Use of rilpivirine in HIV-1 infected individuals in routine clinical practice from 2012 to 2017 in France

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Abstract

Objectives:

We assessed virological outcomes of rilpivirine use in France from 2012 to 2017, in three groups of people living with HIV (PLHIV):(1) antiretroviral (ARV)-naïve PLHIV;(2) ARV-experienced PLHIV switching to rilpivirine while failing therapy; and (3) ARV-experienced PLHIV switching to rilpivirine while virologically controlled.

Methods:

Virological success (VS) was defined as a plasma HIV-1 viral load (VL)<50 copies/mL and virological failure (VF) as two consecutive VL>50 copies/mL or one VL>50 copies/mL followed by a treatment switch prior to the next VL measurement. The cumulative incidence of VS was assessed considering rilpivirine discontinuation, loss to follow-up, and death as competing risks, while estimates of cumulative incidence of VF accounted for loss to follow-up and death.

Results: Among the 2166 ARV-naïve PLHIV initiating rilpivirine, the four-year cumulative incidence of VS was 91.0% and was associated with baseline VL. Among the 2125 ARV-experienced PLHIV switching to rilpivirine while failing therapy, the four-year cumulative incidence of VS was 82.5% and was associated with lower VL, higher CD4, and less than three prior ARVs. Among the 11828 ARV-experienced PLHIV switching to rilpivirine while virologically controlled, the four-year cumulative incidence of VF was 9.6%. The risk of VF was lower among MSM, for PLHIV with CD4≥500/mm^3, without a prior AIDS event, or with a longer VL suppression at baseline.

Conclusion: Rilpivirine-containing regimens yielded high rates of viral suppression in most participants, while it was ineffective when used outside the marketing authorization in naïve participants.

Introduction

Rilpivirine is a second-generation NNRTI that has been available in France since 2012. It is indicated for people living with HIV (PLHIV) with viral load (VL) ≤100 000 copies/mL and no NRTI and NNRTI resistance. Clinical trials have demonstrated the efficacy of rilpivirine associated with emtricitabine and tenofovir [TDF], in treatment-naïve PLHIV with VL≤100 000 copies/mL.[1,2,3] Others clinical trials have shown that the rilpivirine/emtricitabine/TDF combination can maintain virological suppression in antiretroviral (ARV)-experienced virologically-controlled PLHIV.[4-8] In recent trials, the dual therapy dolutegravir/rilpivirine was non-inferior to a current triple antiretroviral therapy (ART) regimen in ARV-experienced virologically-controlled PLHIV at week 48 and efficacy and safety were maintained at week 100.[9,10]

It is important to obtain data from real-life settings to assess how rilpivirine is used in routine care and evaluate its virological efficacy, as a complement to data from clinical trials. The purposes of this observational study were to describe the routine use of rilpivirine in France in ARV-naïve PLHIV, ARV-experienced PLHIV failing therapy, and ARV-experienced virologically-controlled PLHIV and to assess its effectiveness in terms of virological outcomes. We also aimed to assess whether the effectiveness was similar when rilpivirine was used in dual therapy versus in combination with three or more drugs.

Individuals and methods

Individuals and data sources

The French Hospital Database on HIV (FHDH) is a hospital-based multicentre open cohort in which inclusions have been ongoing since 1989.[11] Individuals are eligible if they have documented HIV-1 or HIV-2 infection and give their written informed consent to participate. Data are collected prospectively by trained research assistants using standardized forms which include demographic characteristics, biological markers such as the CD4 and plasma HIV RNA level, and antiretroviral treatments. The FHDH project was approved by the French data protection authority (Commission National de l'Informatique et des Libertés on 27 November 1991, Journal Officiel, 17 January 1992).

Study population

This study was restricted to HIV-1 infected individuals of at least 18 years of age who started rilpivirine between January 1, 2012 and December 31, 2017, at least one year before the last recorded FHDH visit in the centre, with available viral load (VL) and CD4 values within six months before initiating rilpivirine and at least one VL value after. If they satisfied the inclusion criteria, individuals were classified into one of the following groups: (1) ARV-naïve PLHIV; (2) ARV-experienced PLHIV switching to rilpivirine while failing therapy, and (3) ARV-experienced PLHIV switching to rilpivirine while virologically controlled (VL<50 copies/mL).

