Switching to Raltegravir From a Virologically Effective Boosted Protease Inhibitor Regimen: A Comparative Effectiveness Analysis From the French Hospital Database on HIV (FHDH-ANRS CO4)

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Running title: Switching to raltegravir versus continuing PI

Key points: HIV-1-infected individuals who switched from a virologically effective regimen comprising a boosted PI plus 2 NRTIs to a regimen consisting of RAL plus 2 NRTIs had similar clinical and immunovirologic outcomes to individuals who continued on the same regimen.

Abstract: 250 words (250 words)
Text: 2708 words (3000 words)
2 figures, 1 table
2 supplementary figures

Abstract

Background: In individuals with viral load (VL) suppression on a boosted PI regimen, a switch to raltegravir (RAL) can be an option in case of comorbidities, but the SWITCHMRK trials challenged this strategy. Here, among individuals with VL suppression on a boosted PI, we compared outcomes between those who continued on the same regimen and those who switched to RAL.

Methods: In this cohort study from the FHDH, each individual who switched to RAL was matched with up to 3 individuals who continued PI, who were being followed up during the calendar period of the switch and had the same duration of VL suppression (both +/-6 months). The primary endpoint was a composite endpoint of hospitalization, or AIDS event or death, and secondary endpoints the immunovirologic responses. To control for measured confounders, the inverse probability treatment weighting (IPTW) method was applied to estimate hazards ratios between the 2 groups.

Results: We matched 282 RAL switchers with 838 non-switchers. While several variables differed significantly between the groups, including a higher prevalence of comorbidities in the RAL group, the IPTW method yielded standardized differences below 10% for all variables. After IPTW, there was no difference in the risk of hospitalization or AIDS event or death between the 2 groups (respectively 13.6% and 10.5%, HR=1.16 (95%CI:0.74-1.83)) and no difference in the likelihood of virologic failure or CD4 cell gain.

Conclusion: In individuals with controlled VL on a boosted PI regimen who switched to RAL none of the endpoints differed with non-switchers after IPTW.

Introduction

The primary aims of antiretroviral therapy (ART) for HIV infection are to prevent morbidity, and to prolong life by reducing viral load (VL) and promoting CD4+ T-cell recovery with minimal toxicity. The rate of VL suppression on combination antiretroviral therapy (cART) has gradually increased over the past 15 years [1]. A large proportion of individuals are currently treated with boosted protease inhibitors (PIs), because of the potency of those drugs and their high barrier to resistance. However, PIs pose problems of long-term toxicity and interactions with many of the drugs used to treat comorbidities. In particular, PIs have been linked to an increased risk of cardiovascular disease, due at least in part to their effects on lipid metabolism [2,3,4]. Raltegravir (RAL), the first integrase inhibitor, was approved in 2007, for use by treatment-experienced individuals based on the results of the BENCHMRK I and II studies [5], and subsequently in antiretroviral-naive individuals based on the results of the STARTMRK study [6]. RAL is an interesting alternative in situations raising long-term metabolic concerns [7-10] and exhibits few drug-drug interactions [7,8,10]. However, the SWITCHMRK study in which RAL was used to replace lopinavir/ritonavir (LPV/rtv) in individuals with stable viral suppression failed to demonstrate the non-inferiority of RAL at week 24 [7]. In contrast, RAL was shown to be non-inferior to boosted PI regimens at week 48 in the SPIRAL study [8]. In clinical practice, a switch to RAL is often used to avoid long-term metabolic disorders and to manage drug-drug interactions in individuals requiring cancer chemotherapy for example [11,12], or in case of HIV-HCV coinfection [13]. In France, the RACING study [14] showed that RAL was generally prescribed to

individuals who were already on a virologically effective treatment. The purpose of the present study was to compare clinical and biological effectiveness between virologically suppressed individuals who continued on a PI-based regimen and individuals who switched to RAL, in the routine care setting.

Individuals and methods

Individuals and data sources

The French Hospital Database on HIV (FHDH) is a hospital-based open multicentre cohort in which inclusions have been ongoing since 1989 [15]. It includes data from 70 French general and university hospitals distributed throughout France. 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 on standardized forms, which include demographic characteristics, biological markers such as the CD4 cell count and plasma HIV RNA level, the date and type of AIDS-defining and non-AIDS events, antiretroviral treatments, and dates and causes of death. The FHDH project was approved by the French computer watchdog authority (CNIL) on 27 November 1991 (Journal Officiel, 17 January 1992).

