, and neither Sanger sequencing nor UDS detected these mutations at baseline and VF. ¹ These results illustrated another
166 issue concerning the treatment of HIV patient with undetectable pVL, the assessment of resistance and the impact of archived resistance. Indeed,

167 it is currently admitted that Sanger RNA genotyping during previous periods of VF remains the gold standard for documenting resistance mutations
168 and for the monitoring of future treatments.^{9,10} However, in clinical practice and in this study, the HIV DNA genotyping was also performed. The
169 impact of mutations (evidenced in historical RNA or DNA at screening) on the ARV treatment prescribed many years later and after many years
170 of undetectable pVL is not well documented. It has been shown recently that there is a clear trend towards clearance of archived resistance
171 associated mutations to RT inhibitors in cell-associated HIV-1 DNA after a long period of virological control, free from therapeutic selective
172 pressure on these mutations.¹¹

173 In the present study, the number of patients with VF was low and 1/2 showed the emergence of resistance mutations to NNRTI and INI.
174 This result could be compared to that was observed in other dual regimen based on NNRTI and INI. In FLAIR study (cabotegravir/rilpivirine), 3/6
175 patients (50%) had HIV-1 with both resistance associated mutations in RT and integrase genes leading to resistance.¹² In the SWORD-1 and -2
176 studies (dolutegravir/rilpivirine), 3/10 patients presented emerging NNRTIs resistance mutations (30%) at W100, but with no INI resistance
177 mutations.¹³ The combination of dual NNRTI plus INI should be taken into account considering the genetic barrier to resistance of each
178 antiretroviral.

179 It is very reassuring to show that there was no variation of HIV DNA VL in blood during the 2 years of follow-up on the etravirine/raltegravir
180 regimen arguing for the absence of an eventual replenishment of the reservoirs. This was in accordance with data obtained from other dual or
181 monotherapy studies showing no difference versus triple therapy.¹⁴⁻¹⁶

182 Two parameters were associated with the probability to have a VR in patients receiving this combination etravirine/raltegravir (200/400
183 mg) twice daily: age (> 60 years) and alcohol consumption (≥ 2 glasses/day). Nevertheless, given the low number of events (n=19), these results
184 should be taken with cautious. Furthermore, the confidence intervals was too wide for alcohol consumption. Although the alcohol consumption is
185 one of the main factors associated with non-adherence, it should to be taken with cautious in the context of the ANRS-165 ETRAL study as the
186 total etravirine and raltegravir plasma concentrations were adequate in most patients, favoring virologic efficacy and confirming good treatment
187 adherence (> 95%).^{2,17}

188 In conclusion, the dual regimen raltegravir/etravirine represents an effective option for patients in a context of suppressed viraemia. The
189 emergence of mutations in case of VF in this trial was similar to that seen in other NNRTI plus INI dual regimen studies. In addition, this dual
190 maintenance therapy did not modify HIV DNA VL through week 96. This strategy remains to be evaluated in a context of once daily intake.

191

192

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209 **TRANSPARENCY DECLARATION**

210 All other authors: none to declare.

211

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251

252

	VL and drug concentrations			Sanger			UDS		
Interpretation	VL (copies/mL)	RAL C12h (ng/mL)	ETR C12h (ng/mL)	NNRTI	Integrase	Interpretation	NNRTI	Integrase	Interpretation
ETR R RAL S	11 607 (W24) 18 472 (CTR)	132 (W24) 94 (CTR)	547 (W24) 584 (CTR)	K101E Y181C G190A	T66I	ETR R RAL S	K101E: 86.3%, K103N: 12.5%, K103S: 2.2%, Y181C: 100.0%, G190A:100.0%	T66I: 65.4%, Y143C: 2.4%, Q148R: 6.2%, N155H: 18.8%	ETR R RAL R
ETR S RAL S	69 (W64) 75 (CTR)	1418 (VF)	505 (VF)	No mutation	No mutation	ETR S RAL S	No mutation	No mutation	ETR S RAL S
ETR S RAL S	116 (W4) <20 (CTR)	210 (W4)	369 (W4)	No mutation	No mutation	ETR S RAL S	NA	No mutation	RAL S
ETR S RAL R	61 (W4) <20 (CTR)	334 (W4)	574 (W4)	No mutation	NA	ETR S	NA	NA	
	59 (W4)	328 (W4)	328 (W4)	NA	NA		NA	NA	