Statistical analysis

The principles of the analyses were the same as in a previous study assessing darunavir in a similar setting.[12] The baseline for all analyses was the date of rilpivirine initiation. Continuous variables were expressed as medians and IQR and categorical variables as counts and percentages. Virological success (VS) was defined as a VL < 50 copies/mL and virological failure (VF) as two consecutive VL values > 50 copies/mL, or one VL value > 50 copies/mL followed by a treatment switch prior to the next VL measurement. For ARV-naïve PLHIV and ARV-experienced PLHIV switching to rilpivirine while failing

therapy, we assessed the cumulative incidence of VS considering the discontinuation of rilpivirine as a competing risk (individuals who discontinue rilpivirine are likely to be those experiencing a slower reduction in VL). This approach avoids a situation in which most individuals switch from rilpivirine and achieve a reduction in VL while on an alternative treatment. The events of loss to follow-up and death were also considered as competing risks for VS. For ARV-experienced PLHIV switching to rilpivirine while virologically controlled, the cumulative incidence of VF was estimated using an intention-to-continue-treatment approach, ignoring treatment change in order to also adopt a conservative approach. Only the events loss to follow-up and death were considered as competing risks. Individuals were considered to be "lost to follow-up" when there was an interval of more than 18 months between the last follow-up visit and the last database update for the centre in which they were followed. Individuals who experienced neither the outcome of interest nor the competing events were censored at the last follow-up or 48 months, whichever occurred first.

Univariable and multivariable competing-risk regression models, yielding subdistribution hazard ratios (sHR) were used to assess the influence of the type of combination (dual therapy, combination with three or more drugs) on VS or VF.[13] The following potential confounding factors were accounted for the three groups: age, gender and HIV transmission group (MSM, injecting drug users, other men, other women), sub-Saharan origin, prior AIDS event, baseline CD4 (<200/mm^3, 200-350/mm^3, 350-500/mm^3, ≥ 500/mm^3), hepatitis C (HCV) antibody status (negative, positive), and hepatitis B surface antigen (HbsAg) status (negative, positive). Baseline VL (≤30 000, 30 000-100 000, >100 000 copies/mL) was also accounted for ARV-naïve PLHIV and ARV-experienced PLHIV switching to rilpivirine while failing therapy, as was the number of prior ARVs (≤3, 4-6, >6) for ARV-experienced PLHIV switching to rilpivirine while failing therapy and the duration of viral suppression prior to baseline for ARV-experienced PLHIV switching to rilpivirine while virologically controlled. SAS software (v9.4; SAS Institute Inc, Cary, NC, USA) was

used for all statistical analyses.

Results

Baseline characteristics

The baseline characteristics according to group are shown in Table 1. A total of 2166 ARV-naïve PLHIV initiated rilpivirine (group 1), 2125 ARV-experienced PLHIV switched to rilpivirine while failing therapy (group 2) and 11828 ARV-experienced PLHIV switched to rilpivirine while virologically controlled (group 3). No PLHIV started rilpivirine monotherapy. Only 7 ARV-naïve PLHIV started a dual therapy (0.3%). Among ARV-experienced PLHIV who switched to rilpivirine while failing therapy, 76 received dual therapy (3.6%) and among those who switched to rilpivirine while virologically controlled, 555 received dual therapy (4.7%) of which most was with dolutegravir (90.5%). Triple therapy with two NRTIs, particularly TDF and emtricitabine, was the most prescribed for all groups. A minority of ARV-naïve PLHIV initiated rilpivirine with VL>100 000 copies/mL (4.5%) as well as ARV-experienced PLHIV switching to rilpivirine while failing therapy (6.0%). A minority of ARV-naïve PLHIV had prior AIDS event (2.2%), HCV coinfection (3.6%) and HBV coinfection (2.8%), while among ARV-experienced PLHIV overall, 19.3% had a prior AIDS event, 11.3% were HCV coinfected and 6.0% HBV coinfected. The median duration of follow-up was 3.1 years (IQR: 2.0-4.0) for group 1, 3.3 years (IQR: 2.0-4.0) for group 2, and 3.3 years (IQR: 2.1-4.0) for group 3.

ARV-naïve PLHIV

Of the 2166 ARV-naïve PLHIV who initiated rilpivirine, 1950 achieved a VL<50 copies/mL, whereas 137 discontinued rilpivirine, 34 were lost to follow-up and three died before the control of VL. Cumulative incidence estimates showed the one-year probability of VS, discontinuation, loss to follow-up, and death to be 86.3% (95% CI, 84.8-87.8), 5.2% (95% CI, 4.3-6.3), 1.1% (95% CI, 0.7-1.6) and 0.1% (95% CI, 0.0-0.3) respectively, and at four

years to be 91.0% (95% CI, 89.6-92.4), 6.6% (95% CI, 5.7-7.6), 1.6% (95% CI, 1.2-2.3) and 0.1% (95% CI, 0.1-0.4) respectively. Individuals with baseline VL between 30 000 and 100 000 copies/mL or a baseline VL > 100 000 copies/mL were less likely to achieve a VL<50 copies/mL (sHR=0.71, 95% CI, 0.65-0.78 and sHR=0.48, 95% CI, 0.39-0.58, respectively) (Figure 1a and Table 2). The type of combination (dual therapy or combination with three or more drugs) was not significantly associated with VS. Neither HBV nor HCV coinfection were associated with VS.

The main reason for discontinuing rilpivirine before VS were adverse events (43.9%) and treatment failure (23.4%) (Supplementary table1). Among the 1950 individuals with VS, 294 discontinued rilpivirine after reaching a VL < 50 copies/mL, and the probability of discontinuing rilpivirine at four years was 20.4% (95% CI, 18.5-22.6). The main reason for discontinuing rilpivirine after VS was adverse events (49.1%).

