Abst#_O_06

Patients with pre-existent NRTI- and NNRTI-resistance have a higher risk to lose virological suppression under tenofovir/emtricitabine/rilpivirine single tablet regimen

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Background

The combination of tenofovir/emtricitabine/rilpivirine (TDF/FTC/RPV) as single tablet regimen has carried out important improvements in treating HIV-1 infected patients at first-line regimen or switching regimen for simplification/convenience reasons.

However, so far few data are available about the presence and the role of resistance to reverse transcriptase inhibitors (RTIs) before TDF/FTC/RPV switching.

Aim

To evaluate the impact of pre-existent RTI-resistance on the maintenance of virological suppression (VS) in antiretroviral-experienced HIV-1 infected patients with viremia <50 copies/mL switching to TDF/FTC/RPV as single tablet regimen in clinical practice.

Methods (I)

- **Patients were retrospectively selected on the basis of the following criteria:**

  - **Age ≥ 18 years;**
  - **Plasma HIV-1 RNA <50 copies/mL at the time of TDF/FTC/RPV starting;**
  - **At least one viremia measurement available after TDF/FTC/RPV starting;**
  - **CD4 cell count available at the time of TDF/FTC/RPV starting;**
  - **Complete information about therapeutic history;**
  - **Availability of at least one plasma protease/reverse transcriptase genotypic resistance test (GRT) before TDF/FTC/RPV switching.**

- **Analyses were performed on patients that did not discontinue TDF/FTC/RPV. Patients were censored at the last viremia measurement available before TDF/FTC/RPV discontinuation or treatment interruption.**

Methods (II)

- **Pre-existent resistance to nucleos(t)ide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) (according to IAS/Stanford HIVDb 2015) was evaluated in all plasma GRTs available before TDF/FTC/RPV starting.**

- **Pre-existent genotypic susceptibility score (GSS), according to HIVDB algorithm version 7.0.1 and based on the sum of genotype sensitivities to TDF/FTC/RPV, was evaluated by considering all plasma GRTs available before therapy switching.**

Methods (III)

- **Kaplan-Meyer curves were used to evaluate the probability of virological rebound (VR: defined as either a plasma HIV-1 RNA value >50 copies/mL at two consecutive visits, or a plasma HIV-1 RNA value >1000 copies/mL) according to pre-existent resistance and pre-existent GSS.**

- **Uni-multivariable Cox-regression was performed,** separately for pre-existent resistance and pre-existent GSS, including the following confounders: age, gender, B subtype, risk factor, VS duration and number of blips before switching (defined as a plasma HIV-1 RNA value ranging between 51 and 999 copies/mL, preceded and followed by another value below the assay limit of 50 copies/mL), previous treatment, cumulative experience to NNRTIs, baseline and nadir CD4 cell count, number of previous regimens, and pre-therapy plasma HIV-1 RNA as drug-naïve.

Results

Demographic characteristics

Characteristics	N=309
Male, n (%)	245 (79.3)
Age (year), median (IQR)	43 (35-51)
Subtype, n (%):	
B	240 (77.7)
CRF02_AG	20 (6.5)
F	18 (5.8)
C	7 (2.2)
Other[a]	24 (7.8)
Risk factor, n (%):	
Homosexual	149 (48.2)
Heterosexual	96 (31.1)
Drug abuser	40 (12.9)
Other/Unknown	24 (7.8)

[a] A, CRF01_AE, G, CRF12_BF, BF, CRF06_cpx, CRF03_AB, CRF07_BC, CRF01_AE,K, CRF18_cpx, CRF11_cpx, CRF20_BG, CRF31_BC. IQR: interquartile range.

Viro-immunological characteristics

Characteristics	N=309
Time of virological suppression before switching (months), median (IQR)	21 (6-50)
Time of virological suppression before switching (months), n (%):	
<12	122 (39.5)
12-36	86 (27.8)
>36	101 (32.7)
At least one viral blip during virological suppression, n (%)[a]:	71 (23)
Pre-therapy viremia as drug-naïve (copies/mL), n (%)[b]:	
<100,000	101 (44.1)
100,000-500,000	80 (34.9)
>500,000	48 (21)
CD4 cell count (cells/µL) before switching, median (IQR)	568 (447-769)
CD4 cell count nadir (cells/µL), median (IQR)	237 (129-344)

[a] 18 patients had more than one blip. [b] Pre-therapy viremia as drug-naïve was available for 229 patients. IQR: interquartile range.

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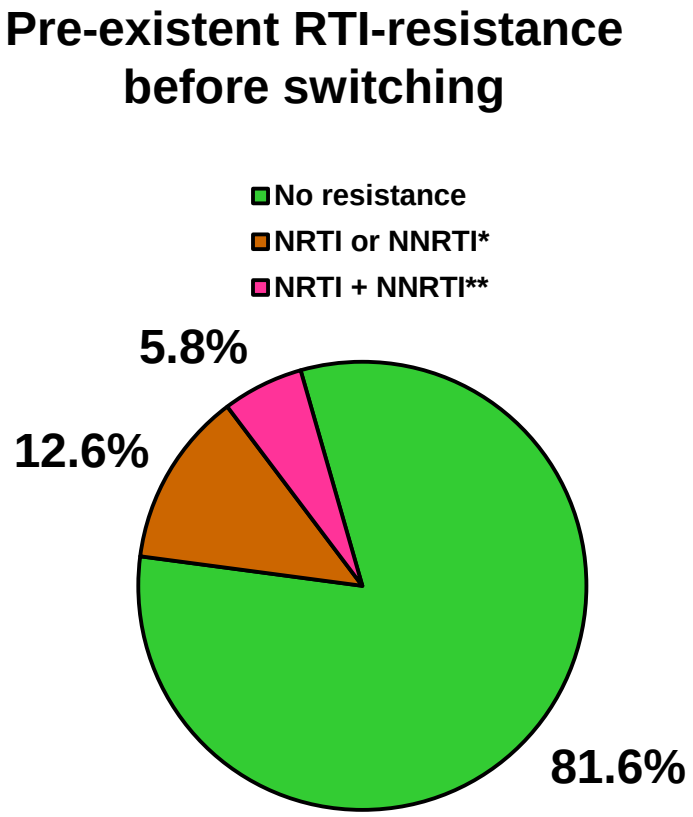
Therapeutic characteristics

Characteristics	N=309
Number of previous regimens, median (IQR)	2 (1-3)
Patients switching from first-line therapy, n (%)	141 (45.6)
Previous experience to NNRTIs, n (%)[a]	172 (55.7)
Usage of TDF + FTC/3TC before switching, n (%)[b]	273 (88.3)
Year of starting TDF/FTC/RPV treatment, median (IQR)	2013 (2013-2014)

[a] 126 patients were treated with a NNRTI before TDF/FTC/RPV switching; of them, 85 switched from TDF/FTC/EFV in STR. [b] Among 273 patients treated with TDF before TDF/FTC/RPV switching, only 6 were treated with 3TC. 3TC: lamivudine. EFV: efavirenz. IQR: interquartile range. STR: single tablet regimen.

