Use of darunavir in HIV-1-infected individuals in routine clinical practice from 2012 to 2016 in France

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Abstract

Objectives:

We assessed virological outcomes of darunavir use in France from 2012 to 2016, in three groups of people living with HIV (PLHIV):(1) antiretroviral (ARV)-naïve PLHIV;(2) ARV-experienced PLHIV switching to darunavir while failing therapy;(3) ARV-experienced PLHIV switching to darunavir 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 darunavir 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 3235 ARV-naïve PLHIV initiating darunavir, the four-year cumulative incidence of VS was 80.9% and was associated with lower VL and higher CD4. Among the 3485 ARV-experienced PLHIV switching to darunavir while failing therapy, the four-year cumulative incidence of VS was 82.2% and was associated with lower VL. Among the 3005 ARV-experienced PLHIV switching to darunavir while virologically controlled, the four-year cumulative incidence of VF was 12.6%. The risk of VF was higher with darunavir monotherapy (subdistribution hazard ratio (sHR)=1.67, 95%CI, 1.15-2.42) while no difference was observed with dual therapy (sHR=1.00, 95%CI, 0.71-1.42) relative to triple therapy or more.

Conclusion: Darunavir-containing regimens yielded similarly high rates of viral suppression in PLHIV whether they were ARV-naïve or ARV-experienced switching to darunavir while failing therapy, or of maintaining VS in ARV-experienced PLHIV switching to darunavir while virologically controlled.

Introduction

The primary objective of antiretroviral (ARV) therapy is to achieve and maintain an HIV viral load below the detection limit of current assays, in order to promote immune reconstitution, to reduce HIV-related morbidity and mortality due to HIV infection, and to avoid the accumulation of resistance mutations.[1,2] In parallel, viral load suppression prevents the transmission of the virus.[3] WHO ambitions an implementation of the 90-90-90 target to accelerate progress towards ending the AIDS epidemic in the post-2015 era: 90% of all people living with HIV infection (PLHIV) diagnosed, 90% of people with an HIV diagnosis treated, and 90% of all people receiving antiretroviral therapy with viral suppression by 2020.[4] Darunavir is a potent PI, with a high genetic barrier, used in treatment-naïve and experienced PLHIV.[5,6] The French expert group recommends using darunavir, if a PI is chosen as the third drug in ARV-naïve PLHIV or as a new third drug in ARV-experienced PLHIV.[7] French guidelines also propose a simplified darunavir-containing regimen, such as dual therapy or monotherapy to optimize treatment in ARV-experienced virologically controlled PLHIV.[8-10] Several studies have shown an increasing risk of virological rebound with a shorter duration of viral load suppression prior to switching to monotherapy.[11-13] The expert group thus recommends waiting for at least two years of sustained virological suppression before starting monotherapy.[7]

it is thus important to generate data from real-life settings to assess how darunavir is used in routine care in France and to evaluate its virological efficacy, in the context of WHO targets and simplification strategies, as a complement to clinical trials. The purposes of this observational study were to describe the routine use of darunavir in ARV-naïve PLHIV, ARV-experienced PLHIV failing therapy, and ARV-experienced virologically-controlled PLHIV, to assess its effectiveness in terms of virological outcomes and whether it differs depending on its being given in the context of monotherapy, dual therapy or triple therapy or more.

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.[14] 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 cell count 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 darunavir between January 1st, 2012 and December 31th, 2016, at least one year before the last recorded FHDH visit in the centre, with available viral load (VL) and CD4 cell count values within six months before initiating darunavir. If they satisfied the inclusion criteria, individuals were included in one of the following groups: (1) ARV-naïve PLHIV; (2) ARV-experienced PLHIV switching to darunavir while failing therapy; (3) ARV-experienced PLHIV switching to darunavir while virologically controlled.

Statistical analysis

The baseline for all analyses was the date of darunavir initiation. Continuous variables were expressed as the median 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 darunavir while failing therapy, we assessed the cumulative incidence of VS considering the discontinuation of darunavir as a competing risk (individuals