Study population

This study was restricted to HIV-1-infected adults who started a first-line cART regimen between 1 January 1997 and 31 December 2012, and who maintained VL <50 copies/ml for at least 6 months on a ritonavir-boosted PI plus two NRTIs and who either continued on the same regimen or switched to RAL plus two NRTIs. Each individual who switched to RAL was matched with up to 3 individuals who continued on a on a boosted PI regimen, were being followed up during the calendar period of the switch to RAL (+/-6 months) and who had the same duration of VL<50 copies/ml (+/-6 months). This matching strategy controls for the duration of

viral control and for the healthcare environment both of which strongly influence the risk of treatment failure, and also provides an artificial index date for individuals who continued on the same PI regimen, namely the date which the matched individual switched to RAL. Only adults whose index date was at least one year before the last recorded database visit in the center and an available CD4 cell count within 6 months before the index date were eligible for inclusion.

Endpoints

The primary endpoint was a composite of hospitalization for a non-AIDS-defining event, the occurrence of an AIDS-defining event or death. Secondary endpoints were the two individual components of the primary endpoint, namely hospitalization or death from a non-AIDS defining cause and AIDS onset or death from an AIDS-defining event. We also analyzed the rate of virological failure, defined as 2 consecutive VL values >50 copies/ml or one VL value >50 copies/ml followed by a treatment switch prior to the next VL measurement; and the rate of immunological success, defined as an gain of at least 100 CD4 cells/mm^3 between the index date and the last visit before month 30. The rate of RAL discontinuing was also analyzed.

Statistical analysis

The baseline for all analyses was the index date. Follow-up was measured from the the index date until death, the date of last follow-up, or 30 months, whichever

occurred first. Because a switch to RAL is often motivated by drug-drug interactions or the risk of long-term PI toxicity, individuals in the two treatment groups (switch to RAL versus continuing PI) were likely to have different characteristics. In order to control for such differences, the endpoints were compared by using propensity scores [16]. The propensity score (PS) for each subject, defined as the conditional probability of switching to RAL given the patient's individual characteristics, was estimated from a logistic regression model that included factors known to be predictive endpoints and factors that might have influenced the decision to switch. The covariates included in the logistic regression model were the following: gender, the HIV transmission group, sub-Saharan origin, and smoking status; at first line cART initiation: the time since HIV-1 diagnosis (months), the CD4 cell count ($<200/\geq200/mm^3$) and VL ($<10\ 000/10\ 000$-$100\ 000/\geq100\ 000$ copies/ml); at the index date: age, the calendar period (2007-2009, ≥2010), the duration of VL undetectability (<50 copies/ml), the CD4 cell count (log_2/mm^3), the NRTI backbone and the boosted PI, the durations of prior PIs and NNRTIs exposure, the number of prior virological failure(s), ALT, AST and total cholesterol, prior AIDS-defining opportunistic infections, AIDS-defining malignancies and non-AIDS malignancies, the history of cardiovascular disease, diabetes and renal impairment, history of solid organ transplantation up to 10 days after the index date, hospitalization for other reasons within 6 months before the index date, and hepatitis C virus (HCV) antibody and hepatitis B surface antigen (HBsAg) status. Absolute standardized differences were used to compare the balance in characteristics between the two groups in the original and weighted samples [17]. The weights were the stabilized

inverse probability of switching treatment, calculated as explained above. The stabilized weight was estimated as P/PS for individuals who switched to RAL, and as (1-P)/(1-PS) for individuals who continued on PI where P is the overall marginal prevalence of treatment exposure [18]. Weighted Cox proportional hazards models were used to compare the two groups, the only variable included in the model being the type of treatment. The individuals who continued on PI served as reference. Weighted Kaplan-Meier estimates were calculated for the rates of clinical, virological and immunological outcomes in each group 30 months after the index date and for the proportion of individuals who continued on RAL in the switch group. As a change in treatment strategy could be considered as a competing event for immunological outcomes, (such individuals are likely to be those experiencing a slower increase in the CD4 cell count), we used a competing-risk approach to evaluate immunological outcomes. A change in treatment strategy was defined as RAL discontinuation in the switch group and as PI discontinuation in the non-switch group. With this approach, when the strategy was changed, follow-up was right-censored at the date of the individual's last visit during the 30-month follow-up period. This conservative approach ensured that no endpoints could be recorded during the period between the change in treatment strategy and the end of the 30-month follow-up period, thereby avoiding a situation in which the majority of individuals change treatment and achieve CD4 cell recovery on the alternative treatment. For clinical and virological endpoints, the intention-to-continue-treatment approach is a conservative approach, that we used.