ARV-experienced PLHIV switching to rilpivirine while failing therapy

Among the 2125 ARV-experienced PLHIV switching to rilpivirine while failing therapy, 1736 reached a VL< 50 copies/mL, whereas 302 discontinued rilpivirine, 29 were lost to follow-up and 7 died before reaching this endpoint. Cumulative incidence estimates showed the one-year probability of VS, discontinuation, loss to follow-up, and death to be 76.1% (95% CI, 74.4-77.8), 10.5% (95% CI, 9.2-11.9), 2.2% (95% CI, 2.0-2.5), and 0.1% (95% CI, 0.0-0.1) respectively, and at four years to be 82.5% (95% CI, 80.8-84.1), 14.8% (95% CI, 13.2-16.6), 7.6% (95% CI, 7.1-8.2), and 0.6% (95% CI, 0.4-0.8) respectively. Individuals with a baseline VL between 30 000 and 100 000 copies/mL or baseline VL > 100 000 copies/mL were less likely to achieve a VL<50 copies/mL (sHR=0.65, 95% CI, 0.57-0.74 and sHR=0.55, 95% CI, 0.46-0.67, respectively) (Figure 1b and Table 3). Individuals who were experienced to more than three prior ARVs or who had baseline CD4 < 200/mm^3 were also less likely to reach a VL<50 copies/mL, whereas neither the

type of combination nor the coinfection with HBV or HCV were significantly associated with VS (Table 3).

The main reason for the discontinuation of rilpivirine before VS was treatment failure (38.1%) (Supplementary table1). Among the 1736 individuals with VS, 430 discontinued rilpivirine after reaching a VL<50 copies/mL and the probability of discontinuing rilpivirine at four years was 31.4% (95% CI, 29.2-33.8). The main reason for discontinuing rilpivirine after VS was adverse events (30.4%).

ARV-experienced PLHIV switching to rilpivirine while virologically controlled

Among the 11828 ARV-experienced PLHIV switching to rilpivirine while virologically controlled, 967 experienced VF (872 with two consecutive VL > 50 copies/mL and 95 with one VL > 50 copies/mL followed by a treatment switch prior to the next VL measurement), whereas 728 were lost to follow-up and 45 died. Cumulative incidence function estimates showed the one-year probability of VF, loss to follow-up, and death to be 4.5% (95% CI, 4.1-4.9), 2.2% (95% CI, 2.0-2.5), and 0.1% (95% CI, 0.0-0.1) respectively, and at four years to be 9.6% (95% CI, 9.1-10.2), 7.6% (95% CI, 7.1-8.2), and 0.6% (95% CI, 0.4-0.8) respectively.

As shown in Table 4, MSM had a lower risk of VF than the other transmission groups. A shorter duration of viral suppression, prior AIDS event, or baseline CD4 <500/mm^3 were associated with a higher risk of VF. The probability of VF at four years after switching to rilpivirine was ranging from 6.1% (95% CI, 5.3-7.0) in participants for whom the duration of viral suppression was > 5 years, to 13.7% (95% CI, 12.6-14.9) among individuals with a duration of viral suppression < 2 years (Figure 2a).

PLHIV switching to dual therapy had a median duration of follow-up of 1.7 years (IQR: 1.1-2.4) and those switching to combination with three or more drugs 3.4 years (IQR: 2.2-4.0). The one-year and four-year probabilities of VF, were 2.8% (95% CI, 1.9-4.1) and 6.1% (95% CI, 4.1-9.2) among those receiving dual therapy, and 4.6% (95% CI, 4.2-5.0)

and 9.8% (95% CI, 9.2-10.5) among those receiving combination with three or more drugs, respectively (figure 2b). There were significant differences in characteristics of ARV-experienced PLHIV switching to dual therapy and those switching to three or more drugs while virologically controlled (supplementary table 2). After accounting for those differences in the multivariable model, there was no evidence of a difference in the risk of VF between dual therapy and combination with three or more drugs (sHR=0.75 (95% CI, 0.49-1.15)).

A total of 2928 individuals discontinued rilpivirine, of whom 2278 individuals (77.8%) had not experienced VF. Among individuals who had not experienced VF, the probability of discontinuing rilpivirine at four years was 26.3% (95%, 25.4-27.3). The main reason for discontinuation was adverse events (60.2%) (Supplementary table1).

Discussion

In this observational study, we showed that rilpivirine-based regimens were associated with a virological success rate > 82% at four years, for the three groups: ARV-naïve (group 1), or ARV-experienced PLHIV switching to rilpivirine while failing therapy (group 2) or while virologically controlled (group 3). Rilpivirine was predominantly prescribed in ARV-experienced PLHIV switching to rilpivirine while they were virologically controlled (73%) and according to the indication of the marketing authorization, mainly to PLHIV with a VL ≤ 100 000 copies / mL.