who discontinue darunavir are likely to be those experiencing a slower reduction in VL). This approach avoids a situation in which most individuals switch from darunavir 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 darunavir 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 (monotherapy, dual therapy, triple therapy or more) on VS or VF.[15] The following potential confounding factors were accounted for: age, gender and transmission group (MSM, injecting drug users, other men, other women), sub-Saharan origin, prior AIDS event, baseline CD4 T cell count (<200/mm^3, 200-350/mm^3, 350-500/mm^3, ≥ 500/mm^3) and HCV antibody status (negative, positive) for the three groups, and VL at baseline in ARV-naïve PLHIV, VL at baseline and number of prior ARVs in ARV-experienced PLHIV switching to darunavir while failing therapy and duration of viral suppression prior to baseline in ARV-experienced PLHIV switching to darunavir 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 3235 ARV-naïve PLHIV initiated darunavir (group 1), 3485 ARV-experienced PLHIV switched to darunavir while failing therapy (group 2) and 3005 ARV-experienced PLHIV switched to darunavir while virologically controlled (group 3). Almost all ARV-naïve PLHIV started a triple therapy or more (96.3%). Among ARV-experienced PLHIV who switched to darunavir while failing therapy, 85.9% were prescribed triple therapy or more and among those who switched to darunavir while virologically controlled, 76.4% received triple therapy or more, 14.5% dual therapy and 9.1% monotherapy. Triple therapy with two NRTIs, particularly tenofovir and emtricitabine, was the most prescribed for all groups. The median follow-up was 2.3 years (IQR: 1.5-3.2) for group 1, 2.5 years (IQR: 1.4-3.4) for group 2, and 2.5 years (IQR: 1.6-3.4) for group 3.

ARV-naïve PLHIV

Of the 3235 ARV-naïve PLHIV who initiated darunavir, 2546 achieved a VL<50 copies/mL, whereas 461 discontinued darunavir, 107 were lost to follow-up and 10 died before controlled VL. Cumulative incidence function estimates showed the probability of VS, discontinuation, loss to follow-up, and death at one year to be 72.3% (95% CI, 70.8-73.9), 12.2% (95% CI, 11.1-13.4), 2.7% (95% CI, 2.2-3.4) and 0.2% (95% CI, 0.1-0.4) respectively, and at four years to be 80.9% (95% CI, 79.8-82.1), 14.9% (95% CI, 13.6-16.3), 3.4% (95% CI, 2.8-4.1) and 0.4% (95% CI, 0.2-0.6) respectively. The probability of VS was associated with a lower VL at baseline, whereas individuals with baseline CD4 T cell counts < 200/mm^3 were less likely to achieve a VL<50 copies/mL (sHR=0.85, 95% CI, 0.75-0.97) (Figure 1a and Table 2). The type of combination was not associated with VS.

The main reason for discontinuing darunavir before VS was adverse events (42.2%). Among the 2546 individuals with VS, 1435 discontinued darunavir after reaching a VL < 50

copies/mL, the probability of discontinuing darunavir at four years was 72.3 [69.7-75.0]. The main reason for discontinuing darunavir after VS was simplification (63.6%).

ARV-experienced PLHIV switching to darunavir while failing therapy

Among the 3485 ARV-experienced PLHIV switching to darunavir while failing therapy, 2762 reached a VL< 50 copies/mL, whereas 370 discontinued darunavir, 105 were lost to follow-up and 25 died before reaching this endpoint. Cumulative incidence function estimates showed the probability of VS, discontinuation, loss to follow-up, and death at one year to be 70.0% (95% CI, 68.5-71.6), 8.0% (95% CI, 7.1-8.9), 2.1% (95% CI, 1.7-2.6), and 0.4% (95% CI, 0.2-0.6) respectively, and at four years to be 82.2% (95% CI, 80.7-83.8), 11.6% (95% CI, 10.6-12.7), 3.4% (95% CI, 2.8-4.1), and 0.9% (95% CI, 0.5-1.4) respectively. The probability of VS was associated with lower VL at baseline, whereas the type of combination was not associated with VS and individuals who were exposed to more than three prior ARVs were less likely to reach a VL<50 copies/mL (Figure 1b and Table 3).

The main reason for the discontinuation of darunavir before VS was adverse events (41.2%). Among the 2762 individuals with VS, 783 discontinued darunavir after reaching a VL<50 copies/mL. The probability of discontinuing darunavir at four years was 41.7 [39.0-44.5]. The main reason for discontinuing darunavir after VS was simplification (48.5%).