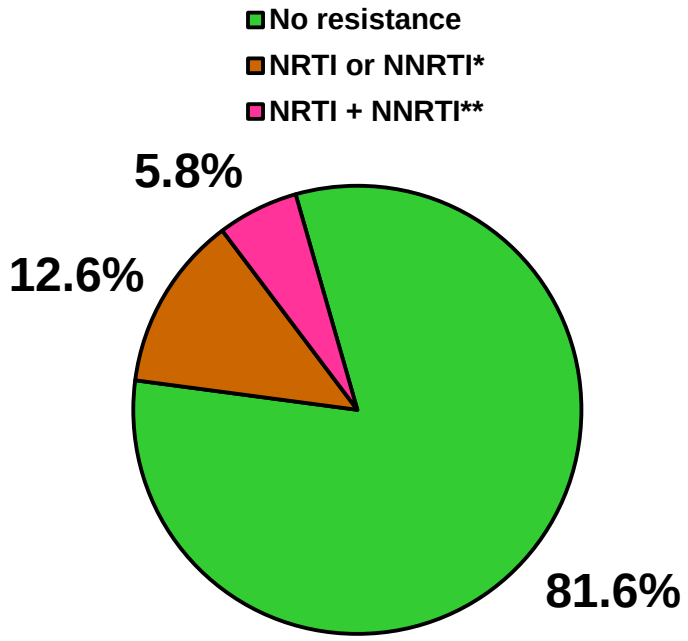
Pre-existent RTI-resistance at TDF/FTC/RPV switching



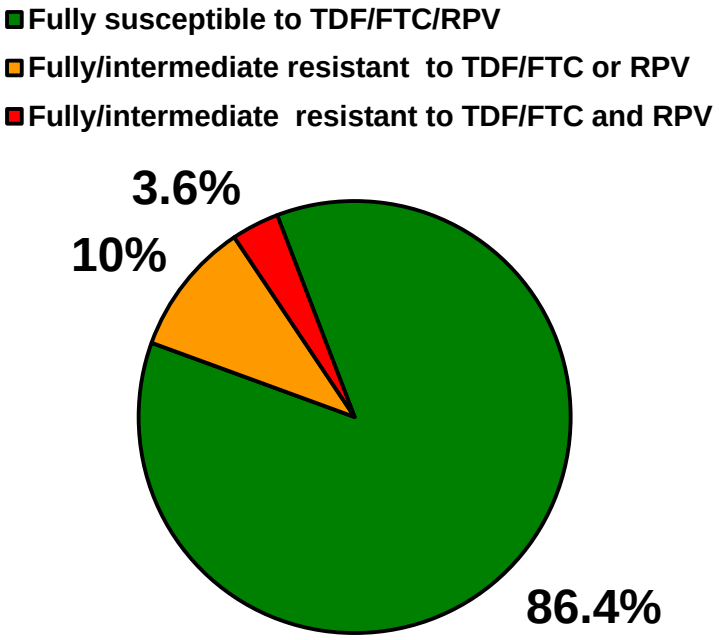
Number of all plasma GRTs available before TDF/FTC/RPV switching, median (IQR): 1 (1-2). GSS according to HIVDB version 7.0.1 based on the sum of genotype sensitivities to TDF/FTC/RPV. IQR: interquartile range. * Presence of at least one pre-existent NRTI- or NNRTI-resistance mutation. ** Presence of at least one concomitant pre-existent NRTI- and NNRTI-resistance mutation.