Some data were missing from the database, notably for ALT, AST, total cholesterol,

smoking status, HCV antibody and HBsAg status. As these parameters were missing for fewer than 50% of individuals, the missing values were replaced with the multiple imputation method, missing values being randomly sampled from their predicted distributions. Ten sets of imputations were used to create 10 complete datasets. All 10 datasets were analyzed and combined with Rubin's rules [19,20]. A sensitivity analysis was also conducted in which ALT, AST, cholesterol, smoking, HCV antibody and HBsAg status, were not used to estimate the propensity scores and in which the numbers of prior of PIs, NNRTIs, and NRTIs were taken into account. SAS software (v9.3; SAS Institute Inc, Cary, NC, USA) was used for all statistical analyses.

Results

Individuals enrolled and baseline characteristics

The study flow chart is shown in Fig. 1. Among 284 individuals who switched from a boosted PI to RAL, 282 individuals were matched with 838 individuals who continued on a boosted PI regimen (atazanavir, darunavir, lopinavir, fosamprenavir or saquinavir). Two switchers were matched with one non-switcher, 4 switchers were matched with 2 non-switchers and 276 switchers were matched with 3 non-switchers. The characteristics of the two groups are described in Table 1. Before IPTW adjustment, several characteristics differed between the groups. Compared to the non-switcher group, the switcher group comprised fewer individuals of SubSaharan origin, more individuals with VL >100 000 copies/ml at first-line cART initiation, fewer individuals on recent boosted PIs (atazanavir or darunavir), and fewer individuals with two or more prior virological failures. As expected, comorbidities were more prevalent in the switch group. Nonetheless, the distribution of the propensity scores in the two groups showed substantial overlap (supplementary material Fig. S1). Absolute standardized differences between the groups before and after IPTW adjustment are reported in Supplementary Fig. S2. After IPTW adjustment, the standardized differences were below 10% for all the characteristics, indicating that an acceptable balance was achieved. Median follow-up was 20.7 months (IQR: 13.3-28.5).

Clinical outcomes

During follow-up, 91 individuals (31 in the switch group and 60 in the non-switch group) were hospitalized at least once for a non-AIDS event or experienced an AIDS-defining event or death. Considering separately the two components of the composite primary endpoint, 79 individuals were hospitalized for a non-AIDS event (n=74) or died from a non-AIDS-defining cause (n=5), while 12 individuals experienced an AIDS-defining event or died from an AIDS-defining event (n=1). The numbers do not add up to 91, as one individual was hospitalized first for renal failure and then for pulmonary mycobacterial infection four months later.

The three most common non-AIDS causes of hospitalization were infections (n=13), malignancies (n=10) and chronic viral hepatitis (n=8). The following AIDS-defining events occurred: Kaposi's sarcoma (n=3), *Pneumocystis jirovecii* pneumonia, pulmonary mycobacterial infection (n=2 each), cytomegalovirus retinitis, Burkitt's lymphoma, progressive multifocal leukoencephalopathy and encephalopathy (n=1 each) and 2 unspecified AIDS-defining events.

As shown in figure 2a, the weighted rate of the primary endpoint at month 30 was 13.6% in the switch group and 10.5% in the non-switch group, a non significant difference, the weighted hazard ratio (HR) was 1.16 (95% CI, 0.74 – 1.83). The weighted rate of hospitalization for a non-AIDS event or death from a non-AIDS event at month 30 was 12.6% in the switch group and 9.0% in the non-switch group, a non significant difference (HR=1.23 (95% CI, 0.76 – 2.00)). The weighted rate of AIDS-defining event or death from AIDS-defining event at month 30 was 1.2% in

the switch group and 1.5% in the non-switch group, a non significant difference (HR=0.87 (95% CI, 0.25 – 3.09)).