ARV-experienced PLHIV switching to darunavir while virologically controlled

Among the 3005 ARV-experienced PLHIV switching to darunavir while virologically controlled, 308 experienced VF (294 with two consecutive VL > 50 copies/ml and 14 with one VL > 50 copies/ml followed by a treatment switch prior to the next VL measurement), whereas 207 were lost to follow-up and 17 died. Cumulative incidence function estimates showed the probability of VF, loss to follow-up, and death at one year to be 7.1% (95% CI, 6.3-8.1), 3.4% (95% CI, 2.8-4.1), and 0.1% (95% CI, 0.05-0.4) respectively, and at four years to be 12.6% (95% CI, 11.1-14.2), 8.9% (95% CI, 8.0-10.0), and 1.0% (95% CI, 0.6-

1.6) respectively. The probability of VF was higher when the duration of viral suppression prior to baseline was shorter (Table 4). The probability of VF at four years after switching to darunavir ranged from 6.5% (95% CI, 4.8-8.8) in participants for which the duration of viral suppression was > 5 years, to 17.5% (95% CI, 15.4-19.8) among individuals with a duration of viral suppression < 2 years (figure 2a). The one-year and four-year probabilities of VF, were respectively 8.9% (95% CI, 6.6-11.9) and 15.6% (95% CI, 11.1-22.0) among individuals undergoing darunavir monotherapy, 6.1% (95% CI, 4.5-8.9) and 10.9% (95% CI, 7.8-15.1) among those undergoing dual therapy, and 7.1% (95% CI, 6.2-8.1) and 12.6% (95% CI, 11.0-14.3) among those undergoing triple therapy or more (figure 2b). In the multivariable model (Table 4), monotherapy was associated with a higher risk of VF than triple therapy or more (sHR=1.67 (95% CI, 1.15-2.42)) while no difference was evidenced between dual therapy and triple therapy or more (sHR=1.00 (95% CI, 0.71-1.42)). The effect of duration of viral suppression prior to baseline on the risk of VF was similar for participants undergoing monotherapy, dual therapy or triple therapy or more (sHR=0.73 (95% CI, 0.61-0.86) for monotherapy, 0.89 (95% CI, 0.78-1.02) for dual therapy, and 0.86 (95% CI, 0.81-0.91) for triple therapy or more).

A total of 1149 individuals discontinued darunavir, of whom 1014 individuals (88.3%) had not experienced VF. Among individuals who had not experienced VF, the probability of discontinuing darunavir at four years was 53.8 [51.2-56.5]. The main reason for discontinuation was “simplification” (45.0%).

Discussion

In this observational study, we showed that darunavir-based regimens were associated with a VS rate > 80% at four years, in three similar sized groups of ARV-naïve (group 1), or ARV-experienced PLHIV switching to darunavir while failing therapy (group 2) or while virologically controlled (group 3).

The darunavir one-year VS rate of 72.2% in ARV-naïve individuals was lower than those reported in randomized controlled trials, such as the Artemis trial (84% at week 48),[16] or the Flamingo trial (83% at week 48),[17] or the Kidar observational study (82% at week 48).[18] This lower VS probability could be partly explained by the real life with less control over observations as compared to randomized controlled trials. We think the discrepancy is more likely explained by a difference in the level of baseline VL at darunavir initiation. Indeed, 51% of ARV-naïve individuals had a baseline VL>100 000 copies/mL whereas the proportion of such individuals was 34% in the Artemis trial, 25% in the Flamingo trial and 28% in the Kidar study. The rates of patients with a baseline VL<100 000 copies/mL reaching a VL <50 copies/mL at week 48 of our study (81%) were similar to those of the Artemis (86%) and Flamingo (87%) trials. Moreover, an observational Canadian study, which included 45% ARV-naïve individuals with a baseline VL>100 000 copies/mL, showed the cumulative incidence of VL<50 copies/mL at month 12 in those receiving darunavir to be 73% similar to our findings.[19]

In our study, the most frequent reason for discontinuing darunavir before VS was adverse events and after VS treatment simplification. An observational study in Belgium that included HIV-infected individuals between 2010 and 2014 also found the main reasons for darunavir discontinuation to be treatment simplification and adverse events.[20] The increasing popularity of available novel and simpler therapies among practitioners between 2011 and 2016 may explain the high rate of darunavir discontinuation for simplification. For example, the Swedish InfCare study showed that starting ARV in 2011 or later increased

the risk of early discontinuation of treatment relative to treatment started between 2009 and 2010.[21]

Among ARV-experienced individuals switching to darunavir while failing therapy, the estimated rate of achieving a VL < 50 copies/mL at one year (70%) was similar to that of randomized trials such as Titan (71%) and Odin (72.1% for once-daily darunavir, 70.9% for twice-daily darunavir).[22,23] Lower rates of VS were obtained in participants with a baseline VL>100 000 copies/mL (55% in our study and the Titan trial).