The one-year VS rate of 86% in ARV-naïve individuals on rilpivirine was similar to that reported in randomized controlled trials, such as the Echo trial (83% at week 48), Thrive trial (86% at week 48) or Star trials (86% at week 48).[1,2,3] The rates of discontinuation at one-year or four years were low (5.2% or 6.6%). In an observational study from the ICONA cohort, the rate of discontinuation was higher (10.1%; 95% CI [7.6-12.7%] at 2-years).[14] The main reasons for discontinuation in this ICONA study were similar to those in our study (treatment failure, 25.0% versus 23.4% and adverse events, 47.1% versus

43.9%). While HBV or HCV coinfection were associated with a lower VS rate at week 48 in the pooled data of the Echo and Thrive trials, we did not find such a trend in our study, even if the proportions of HBV or HCV coinfected PLHIV were similar.[15]

To our knowledge no study has evaluated rilpivirine in ARV-experienced PLHIV switching while failing therapy. Given that marketing authorization is restricted to ARV-naïve-or-experienced PLHIV with VL ≤ 100 000 copies / mL, rilpivirine should not be used outside this context. In our study, 6% of ARV-experienced PLHIV switching while failing had a baseline VL>100 000 copies/mL. Thus, it was not surprising that the rates of VS was only 54% at one year. Even among those who had a baseline VL between 30 000 and 100 000 copies/mL, the rate of VS with the rilpivirine regimen was only 62% at one year. The one-year VS rate of 80% in PLHIV on rilpivirine with a baseline VL≤30 000 copies/mL was close to that estimated in ARV-naïve PLHIV.

Only 4.7% of ARV-experienced PLHIV with controlled VL switched to rilpivirine dual therapy, probably because the rilpivirine/dolutegravir single-tablet regimen was not yet available during the study period. This combination was only marketed in France in 2018.

In our observational study, the rate of VF at one year among ARV-experienced PLHIV switching to rilpivirine while virologically controlled was 4.5%, higher than that in the Spirit (2.5%), GS-US-366-1160 (1.0%) or Sword trials (0.6%), with a possible explanation being a shorter duration of VL suppression in our study. A prior AIDS event, baseline CD4 <500/mm^3, or shorter duration of viral suppression were independently associated with a higher risk of VF, as in many switch studies.[12,16] Dual therapy consisting of rilpivirine with INI or boosted PI was associated with a response rate not significantly different from that of triple therapy and, even accounting for the observational nature of our study, it is reassuring.

The main strength of our study was its large size, 48-month follow-up, and routine clinical setting, providing additional evaluation of the use of rilpivirine in combination with one or

more ARVs in all groups of patients. In this observational setting, we were unable to adjust the results for the genotypic susceptibility score or adherence which are not recorded in the FHDH. However, we feel that our results are nevertheless robust, as we adjusted for the number of prior ARVs in ARV-experienced PLHIV switching to rilpivirine while failing therapy and for prolonged viral suppression in ARV-experienced PLHIV switching to rilpivirine while virologically controlled.

In conclusion, this real-world nationwide cohort shows that rilpivirine was used in France from 2012 to 2017 in ARV-naïve and ARV-experienced PLHIV switching to rilpivirine while failing therapy mainly with a VL≤100 000 copies/mL as per the marketing authorization and in ARV-experienced PLHIV switching to rilpivirine while virologically controlled with a high level of efficacy, similar to that in clinical trials. When rilpivirine was used outside the marketing authorization, it was not effective. Our results show no significant difference in efficacy between the use of dual and triple therapy in ARV-experienced PLHIV switching to rilpivirine while virologically controlled.

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Author's contribution

DC and VP designed the study, analyzed the data, drafted the manuscript, had full access to the data and had final responsibility for the decision to submit the study for publication. AC and SG revised the analysis plan. All authors were involved in the interpretation of the data and critical revision of the manuscript and approved the final version.

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Table 1. Individual characteristics at RPV initiation according to the group ~~clinical situation~~