Pre-existent RTI-resistance at TDF/FTC/RPV switching

Pre-existent RTI-resistance before switching



GSS based on all GRTs available before switching



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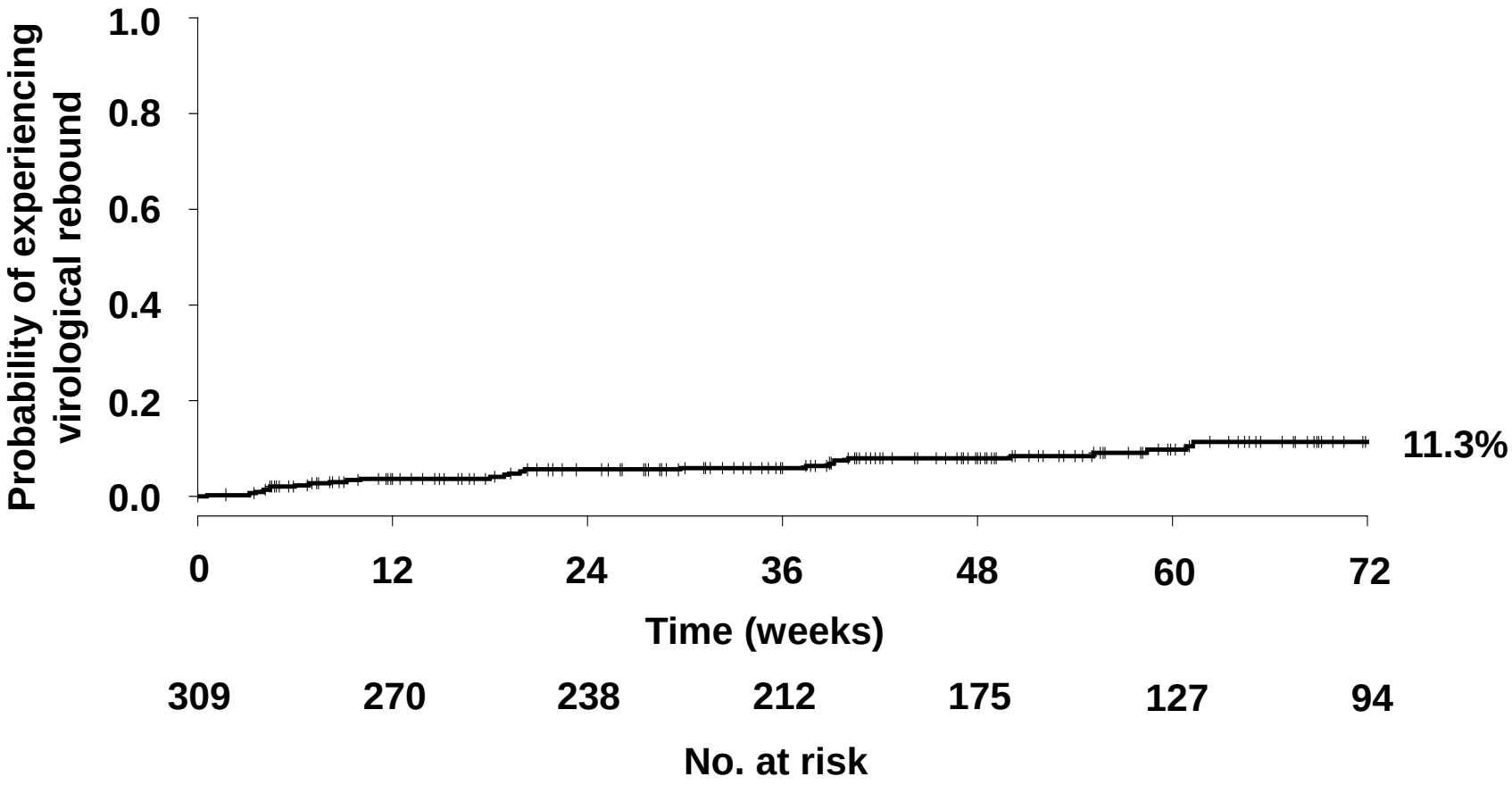
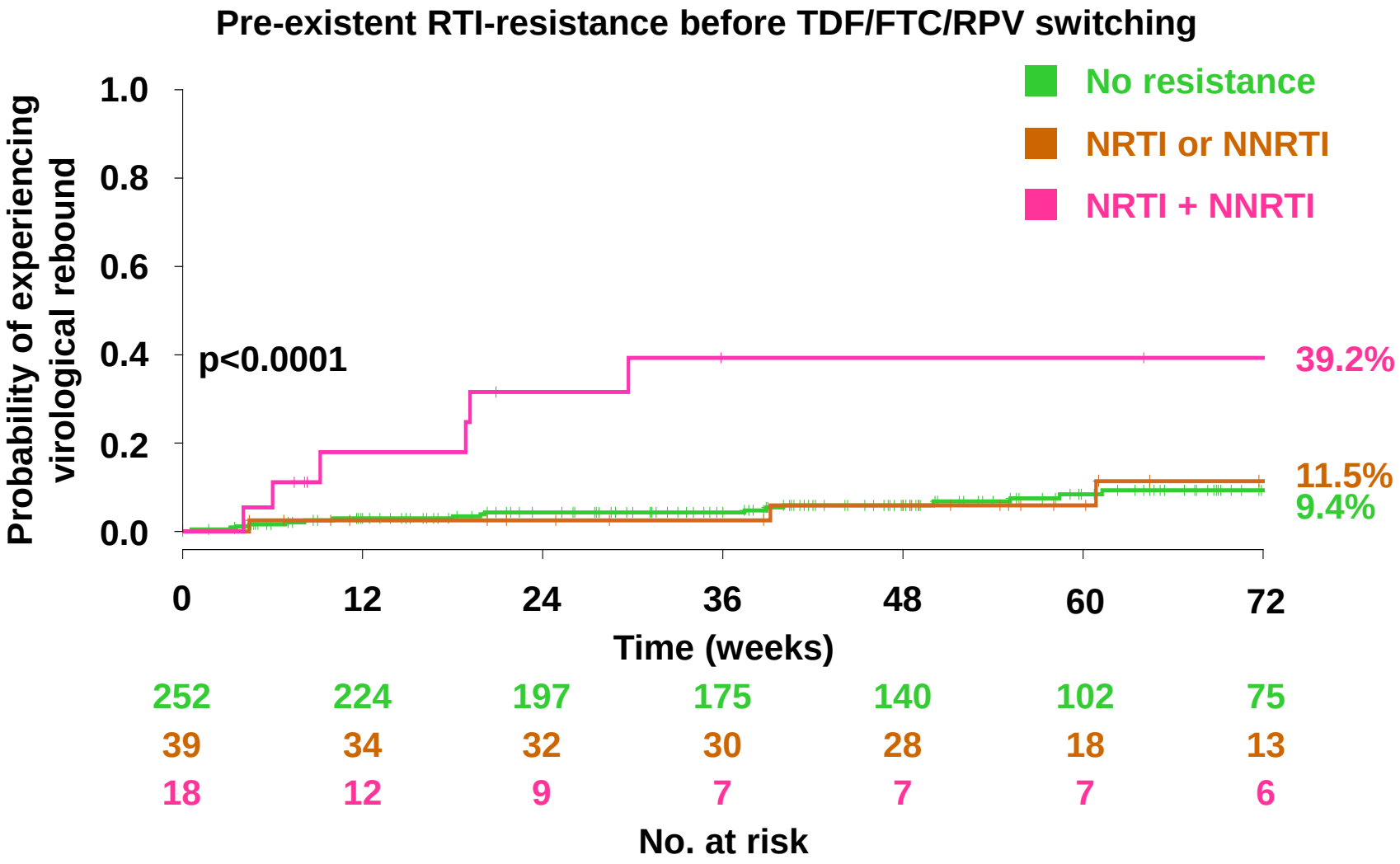
Overall, by 72 weeks after TDF/FTC/RPV starting, the probability of virological rebound was 11.3%.