During the period of this study, only a small number of ARV-experienced PLHIV with controlled VL switched to darunavir monotherapy or as part of a dual therapy, probably because the French guidelines that propose a simplified darunavir-containing regimen, consisting of dual therapy or monotherapy are recent.[7] In this observational study, the rates of VF at one year among ARV-experienced PLHIV switching to darunavir while virologically controlled was similar to that of the Monet trial among patients switching to darunavir monotherapy (8.7%) and those switching to darunavir-containing triple therapy (5.4%).[24] The rate of VF was slightly higher in the Monoi trial among patients switching to darunavir monotherapy (11.0%) at week 48.[25] As in other studies, the duration of viral suppression was associated with the risk of VF.[11-13] Interestingly the effect was similar regardless of the type of combination (monotherapy, dual therapy or triple therapy or more). Prolonged viral suppression was a strong predictor because it may be a marker of several factors associated with VF: good adherence to antiretroviral therapy, favourable genetic factors, low viral reservoir size, and high CD4 cell counts. Another independent factor associated with VF was the strategy of treatment. There was a higher risk of VF with monotherapy than triple therapy or more. A meta-analysis of four clinical trials reporting 8 VS at week 48,[24-27] also showed the efficacy of triple therapy to be superior to that of monotherapy.[28] Finally, the risk of VF was similar for dual therapy and triple therapy, as shown in the Dual-Gesida trial.[8]

The main strength of our study was its large size and routine clinical setting, providing additional evaluation of the use of darunavir in monotherapy or in combination with other antiretrovirals 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, as we adjusted for number of prior ARVs in ARV-experienced PLHIV switching to darunavir while failing therapy and for prolonged viral suppression in ARV-experienced PLHIV switching to darunavir while virologically controlled, we feel our results are nevertheless robust.

In conclusion, this real-world nationwide cohort shows that darunavir was widely used in France from 2012 - 2016 in ARV-naïve and ARV-experienced PLHIV switching to darunavir either while failing therapy or while virologically controlled with a high level of efficacy, similar to that seen in clinical trials. Ours results do not support the use of darunavir monotherapy in ARV-experienced PLHIV switching to darunavir while virologically controlled, while dual therapy was associated with high level efficacy.

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Transparency declaration

DC reports HIV grants from Janssen (2017-2018, 2019-2020) and MSD France (2015-2017), personal fees from Janssen (2016, 2018), MSD France 2017) and Gilead (2018) for lectures, personal fees from Innavirvax (2016) and Merck Switzerland (2017) for consultancy, outside the submitted work. AC has received lecturer or travel fees from Gilead, Janssen, MSD and ViiV during the last three years. SG has received lecturer or travel fees from Gilead, Janssen, MSD, ViiV and Pfizer during the last three years. VP has conducted post-marketing studies for Janssen and MSD during the last three years.

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 DRV initiation according to the clinical situation

	ARV naive (n=3235)		Switch to DRV while failing therapy (n=3485)		Switch to DRV while virologically controlled (n=3005)	
	n, median	%, [IQR]	n, median	%, [IQR]	n, median	%, [IQR]
Age	39	[30-48]	46	[37-52]	48	[40-55]
Gender						
Men	2467	76.3	2039	58.5	1795	59.7
Women	764	23.6	1441	41.3	1209	40.2
Transgender	4	0.1	5	0.1	1	0.0
Sub-Saharan origin						
Yes	745	23.0	1125	32.3	797	26.5
No	2490	77.0	2360	67.7	2208	73.5
Year of HIV-1 diagnosis	2013	[2012-2014]	2001	[1994-2007]	1999	[1992-2006]
Transmission group						
MSM	1511	46.7	882	25.3	946	31.5
Injecting drug users	55	1.7	283	8.1	275	9.2
Heterosexual	1443	44.6	2012	57.7	1529	50.9
Other	226	7.0	308	8.8	255	8.5
Number of prior ARVs	-	-	6	[3-9]	7	[4-10]
Cumulative duration of ARV exposure (months)	-	-	78.2	[34.9-119]	68.1	[21.7-123]
Year of DRV initiation						
2012	908	28.1	1008	28.9	819	27.3
2013	965	29.8	1033	29.6	823	27.4
2014	912	28.2	851	24.4	836	27.8
2015	420	13.0	556	16.0	508	16.9
2016	30	0.9	37	1.1	19	0.6
Type of combination						
Monotherapy: DRV alone	**30**	**0.9**	**110**	**3.2**	**274**	**9.1**
Dual therapy:	**89**	**2.8**	**379**	**10.9**	**436**	**14.5**
2PI	22	0.7	42	1.2	28	0.9
NNRTI+DRV	16	0.5	96	2.8	81	2.7
DRV+RAL or DRV+DTG	40	1.2	174	5.0	209	7.0
DRV+3TC	1		12	0.3	44	1.5
Other	10	0.3	55	1.6	74	2.5
Triple therapy:	**2908**	**89.9**	**2665**	**76.5**	**2125**	**70.7**
2 NRTI+DRV:	2876	88.9	2331	66.9	1908	63.5
Of which:TDF+FTC	*2319*	*71.7*	*1615*	*46.3*	*1100*	*36.6*
Other	32	1.0	334	9.6	215	7.1
Four or more drugs	**208**	**6.4**	**331**	**9.4**	**170**	**5.7**
CD4 (cells/mm^3) at baseline	303	[142-475]	330	[148-529]	587	[416-793]
<200	1064	32.9	1133	32.5	151	5.0
200-350	773	23.9	706	20.3	336	11.2
350-500	673	20.8	669	19.2	614	20.4
≥500	725	22.4	977	28.0	1904	63.4
CD4/CD8 at baseline	0.3	[0.2-0.5]	0.4	[0.2-0.6]	0.8	[0.5-1.1]
Missing	320		285		291	
<0.5	2062	70.7	2076	64.9	649	23.9
≥0.5	853	29.3	1124	35.1	2065	76.1
Viral load (copies/mL) at baseline	5.0	[4.4-5.5]	3.7	[2.5-4.9]	-	-
<50	-	-	-	-	3005	100
<5000	323	10.0	1721	49.4	-	-
5000-100000	1275	39.4	1072	30.8	-	-
>100000	1637	50.6	692	19.9	-	-
Duration of viral suppression prior to baseline (year)						
<2					1340	44.6
2-5					798	26.6
≥ 5					867	28.9
Prior AIDS event						
No	2787	86.2	2348	67.4	2198	73.1
Yes	448	13.8	1137	32.6	807	26.9