Biological outcomes

As shown in figure 2b, virological failure occured in 14 individuals in the switch group (Kaplan-Meier estimate: 6.1% at 30 months) and 60 individuals in the non-switch group (Kaplan-Meier estimate: 8.7% at 30 months), a non significant difference (HR=0.77 (95% CI, 0.43 – 1.36)). As shown in figure 2c, the CD4 cell count rose by at least 100/mm^3 in 145 individuals in the switch group (Kaplan-Meier estimate: 63.3% at 30 months) and 374 individuals in the non-switch group (Kaplan-Meier estimate: 61.0% at 30 months), a non significant difference (HR=1.07 (95% CI, 0.89 – 1.31)).

Durability of raltegravir

Forty-one of the 282 individuals in the switch group, discontinued RAL. The estimated weighted rate of RAL discontinuation at month 30 was 22%.

Sensitivity analysis

Similar results were obtained when cholesterol, smoking status, HCV antibody and HBsAg status were not used to estimate the propensity scores, and when the numbers of prior PIs, NNRTIs and NRTIs were taken into account. No difference in clinical or biological outcomes was found between the switch and non-switch groups.

Discussion

This study shows that, in routine clinical practice, HIV-1-infected individuals who switched from a virologically effective regimen comprising a boosted PI plus 2 NRTIs to a regimen consisting of RAL plus 2 NRTIs had similar clinical and immunovirologic outcomes to individuals who continued on the same regimen. The main strengths of this study are the large sample size and the use of propensity scores to control for confounding factors in this observational setting. The most important confounders in terms of prognosis were taken into account, except for adherence [21, 22] which was not recorded in the FHDH. However, as viral load was controlled in all individuals at baseline, and in most cases, throughout the follow-up period, adherence was probably not a major issue. We also took into account the history of treatment failure and the duration of the ongoing suppressive regimen at the index date, two factors which might have influenced the results of the SWITCHMK study. The raltegravir dosing frequency (once vs twice daily) was not available, but it was not found to influence the risk of virological failure in the ODIS trial [23]. We used IPTW adjustment to control for the many differences in characteristics between the switch and non-switch group. However, the clinical decision to switch to RAL might have been influenced by variables that were not available in the FHDH database, and thus, residual confounding may remain.

No clinical benefit or detriment was found when switching to RAL. The follow-up may have been too short or our power too limited to evidence a significant difference for the clinical outcome if any.

The switch to RAL was not accompanied by an excess risk of virologic failure: virologic suppression was maintained in 93.9% of the switch individuals at month 30, a rate similar to those observed in the SPIRAL [8], ODIS [23], and RACING studies [14]. In the SPIRAL study, virologic efficacy was similar in individuals who switched to RAL and those who continued on a ritonavir-boosted PI regimen [8], whereas in the SWITCHMK trial the rate of virological success at week 24 was 84.4% overall, and was lower in individuals who switched to RAL than in those who continued on lopinavir/ritonavir [7]. In our study, there was not statistically significant difference between the rates of virological success. At month 6, the rate of virological success was 95.4% in individuals who switched to RAL and 97.4% in individuals who continued on ritonavir-boosted protease inhibitors. A longer prior duration of virologic suppression has been linked to a lower risk of virologic failure after a treatment switch [24]. In our study and the SPIRAL trial, all individuals were virologically suppressed for at least 6 months prior to the switch, compared to at least 3 months in the SWITCHMRK trial. The low rate of virological failure observed here suggests that clinicians have integrated the results of the SWITCHMRK trial and thus avoid prescribing raltegravir to individuals with an unfavorable resistance profile. As in the SWITCHMK and SPIRAL studies, we found no significant difference in the CD4 T-cell count at month 30 between the switch and non-switch groups [7,8].

The rate of RAL discontinuation was 7% at month 6 and 11% at month 12, values similar to those observed in the SWITCHMK2 trial (6% at week 24) and the SPIRAL trial (9% at week 48) [7,8].

Conclusion

This study shows that clinical, virological and immunological efficacy is maintained when HIV-infected pretreated individuals on a virologically effective boosted PI regimen are switched to RAL, a frequent decision in clinical practice. As the HIV population ages and comorbidities become increasingly prevalent, RAL, an antiretroviral that carries a minimal risk of drug-drug interactions, is a drug of choice.