Patients (N=309) followed until the last viremia measurement available before TDF/FTC/RPV discontinuation or treatment interruption.

Patients with pre-existent concomitant NRTI- and NNRTI-resistance had a higher probability of experiencing virological rebound compared to those harboring pre-existent NRTI- or NNRTI-resistance and to those without pre-existent RTI-resistance.



Patients (N=309) followed until the last viremia measurement available before TDF/FTC/RPV discontinuation or treatment interruption.

By Cox uni-multivariable models, a significant higher hazard ratio of virological rebound was found in patients with pre-existent concomitant NRTI- and NNRTI-resistance compared to those without RTI-resistance, and in patients with pre-therapy viremia >500,000 copies/mL compared to those with pre-therapy viremia <100,000 copies/mL.

Variables	Hazard ratio of experiencing virological rebound			
	Crude		Adjusted[a]	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Pre-existent RTI-resistance before TDF/FTC/RPV switching:				
No resistance[b]	1		1	
NRTI or NNRTI	1.06 (0.23-4.77)	0.943	1.07 (0.19-5.92)	0.935
NRTI + NNRTI	**7.52 (2.39-23.68)**	**0.001**	**7.25 (1.47-29.15)**	**0.022**
Pre-therapy viremia (copies/mL) as drug-naïve:				
<100,000[b]	1		1	
100,000-500,000	1.59 (0.43-5.93)	0.488	1.84 (0.44-7.68)	0.401
>500,000	**4.85 (1.46-16.12)**	**0.010**	**5.69 (1.31-24.74)**	**0.020**

[a] Adjusted for: age, gender, B subtype, risk factor, months of virological suppression before TDF/FTC/RPV switching, at least one viral load blip before TDF/FTC/RPV switching, pre-existent RTI-resistance before TDF/FTC/RPV switching, usage of TDF+FTC/3TC at TDF/FTC/RPV switching, third drug of the regimen at TDF/FTC/RPV switching, cumulative experience to NNRTIs before TDF/FTC/RPV switching, baseline and nadir CD4 cell count, number of previous regimens before TDF/FTC/RPV switching, pre-therapy viremia as drug-naïve. [b] Reference group (dummy). CI: confidence interval. HR: hazard ratio. Boldface indicates factors that were significantly associated ($p<0.05$) with virological rebound.

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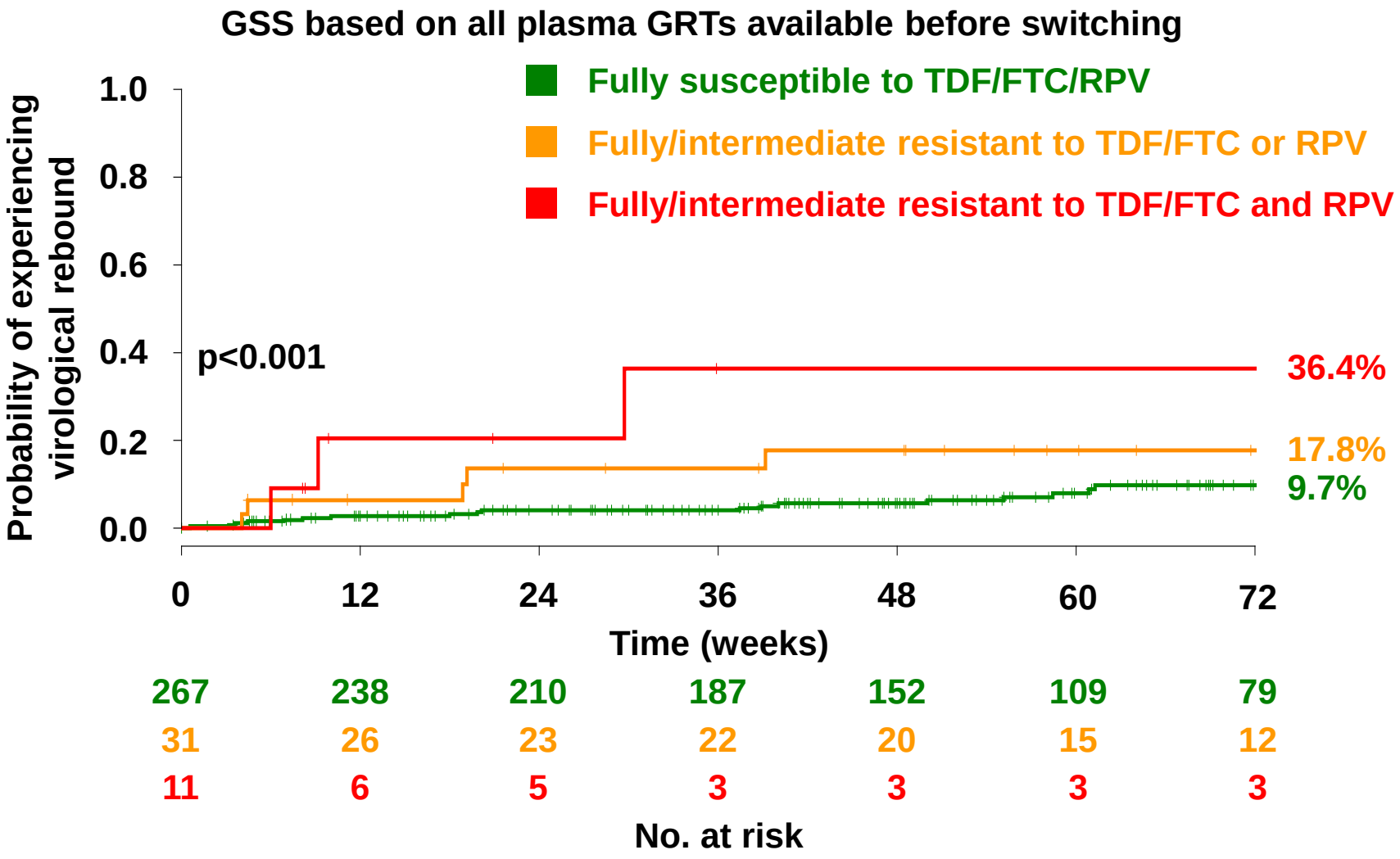
By 72 weeks of therapy, patients having a fully or intermediate resistant virus to both TDF/FTC and RPV showed a higher probability of experiencing virological rebound compared to those having a virus fully or intermediate resistant to TDF/FTC or RPV, and those having a virus fully susceptible to TDF/FTC/RPV.