	ARV naive (n=3235)		Switch to DRV while failing therapy (n=3485)		Switch to DRV while virologically controlled (n=3005)	
	n, median	%, [IQR]	n, median	%, [IQR]	n, median	%, [IQR]
HCV antibody status						
Negative	3105	96.0	3078	88.3	2581	85.1
Positive	130	4.0	407	11.7	424	14.1
PCP prophylaxis						
Not eligible (CD4>200)	2171	67.1	2352	67.5	2854	95.0
No	674	20.8	911	26.1	136	4.5
Yes	390	12.1	222	6.4	15	0.5

Abbreviations: ARV, antiretrovirals; DRV, darunavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; VL, viral load; PCP, pneumocystis pneumonia

Table 2. Factors associated with 48-month virological success among ARV-naive individuals: univariable and multivariable competing risk regression analyses. The events "DRV discontinuation", "lost to follow-up" and "deaths" were considered as competing risks to virological success. N=3235 of whom 2546 reached a VL<50 copies/mL.

Characteristics	Univariable analysis		Multivariable analysis	
	sHR (95% CI)	P	sHR (95% CI)	P
Age (per 10-year increment)	0.98 (0.95-1.02)	0.30	1.02 (0.98-1.06)	0.29
Gender and transmission group				
MSM	1	0.0001	1	0.008
Injecting drug users	0.65 (0.48-0.88)		0.72 (0.51-1.03)	
Other men	0.89 (0.81-0.97)		0.93 (0.84-1.04)	
Other women	1.08 (0.98-1.20)		1.11 (0.98-1.26)	
Sub-Saharan origin				
Yes	1	0.39	1	0.18
No	1.04 (0.95-1.14)		1.08 (0.96-1.21)	
Type of combination				
Monotherapy: DRV alone	1.44 (0.90-2.31)	0.25	1.35 (0.83-2.21)	0.45
Dual therapy	0.92 (0.72-1.17)		0.95 (0.75-1.21)	
Triple therapy or more	1		1	
Log(VL) at baseline (copies/mL)	0.77 (0.74-0.81)	<0.0001	0.79 (0.75-0.83)	<0.0001
Prior AIDS event				
No	1	0.0003	1	0.69
Yes	0.81 (0.72-0.91)		0.97 (0.86-1.11)	
CD4 count (/mm^3)				
<200	0.73 (0.65-0.82)	<0.0001	0.85 (0.75-0.97)	0.009
200-350	0.83 (0.74-0.93)		0.91 (0.80-1.03)	
350-500	1.00 (0.89-1.14)		1.03 (0.90-1.17)	
≥ 500	1		1	
HCV antibody status				
Negative	1	0.03	1	0.15
Positive	0.79 (0.63-0.98)		0.82 (0.63-1.07)	

Table 3. Factors associated with 48-month virological success among ARV-experienced individuals switching to DRV while failing therapy: univariable and multivariable competing risk regression analyses. The events "DRV discontinuation", "lost to follow-up" and "deaths" were considered as competing risks to virological success. N=3485 of whom 2762 reached a VL<50 copies/mL.