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Potential conflicts of interest

A.S. has received fees for participation in review activities from Merck Sharp & Dohme-Chibret and payment for development of educational presentations from ViiV Healthcare and Janssen-Cilag. J.-J.P. has received grants from Merck Sharp & Dohme-Chibret, and ViiV Healthcare and consultancy fees from Bristol-Myers Squibb, Gilead Sciences and Janssen-Cilag. D. C. was a member of the French Gilead HIV board up to 2015. In the past 3 years she gave lectures for Janssen-Cilag, Merck-Sharp & Dohme-Chibret, ViiV and received travel/accommodations/meeting expenses from Gilead, ViiV, Janssen-Cilag. She conducted post-marketing studies for Janssen-Cilag, Merck-Sharp & Dohme-Chibret and ViiV. She is currently a consultant of Innavirvax. All other authors report no potential conflicts.
All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Members of FHDH-ANRS CO4 are listed at
http://www.ccde.fr/main.php?main_file=fl-1171464013-677.html.

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Table 1. Characteristics of individuals.

	Before IPTW adjustement					After IPTW adjustement			
	Continuing PI n=838		**Switch to RAL** n=282		P*	**Continuing PI** n=847**		**Switch to RAL** n=273**	
Gender									
M	531	63.4%	179	63.5%	0.97	536	63.3%	170	62.2%
Transmission group									
MSM	263	31.4%	104	36.9%	0.32	283	33.4%	90	32.9%
IDU	80	9.5%	23	8.2%		76	8.9%	23	8.3%
Heterosexual	433	51.7%	132	46.8%		426	50.4%	140	51.5%
Other	62	7.4%	23	8.2%		62	7.3%	20	7.4%
Sub-Saharan origin									
Yes	182	21.7%	38	13.5%	0.003	168	19.8%	53	19.6%
Smoking status									
Never smoked	345	41.2%	96	34.0%	0.16	333	39.3%	107	39.1%
Former smoker	230	27.4%	87	30.9%		242	28.5%	77	28.4%
Current smoker	263	31.4%	99	35.1%		272	32.1%	89	32.5%
At first-line cART :									
Time since HIV-1 diagnosis (months) (mean (sd))	42.8	(57.1)	42.0	(58.3)	0.84	41.9	(57.4)	41.0	(57.9)
CD4 (cells/mm3)									
<200	347	41.4%	115	40.8%	0.85	354	41.9%	120	43.8%
Viral load (copies/ml)									
<=10 000	257	30.7%	63	34.8%	0.005	242	28.6%	71	26.0%
]10 000 -100 000]	301	35.9%	98	34.8%		302	35.7%	10	36.9%
>100 000	280	33.4%	121	42.9%		303	35.8%	101	37.1%
At the index date:									
Age (years) at index date (mean (sd))	45.9	(10.9)	47.6	(10.9)	0.02	46.3	(11.2)	46.3	(10.0)
Period									
2007-2009	372	44.4%	119	42.2%	0.52	362	42.8%	116	42.5%
>=2010	466	55.6%	163	57.8%		484	57.2%	157	57.5%
Duration of undetectability (months) (mean (sd))	40.5	(31.2)	40.8	(31.5)	0.89	40.7	(31.7)	40.4	(30.8)
CD4 (cells/mm^3) (mean (sd))	572	(264)	586	(274)	0.44	572	(264)	586	(274)
Type of boosted PI									
ATV/ATV/r or DRV/r	426	50.8%	112	39.7%	0.001	409	48.3%	124	45.4%
LPV/r or FPV/r or SQV/r	412	49.2%	170	60.3%		438	51.7%	149	54.6%
Type of NRTIs backbone									
ABC/3TC	192	22.9%	67	23.8%	0.76	195	23.1%	59	21.5%
AZT/3TC	93	11.1%	37	13.1%		98	11.6%	33	11.9%
TDF/FTC	486	58.0%	155	55.0%		487	57.5%	159	58.1%
Others	67	8.0%	23	8.2%		67	7.9%	23	8.5%
Duration of prior PIs exposure (months) (mean (sd))	63.8	(44.5)	55.9	(38.4)	0.007	61.2	(43.5)	59.4	(39.1)
Duration of prior NNRTIs exposure (months) (mean (sd))	11.0	(23.5)	10.0	(23.5)	0.58	10.8	(23.3)	9.8	(21.6)
Number of prior PIs									
1	361	43.1%	135	47.9%	0.32	387	45.7%	123	45.2%
2	288	34.4%	90	31.9%		282	33.3%	88	32.4%
3	115	13.7%	40	14.2%		113	13.3%	40	13.5%
>3	74	8.8%	17	6.0%		65	7.6%	24	9.0%
Number of prior NRTIs									
2	294	35.1%	105	37.2%	0.70	310	36.7%	98	35.9%
3	102	12.2%	28	9.9%		101	12.0%	23	8.6%
4	198	23.6%	70	24.8%		198	23.4%	72	26.2%
>4	244	29.1%	79	28.0%		237	28.0%	80	29.3%
Number of prior NNRTIs									
0	555	66.2%	184	65.2%	0.80	562	66.4%	170	62.2%
1	241	28.8%	81	28.7%		245	28.9%	83	30.6%
2	42	5.0%	17	6.0%		40	4.7%	20	7.2%
Number of prior virological failure(s)									
0	546	65.2%	184	65.2%	0.006	559	66.1%	184	67.3%
1	131	15.6%	63	22.3%		140	16.5%	44	16.1%
2 ou 3	133	15.9%	32	11.3%		124	14.7%	41	14.9%
>3	28	3.3%	3	1.1%		23	2.7%	5	1.8%