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Cox uni-multivariable analysis showed that the hazard ratio of experiencing virological rebound was significant higher in patients who showed a virus fully or intermediate resistant to both TDF/FTC and RPV, and in patients with pre-therapy viral load >500,000 copies/mL.

Variables	Hazard ratio of experiencing virological rebound			
	Crude		Adjusted[a]	
	HR (95% CI)	p-value	HR (95% CI)	p-value
GSS based on all plasma GRTs available before switching:				
Fully susceptible TDF/FTC/RPV[b]	1		1	
Fully/intermediate resistant to TDF/FTC or RPV	1.70 (0.38-7.63)	0.487	1.55 (0.22-10.84)	0.661
Fully/intermediate resistant to TDF/FTC and RPV	**10.13 (2.83-36.24)**	**<0.0001**	**9.88 (1.15-26.07)**	**0.015**
Pre-therapy viremia (copies/mL) as drug-naïve:				
<100,000[b]	1		1	
100,000-500,000	1.59 (0.43-5.93)	0.488	1.63 (0.40-6.60)	0.490
>500,000	**4.85 (1.46-16.12)**	**0.010**	**4.32 (1.02-18.33)**	**0.047**

[a] Adjusted for: age, gender, B subtype, risk factor, months of virological suppression before TDF/FTC/RPV switching, at least one viral load blip before TDF/FTC/RPV switching, GSS based on all plasma GRTs available before switching, usage of TDF+FTC/3TC at TDF/FTC/RPV switching, third drug of the regimen at TDF/FTC/RPV switching, cumulative experience to NNRTIs before TDF/FTC/RPV switching, baseline and nadir CD4 cell count, number of previous regimens before TDF/FTC/RPV switching, pre-therapy viremia as drug-naïve. [b] Reference group (dummy). HR: hazard ratio. Boldface indicates factors that were significantly associated (p<0.05) with virological rebound.

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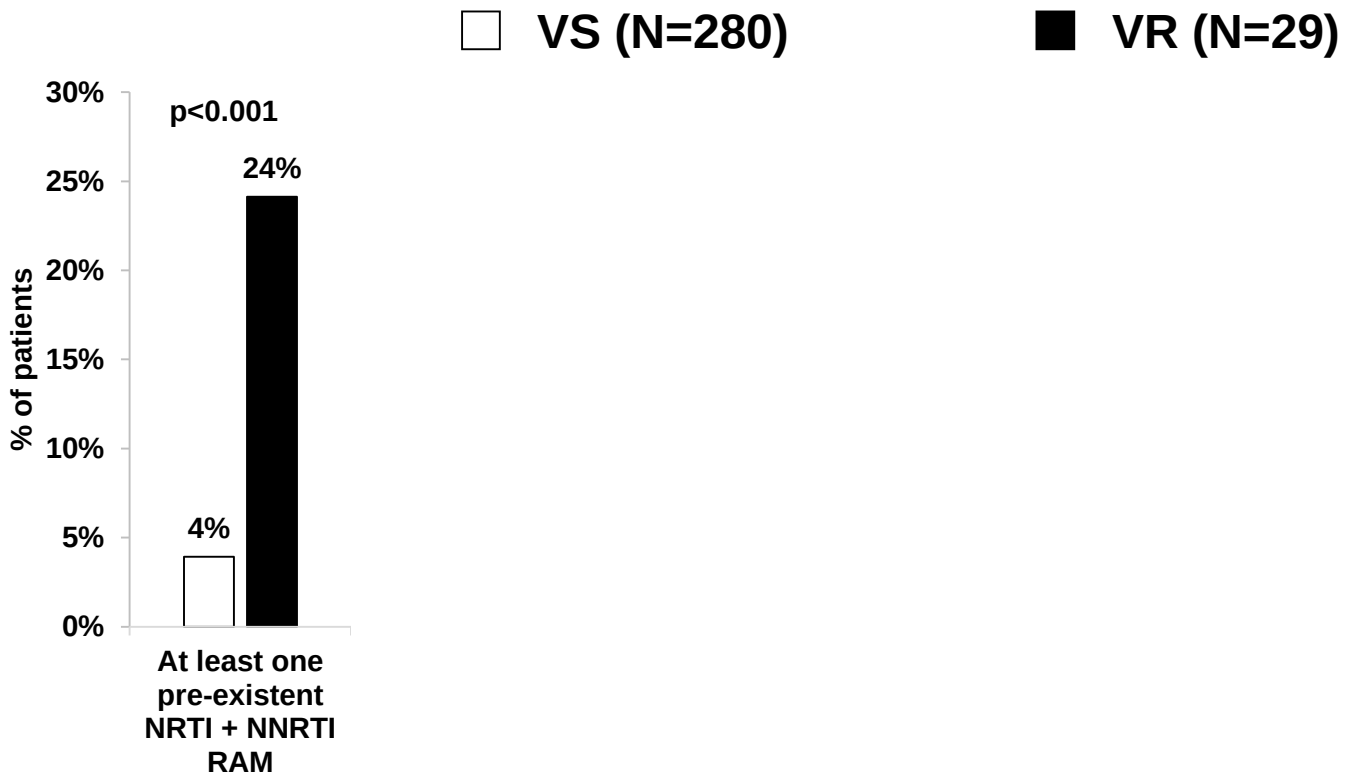
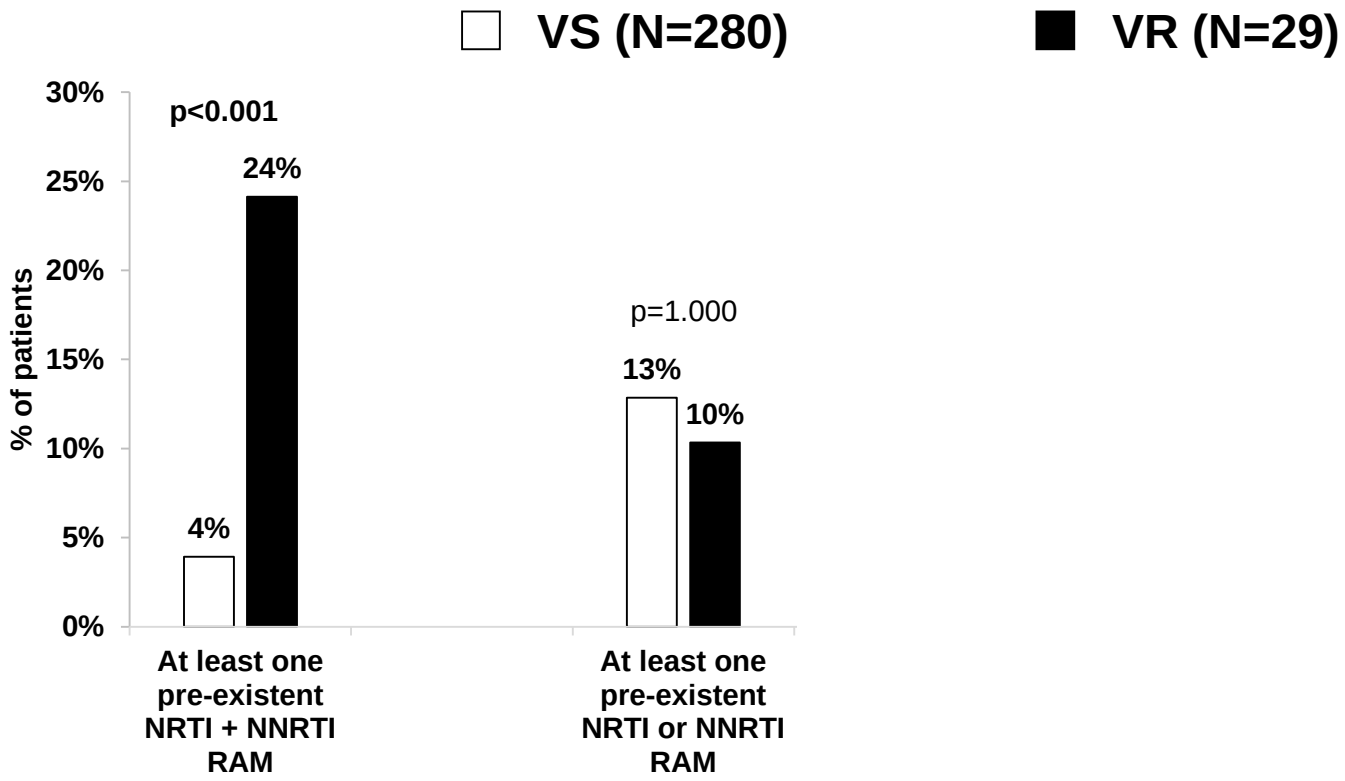
The combination of at least one NRTI and at least one NNRTI pre-existent RAM was more frequently observed among patients experiencing virological rebound compared to those who maintained virological suppression.