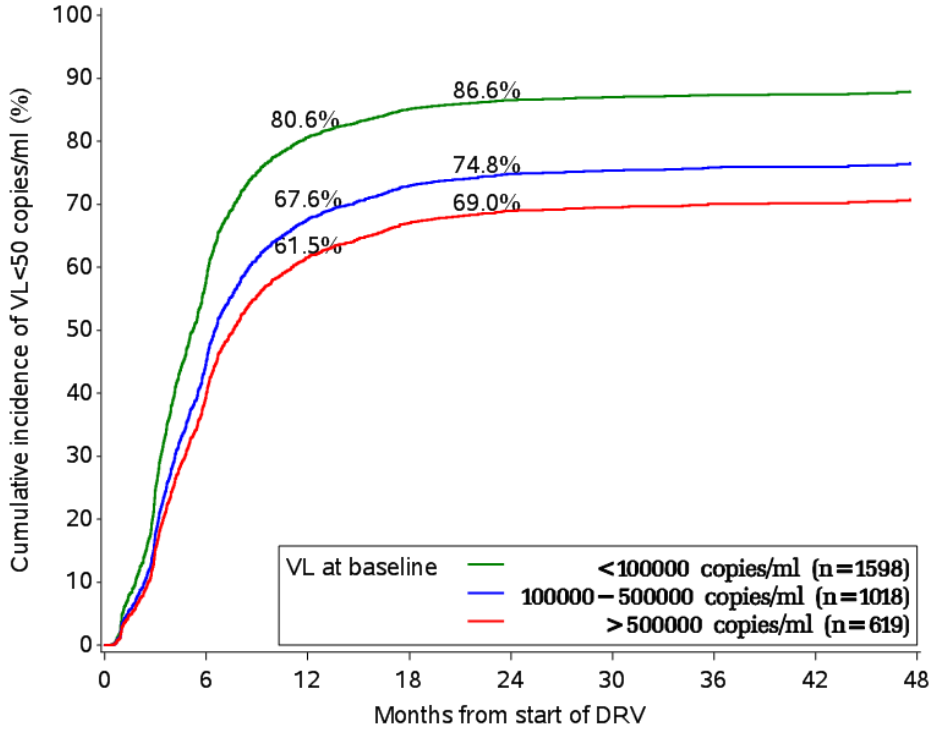
Characteristics	Univariable analysis		Multivariable analysis	
	sHR (95% CI)	P	sHR (95% CI)	P
Age (per 10-year increment)	1.03 (1.00-1.06)	0.08	1.01 (0.98-1.05)	0.52
Gender and transmission group				
MSM	1	0.16	1	0.63
Injecting drug users	0.88 (0.76-1.03)		0.99 (0.82-1.19)	
Other men	0.91 (0.82-1.00)		0.96 (0.86-1.07)	
Other women	0.96 (0.88-1.06)		1.02 (0.92-1.14)	
Sub-Saharan origin				
Yes	1	0.14	1	0.18
No	1.06 (0.98-1.15)		1.07 (0.97-1.17)	
Number of prior ARVs				
≤ 3	1	0.39	1	0.03
>3	0.97 (0.89-1.05)		0.91 (0.83-0.99)	
Type of combination				
Monotherapy: DRV alone	0.98 (0.77-1.26)	0.19	0.83 (0.65-1.08)	0.31
Dual therapy	1.12 (0.99-1.26)		1.04 (0.91-1.18)	
Triple therapy or more	1		1	
Log(VL) at baseline (copies/mL)	0.71 (0.65-0.78)	<0.0001	0.83 (0.81-0.86)	<0.0001
Prior AIDS event				
No	1	0.01	1	0.93
Yes	0.90 (0.84-0.98)		1.00 (0.92-1.09)	
CD4 count (/mm^3)				
<200	0.64 (0.58-0.70)	<0.0001	0.87 (0.77-0.98)	0.07
200-350	0.82 (0.73-0.92)		0.94 (0.84-1.06)	
350-500	0.91 (0.82-1.02)		0.99 (0.88-1.11)	
≥ 500	1		1	
HCV antibody status				
Negative	1	0.17	1	0.21
Positive	0.92 (0.81-1.04)		0.91 (0.78-1.06)	

Table 4. Factors associated with virological failure among ARV-experienced individuals switching to DRV while virologically controlled: univariable and multivariable competing risk regression analyses . The events "lost to follow-up" and "deaths", were considered as competing risks to virological failure. N=3005 of whom 308 have virological failure.