	26 (CTR)							
RAL S	58 (W12) <20 (CTR)	40 (W12)	249 (W12)	NA	NA		NA	NA
ETR R RAL S	160 (W12) <20 (CTR)	2,253 (W12)	697 (W12)	No mutation	NA	ETR S	NA	NA
RAL S	95 (W24) <20 (CTR)	157 (W24)	519 (W24)	No mutation	No mutation	ETR S RAL S	No mutation	S147G (1.1%) RAL S
	60 (W36) <20 (CTR)	182 (W36)	441 (W36)	NA	NA		NA	NA
ETR S RAL S	296 (W48) <20 (CTR)	108 (W24) NA (W48)	146 (W24) NA (W48)	NA	NA		NA	NA
ETR I RAL S	543 (W48) <20 (CTR)	1,599 (W48)	172 (W48)	NA	No mutation	RAL S	NA	NA
	127 (W48) 49 (W64)	42 (W48)	487 (W48)	NA	NA		NA	NA
	57 (W64) <20 (CTR)	853 (w64)	704 (w64)	NA	NA		NA	NA

ETR S	163 (W64)	1497 (w64)	440 (w64)	No mutation	E138K	ETR S	NA	NA
RAL S	<20 (CTR)					RAL S		
	89 (W80)	719 (w80)	622 (w80)	NA	No mutation	RAL S		
	<20 (CTR)							
	120 (W80)	224 (w80)	490 (w80)	NA	NA		NA	NA
	<20 (CTR)							
	210 (W80)			NA	NA		NA	NA
	<20 (W96)							
	212 (W96)			NA	No mutation	RAL S	NA	NA
	49 (CTR)							
	75 (W96)	2937 (w96)	747 (w96)	NA	NA		NA	NA
	<20 (CTR)							
	95 (W96)	353 (w96)	842 (w96)	NA	NA		NA	NA
	20 (CTR)							

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254

255 Table 1: Details of Sanger and UDS resistance mutations and pharmacological results (CTR: control; NA: non-amplified; R: resistant; I: intermediate resistance; S: susceptible)

256

	Univariate and Multivariable Cox proportional hazards model					
	Patients who experienced a pVL>50 copies/mL		Univariate analysis		Multivariable analysis	
	No	Yes	HR (95% CI)	p-value	HR (95% CI)	p-value
Age, years, median (IQR)	52 (48-57)	54 (48-64)	1.03 (0.99-1.08)	0.065		
Age group, n (%)						
• <60 years	123 (91%)	12 (9%)	1		1	
• >60 years	23 (77%)	7 (23%)	2.72 (1.07-6.91)	0.035	3.72 (1.37-10.12)	0.010
Gender-sex, n (%)						
• Male	102 (87%)	15 (13%)	1			
• Female	44 (92%)	4 (8%)	0.62 (0.20-1.85)	0.615		
Origin-ethnicity, n (%)				0.669		
• Caucasian	111 (90%)	13 (10%)	1			
• Sub-saharan Africa	21 (88%)	3 (13%)	1.16 (0.33-4.06)	0.821		
• Other	14 (82%)	3 (18%)	1.77 (0.51-6.23)	0.371		
CDC stage, n (%)				0.673		
• A	87 (89%)	11 (11%)	1			
• B	26 (84%)	5 (16%)	1.44 (0.50-4.15)	0.498		
• C	33 (92%)	3 (8%)	0.78 (0.22-2.80)	0.702		
Transmission group, n (%)				0.232		
• Men who sex with men	55 (83%)	11 (17%)	1			
• Heterosexual	66 (92%)	6 (8%)	0.46 (0.17-1.24)	0.124		
• Other	25 (93%)	2 (7%)	0.28 (0.10-1.96)	0.279		
Previous antiretroviral treatment intake						
• Twice daily	41 (91%)	4 (9%)	1			
• Once daily	105 (88%)	15 (12%)	1.37 (0.46-4.14)	0.573		