	ARV naive (n=2166)		Switch to RPV with VL>50 copies/mL (n=2125)		Switch to RPV with VL<50 copies/mL (n=11828)	
	n or median	% or [IQR]	n or median	% or [IQR]	n or median	% or [IQR]
Age	37	[30-47]	43	[35-51]	46	[38-54]
Gender						
Men	1580	72.9	1152	54.2	7669	64.8
Women	567	26.2	963	45.3	4120	34.8
Transgender	19	0.9	10	0.5	39	0.3
Sub-Saharan origin						
Yes	390	18.0	607	28.6	2813	23.8
No	1776	82.0	1518	71.4	9015	76.2
Year of HIV-1 diagnosis	2013	[2011-2014]	2005	[1997-2011]	2004	[1997-2010]
Transmission group						
MSM	1113	51.4	635	29.9	4614	39.0
Injecting drug users	38	1.8	150	7.1	717	6.1
Heterosexual	903	41.7	1175	55.3	5729	48.4
Other	112	5.2	165	7.8	768	6.5
Number of prior ARVs	-	-	4	[3-8]	5	[3-7]
Cumulative duration of ARV exposure (months)	-	-	76.2	[18.0-163.4]	80.1	[31.7-163.5]
Year of RPV initiation						
2012	163	7.5	278	13.1	1392	11.8
2013	657	30.3	694	32.7	3645	30.8
2014	651	30.1	523	24.6	2937	24.8
2015	381	17.6	331	15.6	2106	17.8
2016	296	13.7	282	13.3	1620	13.7
2017	18	0.8	17	0.8	123	1.0
Type of combination						
Dual therapy:	**7**	**0.3**	**76**	**3.6**	**555**	**4.7**
RPV+DTG	3	0.1	55	2.6	502	4.2
RPV+RAL	0	0.0	4	0.2	29	0.3
RPV+PI/r	4	0.2	17	0.8	24	0.2
Triple therapy:	**2148**	**99.2**	**1963**	**92.4**	**11098**	**93.8**
2 NRTI+RPV:	2145	99.0	1868	87.9	10957	92.6
Of which: TDF+FTC	*2113*	*97.6*	*1802*	*84.8*	*10277*	*86.9*
Other	3	1.0	95	4.5	141	1.2
Four or more drugs	**11**	**0.5**	**86**	**4.0**	**175**	**1.5**
CD4 (cells/mm^3) at baseline	473	[350-636]	466	[304-650]	627	[465-823]
<200	140	6.5	264	12.4	281	2.4
200-350	400	18.5	404	19.0	1026	8.7
350-500	652	30.1	505	23.8	2222	18.8
≥500	974	45.0	952	44.8	8299	70.2
CD4/CD8 at baseline	0.5	[0.3-0.8]	0.5	[0.3-0.8]	0.9	[0.6-1.2]
Missing	211		206		964	
<0.5	1722	88.1	1643	85.6	6799	62.6
≥0.5	233	11.9	276	14.4	4065	37.4
Viral load (copies/mL) at baseline	4.2	[3.7-4.6]	3.7	[2.5-4.9]	-	-
<50	-	-	-	-	11828	100
≤30000	1456	67.2	1720	80.9	-	-
30000-60000	389	18.0	179	8.4	-	-
60000-100 000	224	10.3	98	4.6	-	-
>100 000	97	4.5	128	6.0	-	-
Duration of VL suppression at baseline (year)					2.8	[0.9-6.0]
<2					4831	40.8
2-5					3290	27.8
≥ 5					3707	31.3
Prior AIDS event						
No	2118	97.8	1717	80.8	9539	80.6
Yes	48	2.2	408	19.2	2289	19.4
HCV antibody status						

	ARV naive (n=2166)		Switch to RPV with VL>50 copies/mL (n=2125)		Switch to RPV with VL<50 copies/mL (n=11828)	
	n or median	% or [IQR]	n or median	% or [IQR]	n or median	% or [IQR]
Negative	2087	96.4	1880	88.5	10495	88.7
Positive	79	3.6	245	11.5	1333	11.3
HBsAg status						
Negative	2106	97.2	1994	93.8	11123	94.0
Positive	60	2.8	131	6.2	705	6.0

Abbreviations: ARV, antiretrovirals; RPV, rilpivirine; DTG, dolutegravir; RAL, raltegravir; TDF, tenofovir; FTC, emtricitabine; VL, viral load

Table 2. Factors associated with 48 month virological success among ARV naive individuals: univariable and multivariable competing risk regression analyses. The events "RPV discontinuation", "lost to follow-up" and "deaths" were considered as competing risk for the virological success. N=2166 of whom 1950 reached VL<50 copies/mL.

Characteristics	Univariable analysis		Multivariable analysis	
	sHR (95% CI)	P	sHR (95% CI)	P
Age (per 10-years increment)	0.98 (0.95-1.03)	0.56	1.00 (0.97-1.05)	0.79
Gender and transmission group				
MSM	1	0.02	1	0.22
Injecting drug users	0.97 (0.64-1.46)		0.94 (0.60-1.48)	
Other men	0.83 (0.74-0.94)		0.88 (0.78-1.00)	
Other women	0.95 (0.85-1.06)		0.92 (0.81-1.05)	
Sub-Saharan origin				
Yes	1	0.21	1	0.83
No	1.08 (0.96-1.22)		1.02 (0.88-1.18)	
Type of combination				
Dual therapy	1.60 (0.78-3.27)	0.20	1.84 (0.89-3.83)	0.10
Triple therapy or more	1		1	
VL at baseline (copies/mL)				
≤30000	1	<0.0001	1	<0.0001
30000-100 000	0.70 (0.64-0.77)		0.71 (0.65-0.78)	
>100 000	0.45 (0.37-0.55)		0.48 (0.39-0.58)	
Prior AIDS event				
No	1	0.07	1	0.80
Yes	0.74 (0.54-1.02)		0.96 (0.70-1.32)	
CD4 (cells/mm^3)				
<200	0.65 (0.53-0.79)	<0.0001	0.81 (0.65-1.01)	0.08
200-350	0.85 (0.75-0.96)		0.91 (0.80-1.04)	
350-500	1.00 (0.90-1.11)		1.03 (0.93-1.15)	
≥ 500	1		1	
HCV antibody status				
Negative	1	0.57	1	0.88
Positive	1.08 (0.84-0.38)		1.02 (0.77-1.36)	
HBsAg status				
Negative	1	0.88	1	0.66
Positive	1.02 (0.77-1.36)		1.07 (0.78-1.47)	