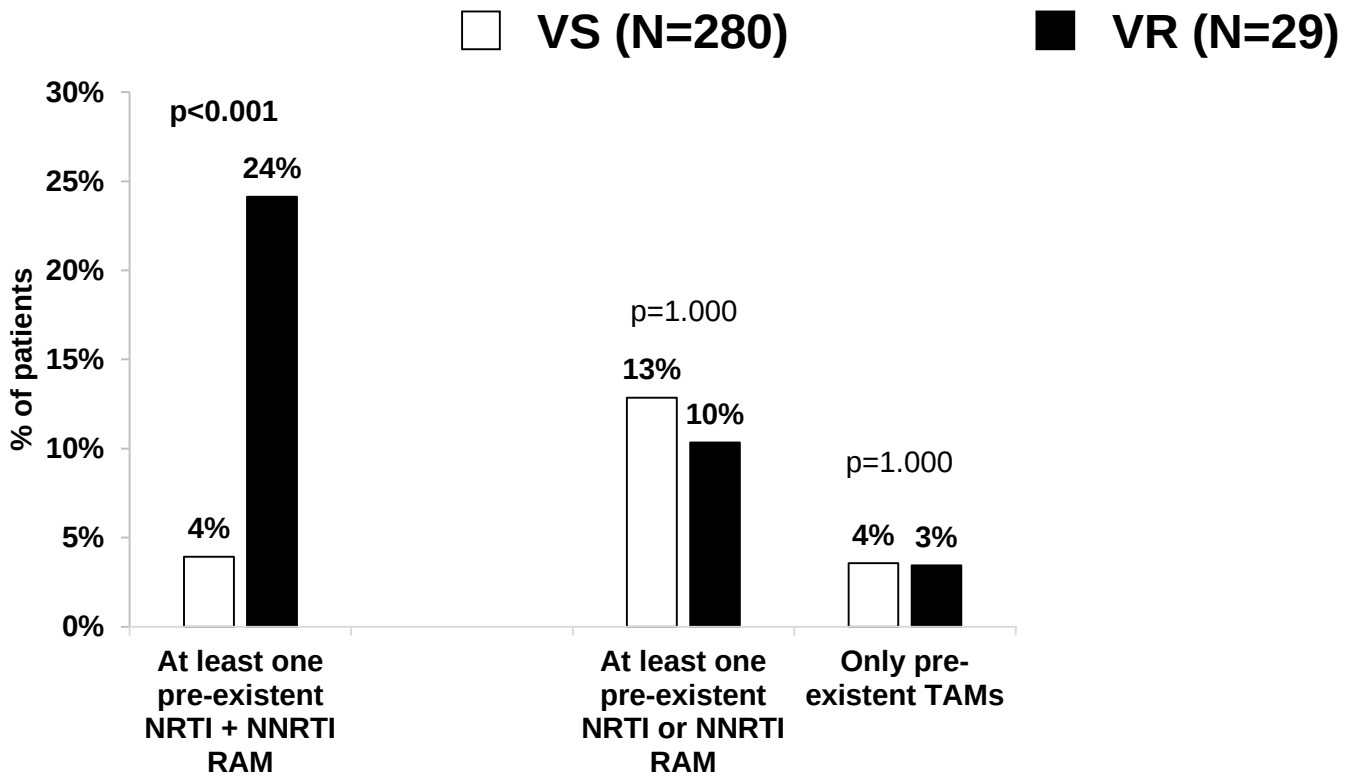
P-values by Fisher's exact test. RAMs: resistance associated mutations. VR: virological rebound. VS: virological suppression.