Previous antiretroviral treatment					0.267		
• Monotherapy	34 (97%)	1 (3%)	1				
• Dual therapy	16 (89%)	2 (11%)	4.08 (0.37-45.00)		0.251		
• Triple therapy or more	96 (86%)	16 (14%)	5.26 (0.70-39.68)		0.107		
Presence of TDF in previous antiretroviral treatment							
• No	90 (94%)	6 (6%)			1		
• Yes	56 (81%)	13 (19%)	3.22 (1.22-8.48)		0.018	2.61 (0.92-7.45)	0.072
Duration of antiretroviral treatment, years	17 (11-19)	18 (13-19)	1.03 (0.95-1.11)		0.516		
Baseline CD4 cell count, cells/mm ³	701 (530-904)	704 (548-880)	1.00 (0.99-1.00)		1.000		
Baseline CD8 cell count, cells/mm ³	718 (545-996)	686 (562-979)	1.00 (0.99-1.00)		0.837		
CD4/CD8 ratio	0.93 (0.66-1.24)	0.97 (0.67-1.27)	0.88 (0.39-2.00)		0.756		
Nadir CD4 cell count, cells/mm ³	208 (89-283)	244 (122-301)	1.00 (0.99-1.00)		0.623		
Time since HIV diagnosis, years	20 (12-24)	19 (14-25)	1.03 (0.97-1.10)		0.339		
Duration of suppressed viraemia, years	7 (4-9)	5 (2-8)	0.89 (0.77-1.02)		0.085		
Duration of suppressed viraemia,							
• < 4 years	39 (81%)	9 (19%)	1		1		
• > 4 years	99 (92%)	9 (8%)	0.41 (0.16-1.04)		0.059	0.47 (0.18-1.26)	0.133
Pre-ART plasma viral load, log ₁₀ copies/mL	4.78 (4.22-5.49)	5.10 (4.56-5.34)	1.32 (0.68-2.58)		0.417		
Baseline HIV DNA VL, log copies/10 ⁶ cells	2.14 (1.82-2.47)	2.29 (1.86-2.40)	1.30 (0.41-4.17)		0.657		
Subtype, n (%)					0.906		
• B	68 (91%)	7 (9%)	1				
• CRF02_AG	2 (100%)	0 (0%)	0		0.990		
• Other	15 (94%)	1 (6%)	0.62 (0.08-5.06)		0.657		
ETR resistance mutation							
• No	132 (90%)	15 (10%)	1		1		
• At least one	14 (78%)	4 (22%)	2.41 (0.80-7.27)		0.117	2.04 (0.60-6.95)	0.256
K103N resistance mutation							

• No	134 (90%)	15 (10%)	1		1	
• Yes	12 (75%)	4 (25%)	2.71 (0.90-8.17)	0.077	1.79 (0.55-5.89)	0.335
G-to-A mutations number	9 (6-12)	10 (8-14)	1.004 (0.955-1.057)	0.867		
Tobacco consumption				0.639		
• No smoker	65 (88%)	9 (12%)	1			
• Former smoker	29 (94%)	2 (6%)	0.56 (0.12-2.59)	0.459		
• Active smoker	52 (87%)	8 (13%)	1.18 (0.46-3.07)	0.729		
Alcohol consumption						
• Never	69 (99%)	1 (1%)	1		1	
• Occasional/regular (≥ 2 glasses per day)	77 (81%)	18 (19%)	15.14 (2.02-113.44)	0.008	11.27 (1.49-85.10)	0.019
Presence of comorbidities,						
• No	71 (89%)	9 (11%)	1			
• Yes	75 (88%)	10 (12%)	1.02 (0.42-2.51)	0.964		

258

259 **Table 2:** Univariate and Multivariable Cox proportional hazards model of factors predictive of the occurrence of plasma virological rebound (pVL > 50 copies/mL) with
 260 etravirine/raltegravir therapy among HIV-infected patients. Variables with univariate p-values <0.2 were retained for the multivariable analysis.

261 Continuous variables are described as median with interquartile range and categorical variables with number and percentage.

262 VL: viral load; HR: hazard ratio; CI: Confidence Interval; ETR: etravirine; TDF: tenofovir disoproxil fumarate.

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