Table 3. Factors associated with 48 month virological success among ARV experienced individuals switching to RPV with VL>50 copies/mL: univariable and multivariable competing risk regression analyses. The events "RPV discontinuation", "lost to follow-up" and "deaths" were considered as competing risk for the virological success. N=2125 of whom 1736 reached VL<50 copies/mL.

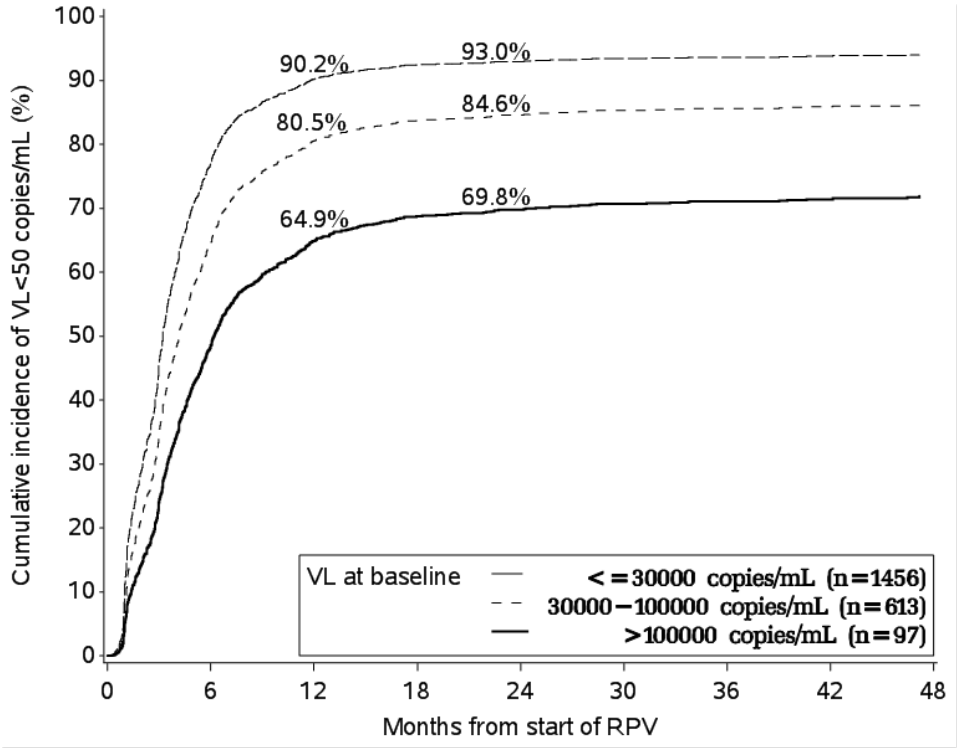
Characteristics	Univariable analysis		Multivariable analysis	
	sHR (95% CI)	P	sHR (95% CI)	P
Age (per 10-years increment)	1.02 (0.97-1.06)	0.48	1.03 (0.97-1.08)	0.28
Gender and transmission group				
MSM	1	0.37	1	0.31
Injecting drug users	0.90 (0.74-1.09)		0.94 (0.75-1.19)	
Other men	0.91 (0.79-1.04)		0.93 (0.80-1.08)	
Other women	0.99 (0.88-1.10)		1.05 (0.92-1.20)	
Sub-Saharan origin				
Yes	1	0.68	1	0.77
No	1.02 (0.92-1.13)		1.02 (0.90-1.15)	
Number of prior ARVs				
≤ 3	1	0.001	1	0.004
4-6	0.83 (0.74-0.94)		0.84 (0.75-0.95)	
>6	0.84 (0.75-0.94)		0.84 (0.74-0.95)	
Type of combination				
Dual therapy	1.17 (0.90-1.51)	0.24	1.12 (0.85-1.49)	0.42
Triple therapy or more	1		1	
VL at baseline (copies/mL)				
≤30000	1	<0.0001	1	<0.0001
30000-100 000	0.59 (0.52-0.67)		0.65 (0.57-0.74)	
>100 000	0.48 (0.40-0.58)		0.55 (0.46-0.67)	
Prior AIDS event				
No	1	0.008	1	0.68
Yes	0.84 (0.74-0.96)		0.97 (0.85-1.11)	
CD4 (cells/mm^3)				
<200	0.55 (0.46-0.64)	<0.0001	0.71 (0.59-0.86)	0.0004
200-350	0.86 (0.76-0.97)		0.95 (0.83-1.09)	
350-500	1.03 (0.92-1.16)		1.07 (0.95-1.21)	
≥ 500	1		1	
HCV antibody status				
Negative	1	0.89	1	0.40
Positive	1.01 (0.87-1.17)		1.08 (0.90-1.30)	
HBsAg status				
Negative	1	0.86	1	0.97
Positive	0.98 (0.80-1.20)		1.00 (0.81-1.23)	

Table 4. Factors associated with virological failure among ARV experienced individuals switching to RPV while maintening viral supression <50 copies/mL: univariable and multivariable competing risk regression analyses . The events "lost to follow-up" and "deaths", are considered as competing risk for the virological failure. N=11828 of whom 967 have virological failure.