	Before IPTW adjustement					After IPTW adjustement			
	Continuing PI n=838		**Switch to RAL** n=282		P*	**Continuing PI** n=847**		**Switch to RAL** n=273**	
Cholesterol (mmol/L) (mean (sd))	5.14	(0.91)	5.34	(0.98)	0.11	5.14	(0.91)	5.34	(0.98)
ALT (X normal values) (mean (sd))	0.87	(0.62)	1.00	(0.60)	0.01	0.87	(0.62)	1.00	(0.60)
AST (X normal values) (mean (sd))	0.87	(0.53)	0.97	(0.68)	0.06	0.87	(0.53)	0.97	(0.68)
Prior AIDS-defining opportunistic infections									
Yes	186	22.2%	60	21.3%	0.75	184	21.7%	55	20.2%
Prior AIDS-defining malignancies									
Yes	40	4.8%	7	2.5%	0.10	36	4.2%	12	4.5%
Prior non-AIDS malignancies									
Yes	22	2.6%	11	3.9%	0.27	24	2.9%	7	2.7%
Prior stroke or MI									
Yes	12	1.4%	8	2.8%	0.12	14	1.7%	4	1.5%
Prior diabetes									
Yes	29	3.5%	10	3.5%	0.95	32	3.8%	11	3.9%
Prior renal impairment									
Yes	46	5.5%	26	9.2%	0.03	52	6.1%	19	6.9%
Solid organ transplantation up to 10 days after the index date									
Yes	1	0.1%	6	2.1%	0.0002	6	0.7%	2	0.7%
Hospitalization for other reasons within 6 months before the index date									
Yes	3	0.4%	3	1.1%	0.16	4	0.4%	1	0.5%
Number of Comorbidities (History of non AIDS malignancies, stroke or MI, diabetes, renal impairment, solid organ transplantation)									
0	743	88.7%	233	82.6%	0.04	739	87.3%	237	86.8%
1	81	9.7%	38	13.5%		88	10.4%	29	10.6%
2	13	1.5%	10	3.5%		19	2.2%	6	2.2%
>2	1	0.1%	1	0.4%		1	0.1%	1	0.4%
HCV antibody									
Positive	120	14.3%	42	14.9%	0.70	126	14.9%	37	13.5%
HBsAg									
Positive	56	6.7%	11	3.9%	0.09	49	5.8%	16	6.1%

*P values were derived from Chi-Square test for categorical variables and from differences of least Squares Means test for continuous variables.

**Synthetic n values derived from weights. The sum of weights was 1.01 in continuing PI group and 0.97 in Switch to RAL group.

Abreviations: cART Combination AntiRetroviral Therapy; HIV-1 Human Immunodeficiency Virus type 1; undetectability VL <50 copies/ml; PI Protease Inhibitor; NNRTI Non-Nucleoside Reverse Transcriptase Inhibitor; NRTI Nucleoside Reverse Transcriptase Inhibitor; RAL Raltegravir; ATV Atazanavir; ATV/r ritonavir-boosted Atazanavir; DRV/r ritonavir-boosted Darunavir; LPV/r ritonavir-boosted Lopinavir; FPV/r ritonavir-boosted Fosamprenavir; SQV/r ritonavir-boosted Saquinavir; ABC Abacavir; 3TC Lamivudine; AZT Zidovudine; TDF Tenofovir; MI Myocardial Infarction ; HCV hepatitis C virus; HBsAg Hepatitis B Surface Antigen.