By contrast, the proportion of patients with pre-existent RAMs for only one drug-class (NRTI or NNRTI) was similar among patients experiencing virological rebound and those who maintained virological success.



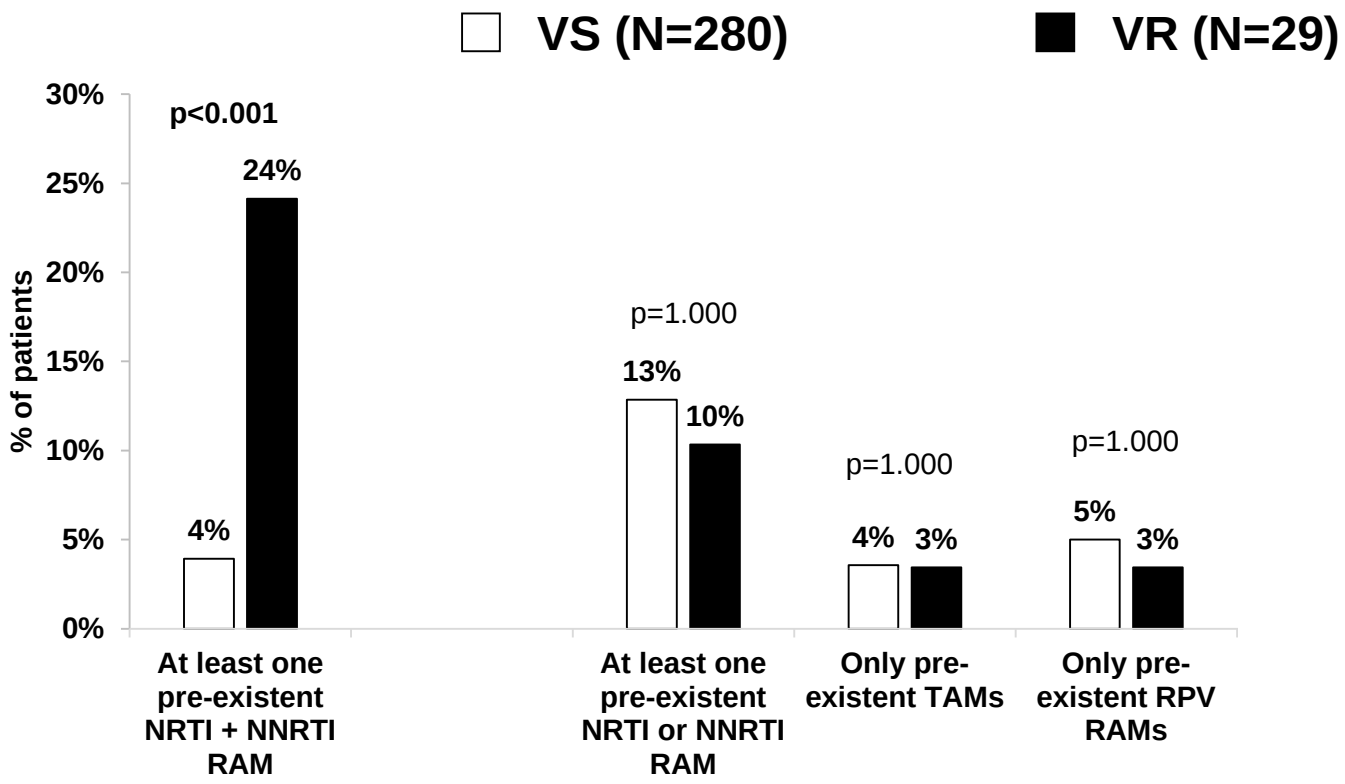
P-values by Fisher's exact test. RAMs: resistance associated mutations. VR: virological rebound. VS: virological suppression.

In particular, the proportion of patients carrying only pre-existent TAMs was similar among those who experienced virological rebound and those who maintained virological suppression.