Characteristics	Univariable analysis		Multivariable analysis	
	sHR (95% CI)	P	sHR (95% CI)	P
Age (per 10-years increment)	0.94 (0.88-1.00)	0.04	1.03 (0.97-1.10)	0.37
Transmission group				
MSM	1	<0.0001	1	<0.0001
Injecting drug users	1.59 (1.22-2.07)		1.55 (1.12-2.15)	
Other men	1.68 (1.41-2.00)		1.51 (1.26-1.82)	
Other women	1.69 (1.45-1.98)		1.56 (1.30-1.87)	
Sub-Saharan origin				
Yes	1	<0.0001	1	0.13
No	0.67 (0.59-0.77)		0.88 (0.75-1.04)	
Type of combination				
Dual therapy	0.62 (0.40-0.94)	0.02	0.75 (0.49-1.15)	0.19
Triple therapy or more	1		1	
Duration of VL suppression at baseline (per 1-year increment)	0.88 (0.86-0.90)	<0.0001	0.88 (0.86-0.90)	<0.0001
Prior AIDS event				
No	1	0.0001	1	0.0008
Yes	1.33 (1.15-1.55)		1.30 (1.12-1.52)	
CD4 (cells/mm^3)				
<200	2.37 (1.74-3.24)	<0.0001	1.61 (1.17-2.21)	0.0004
200-350	1.79 (1.48-2.17)		1.40 (1.14-1.70)	
350-500	1.36 (1.17-1.60)		1.20 (1.02-1.41)	
≥ 500	1		1	
HCV antibody status				
Negative	1	0.20	1	0.16
Positive	1.13 (0.94-1.37)		1.19 (0.94-1.52)	
HBsAg status				
Negative	1	0.17	1	0.32
Positive	1.19 (0.93-1.53)		1.14 (0.88-1.47)	

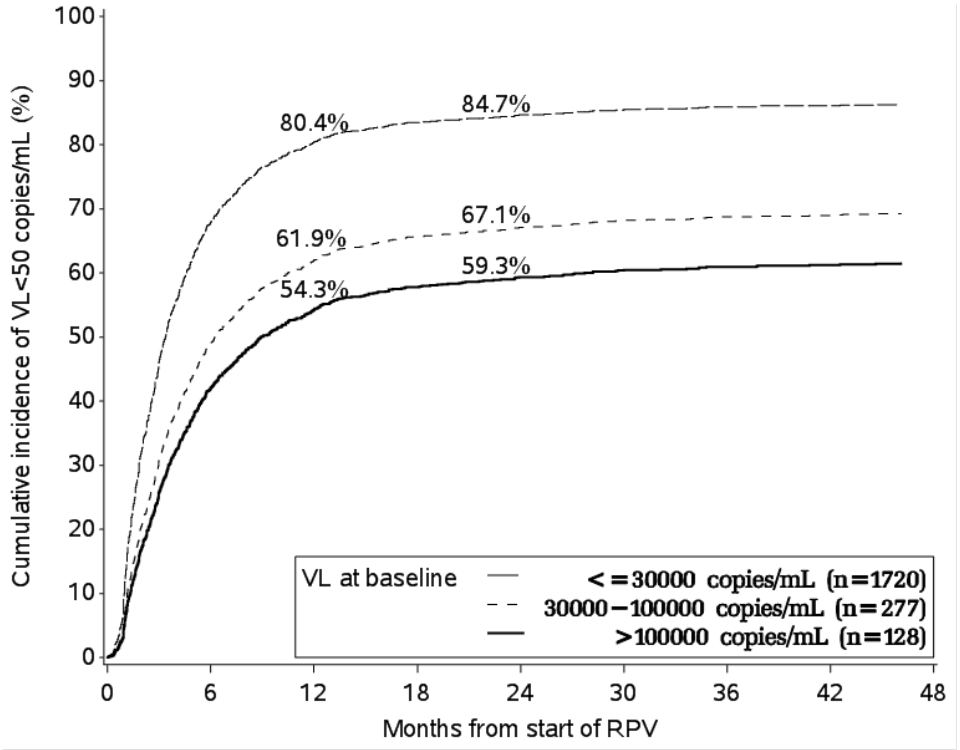
Fig. 1. Cumulative incidence of virological success (VL<50 copies/mL) according to VL at baseline in (a) ARV-naïve individuals and (b) ARV-experienced individuals switching to RPV while failing therapy

a. ARV naïve individuals (n=2166)