Characteristics	Univariable analysis		Multivariable analysis	
	sHR (95% CI)	P	sHR (95% CI)	P
Age (per 10-year increment)	0.93 (0.85-1.03)	0.16	0.99 (0.89-1.10)	0.89
Gender and transmission group				
MSM	1	0.54	1	0.58
Injecting drug users	1.15 (0.76-1.74)		1.23 (0.74-2.03)	
Other men	1.22 (0.90-1.67)		1.21 (0.88-1.67)	
Other women	1.20 (0.91-1.58)		1.21 (0.87-1.69)	
Sub-Saharan origin				
Yes	1	0.32	1	0.72
No	0.88 (0.69-1.13)		1.06 (0.77-1.45)	
Type of combination				
Monotherapy: DRV alone	1.26 (0.88-1.81)	0.25	1.67 (1.15-2.42)	0.02
Dual therapy	0.86 (0.61-1.21)		1.00 (0.71-1.42)	
Triple therapy or more	1		1	
Duration of viral suppression prior to baseline (per 1-year increment)	0.85 (0.80-0.89)	<0.0001	0.84 (0.80-0.89)	<0.0001
Prior AIDS event				
No	1	0.47	1	0.50
Yes	1.10 (0.86-1.40)		1.09 (0.84-1.42)	
CD4 count (/mm^3)				
<200	1.89 (1.26-2.84)	0.02	1.41 (0.93-2.15)	0.45
200-350	1.11 (0.78-1.60)		1.01 (0.70-1.47)	
350-500	1.07 (0.80-1.42)		1.03 (0.77-1.38)	
≥ 500	1		1	
HCV antibody status				
Negative	1	0.55	1	0.75
Positive	0.90 (0.65-1.26)		0.94 (0.62-1.42)	

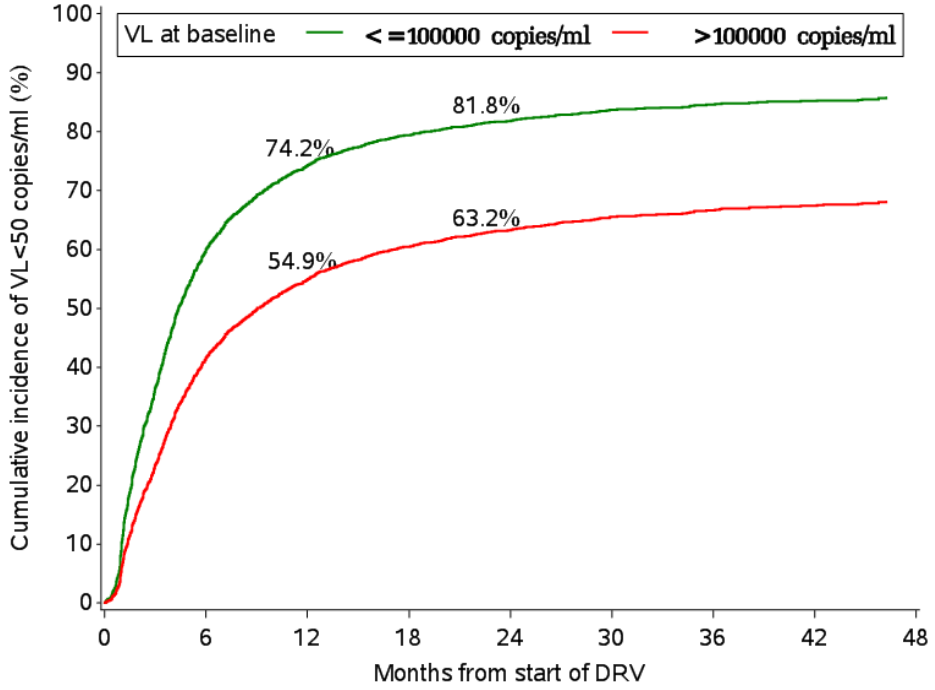
Fig. 1. Cumulative incidence of virological success (VL<50 copies/ml) according to VL at baseline in (a) ARV-naïve individuals and (b) ARV-experienced individuals switching to DRV while failing therapy