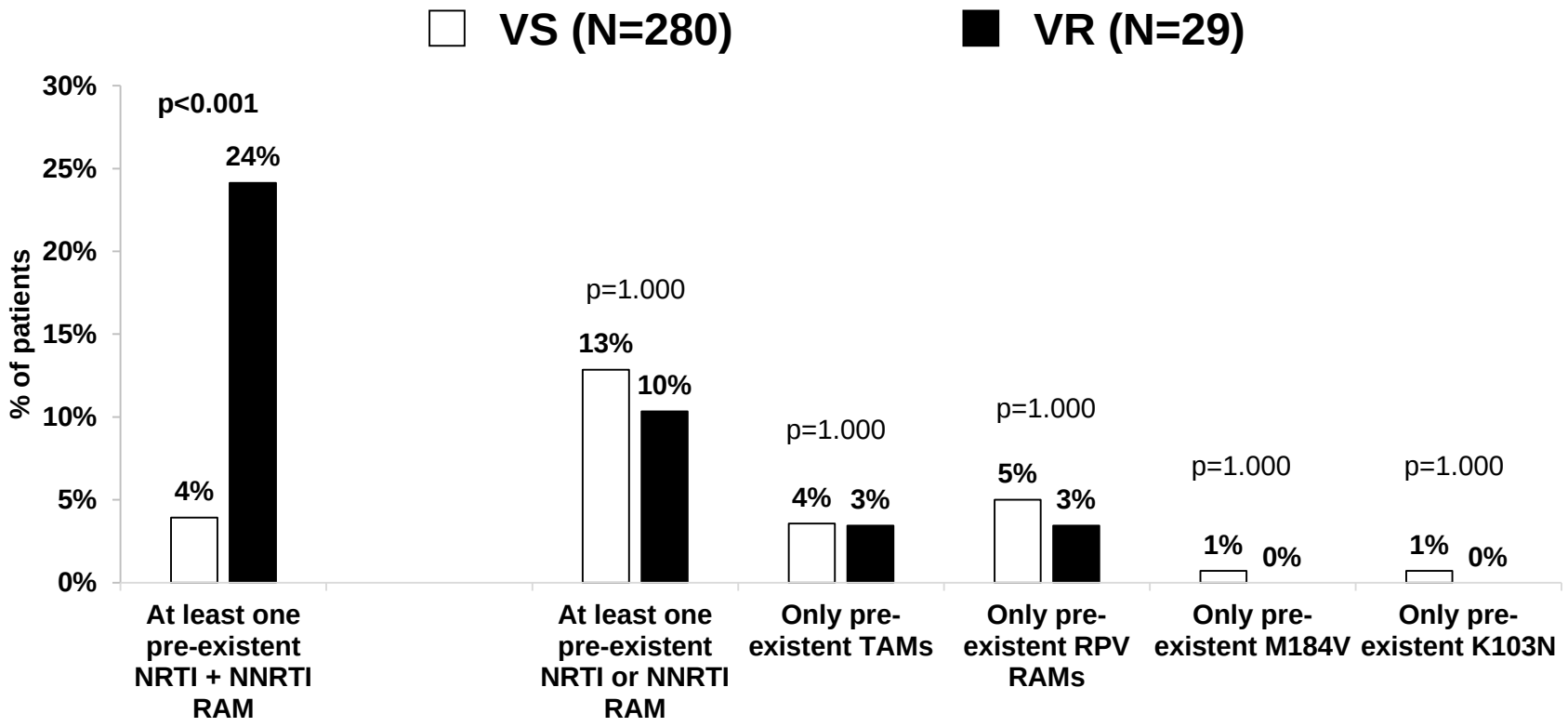
P-values by Fisher's exact test. RAMs: resistance associated mutations. TAMs: thymidine analogue mutations. VR: virological rebound. VS: virological suppression.

Similarly, the presence of isolated pre-existent RPV RAMs was not associated to virological response.



P-values by Fisher's exact test. RAMs: resistance associated mutations. TAMs: thymidine analogue mutations. VR: virological rebound. VS: virological suppression.

Finally, two patients harbouring the pre-existent isolated M184V, and other two patients harbouring the pre-existent isolated K103N maintained virological suppression.



P-values by Fisher's exact test. RAMs: resistance associated mutations. TAMs: thymidine analogue mutations. VR: virological rebound. VS: virological suppression.

Among the 29 patients who experienced virological rebound, 10 had an available GRT after virological rebound. Of them, 6 showed resistance to at least one drug class.

ID	Pressure (weeks)[a]	VL at GRT (log_{10} copies/mL)	No. of previous GRTs[b]	Pre-existent RAMs		RAMs at GRT after VR	
				NRTI	NNRTI	NRTI	NNRTI
832	51	2.6	3	D67N, K70R, M184V, K219Q	K103N, V106A, E138G, G190A, F227L	K70R, M184V, K219Q	K103N, E138G, **Y181C**, G190A, **P225H**
940	94	4.6	1	D67N, K70R, K219E	K103N	D67N, K70R, **L74I**, **M184V**, K219E	K103N, **V108I**, **Y181C**
1770	22	3.1	1	D67N, K70R, M184V, K219E	K103N, P225H	**M41L**, D67N, K70R, M184V, K219E	K103N, **E138G**, P225H
2346	32	4.3	2	D67N, K70R, K219E/Q	K103N, P225H	D67N, K70R, **M184V**, K219E	K103N, **V108I**, **Y181C**, P225H
7024	23	3.7	5	M184V	K103N, P225H	M184V	**V179L**, **Y181C**, **F227C**
7055	84	2.2	2	None	None	None	None
9952	94	4.5	3	None	None	None	None
10783	66	2.0	2	None	None	**M184I**	**E138K**
14195	7	2.1	2	None	None	None	None
16082	10	2.7	1	None	None	None	None

[a] Weeks from TDF/FTC/RPV starting to GRT date. [b] Number of all GRTs available before TDF/FTC/RPV switching. Boldface indicates the new RAMs detected after VR. RAMs: resitance associated mutations. VL: viral load.

In particular, five patients showed new RAMs and one patient without any pre-existent resistance acquired novel RAMs.

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				NRTI	NNRTI	NRTI	NNRTI
832	51	2.6	3	D67N, K70R, M184V, K219Q	K103N, V106A, E138G, G190A, F227L	K70R, M184V, K219Q	K103N, E138G, **Y181C**, G190A, **P225H**
940	94	4.6	1	D67N, K70R, K219E	K103N	D67N, K70R, **L74I**, **M184V**, K219E	K103N, **V108I**, **Y181C**
1770	22	3.1	1	D67N, K70R, M184V, K219E	K103N, P225H	**M41L**, D67N, K70R, M184V, K219E	K103N, **E138G**, P225H
2346	32	4.3	2	D67N, K70R, K219E/Q	K103N, P225H	D67N, K70R, **M184V**, K219E	K103N, **V108I**, **Y181C**, P225H
7024	23	3.7	5	M184V	K103N, P225H	M184V	**V179L**, **Y181C**, **F227C**
7055	84	2.2	2	None	None	None	None
9952	94	4.5	3	None	None	None	None
10783	66	2.0	2	None	None	**M184I**	**E138K**
14195	7	2.1	2	None	None	None	None
16082	10	2.7	1	None	None	None	None

[a] Weeks from TDF/FTC/RPV starting to GRT date. [b] Number of all GRTs available before TDF/FTC/RPV switching. Boldface indicates the new RAMs detected after VR. RAMs: resitance associated mutations. VL: viral load.

Conclusions

In clinical practice, treatment **simplification with TDF/FTC/RPV as single table regimen is associated with a very high rate of virological suppression maintenance (89%)**, particularly in patients without pre-existent RTI-resistance.

By contrast, **concomitant pre-existent NRTI- and NNRTI-resistance and pre-therapy viremia >500,000 copies/mL are associated with a higher risk to lose virological suppression**, highlighting the need for an accurate selection of patients to be switched to TDF/FTC/RPV as single tablet regimen.

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- The Patients