The cumulative incidence of VL<50 copies/mL was estimated considering RPV discontinuation, loss to follow-up and death as competing risks

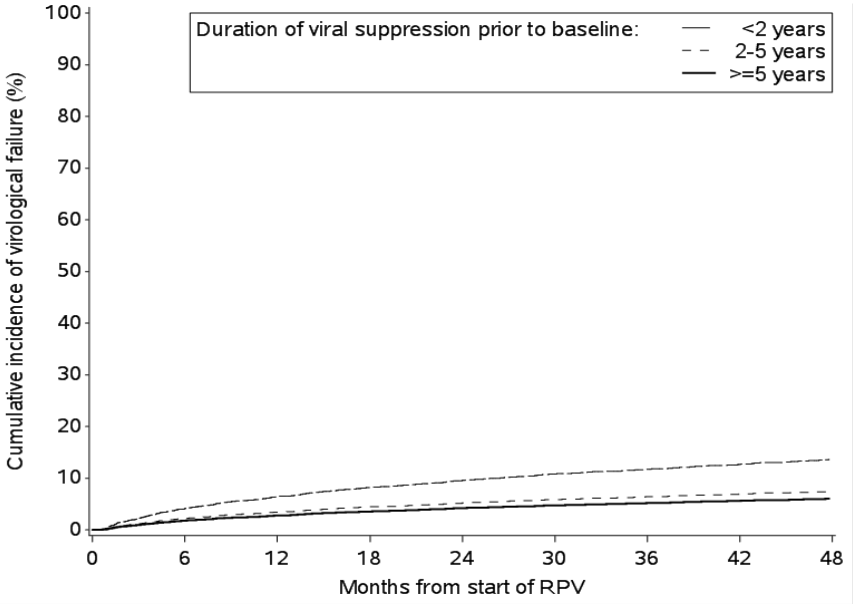
b. ARV-experienced individuals switching to RPV while failing therapy (n=2125)



The cumulative incidence of VL<50 copies/mL was estimated considering RPV discontinuation, loss to follow-up and death as competing risks

Fig. 2. Cumulative incidence of virological failure (two consecutive VL>50 copies/mL or one VL>50 copies/mL followed by a treatment switch prior to another VL measurement) according to (a) duration of viral suppression prior to baseline and (b) type of combination for ARV-experienced individuals switching to RPV while virologically controlled (n=11828)

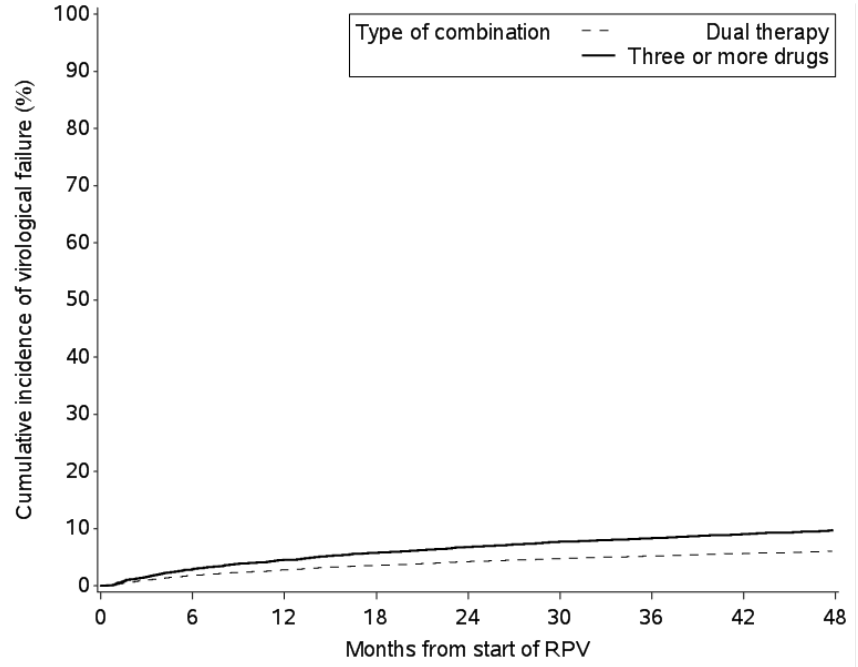
a. Duration of viral suppression prior to baseline



<2 years	4831	4521	4211	3836	3424	2996	2476	1922	1300
2-5 years	3290	3192	2972	2707	2415	2117	1792	1415	976
≥ 5 years	3707	3597	3335	2992	2586	2228	1839	1443	981

The cumulative incidence of virological failure was estimated considering loss to follow-up and death as competing risks

b. Type of combination



Dual therapy	555	529	452	309	188	113	53	24	14
Three ore more drugs	11273	10781	10067	9226	8230	7226	6061	4756	3243

The cumulative incidence of virological failure was estimated considering loss to follow-up and death as competing risks