a. ARV naïve individuals



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

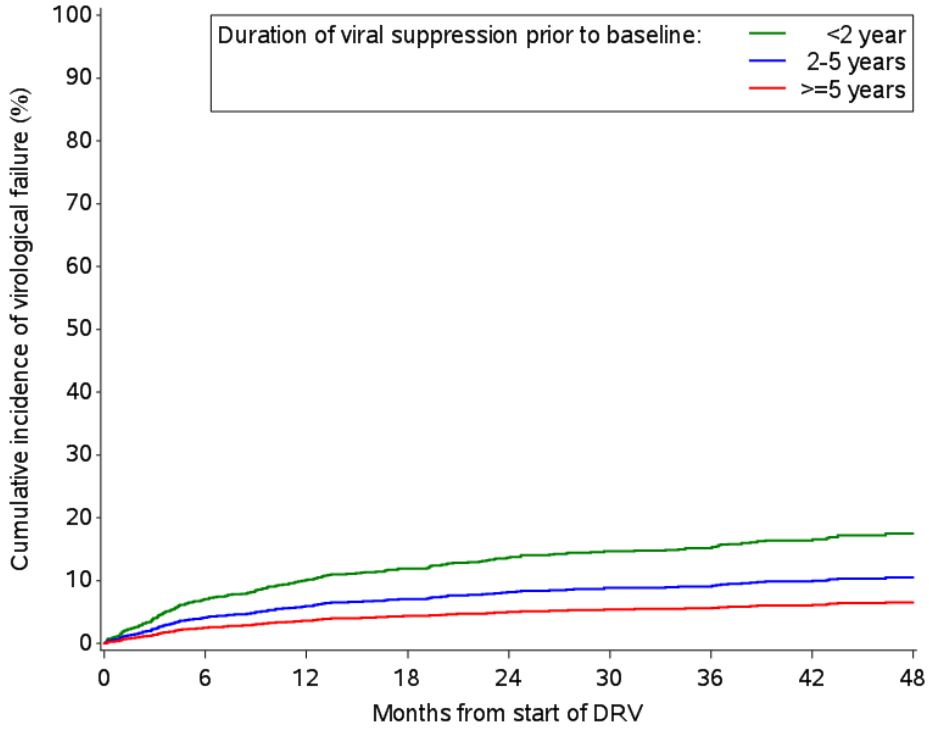
b. ARV-experienced individuals switching to DRV while failing therapy



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

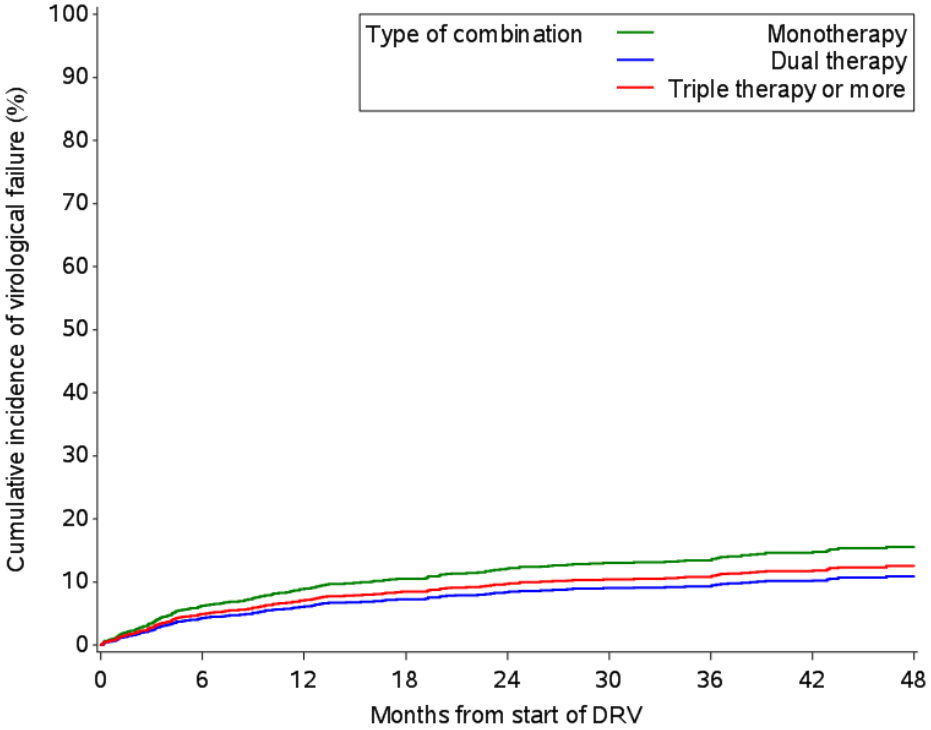
Fig. 2. Cumulative incidence of virological failure (two consecutive VL>50 copies/ml or one VL>50 copies/ml followed by a treatment switch prior to another VL measurement) according to (a) duration of viral suppression prior to baseline and (b) type of combination for ARV-experienced individuals switching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

a. Duration of viral suppression prior to baseline



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

b. Type of combination



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