Figure 1. Individuals selection.

Figure 2. Weighted Kaplan-Meier plots according treatment strategy of times (a) to hospitalization or AIDS or death b) to 2 consecutive VL>50 copies/ml or 1 VL>50 copies/ml followed by a treatment switch prior to another VL measurement (c) to a gain of at least 100 CD4 cells/mm^3.

Figure 1. Individuals selection.

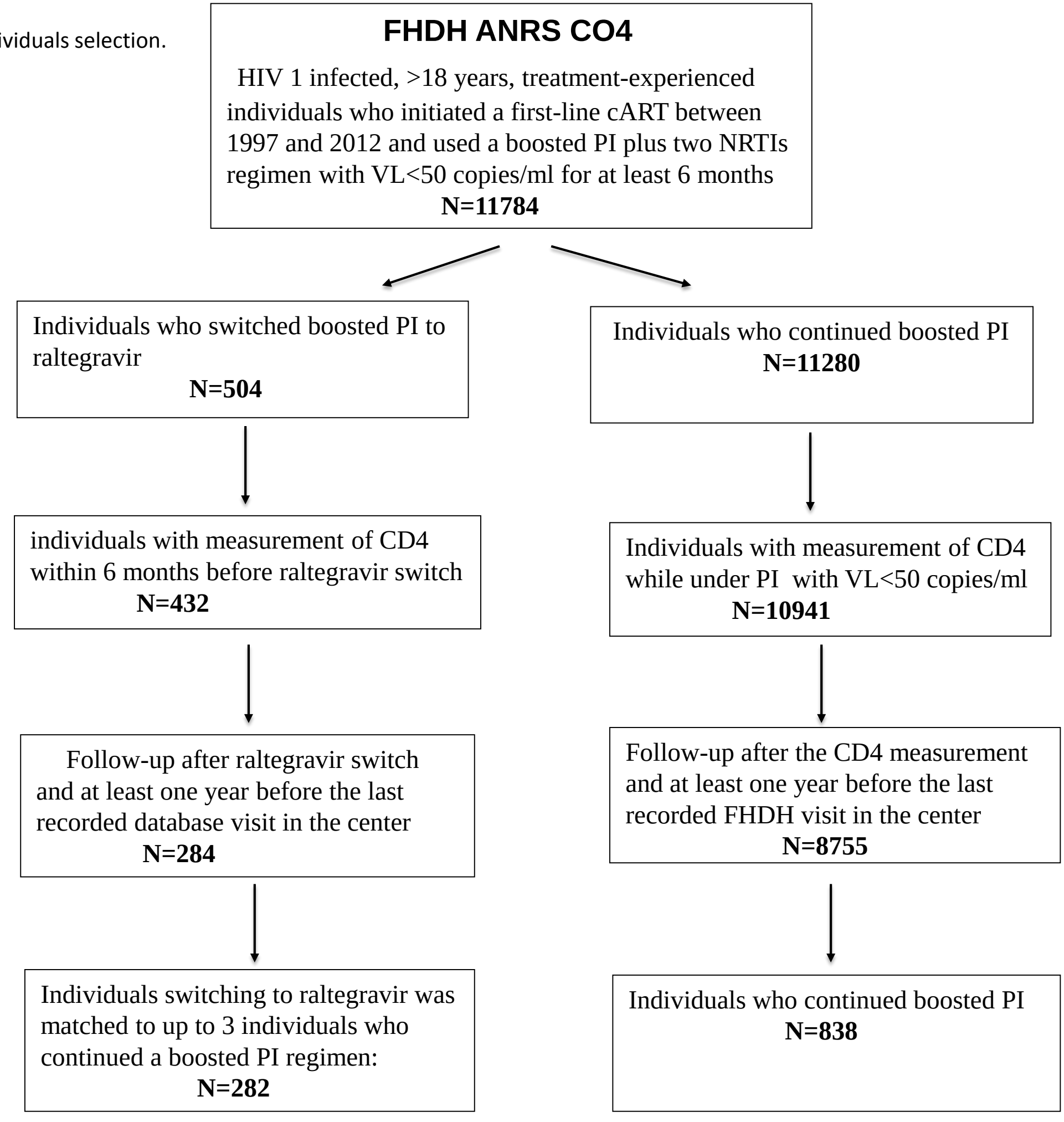
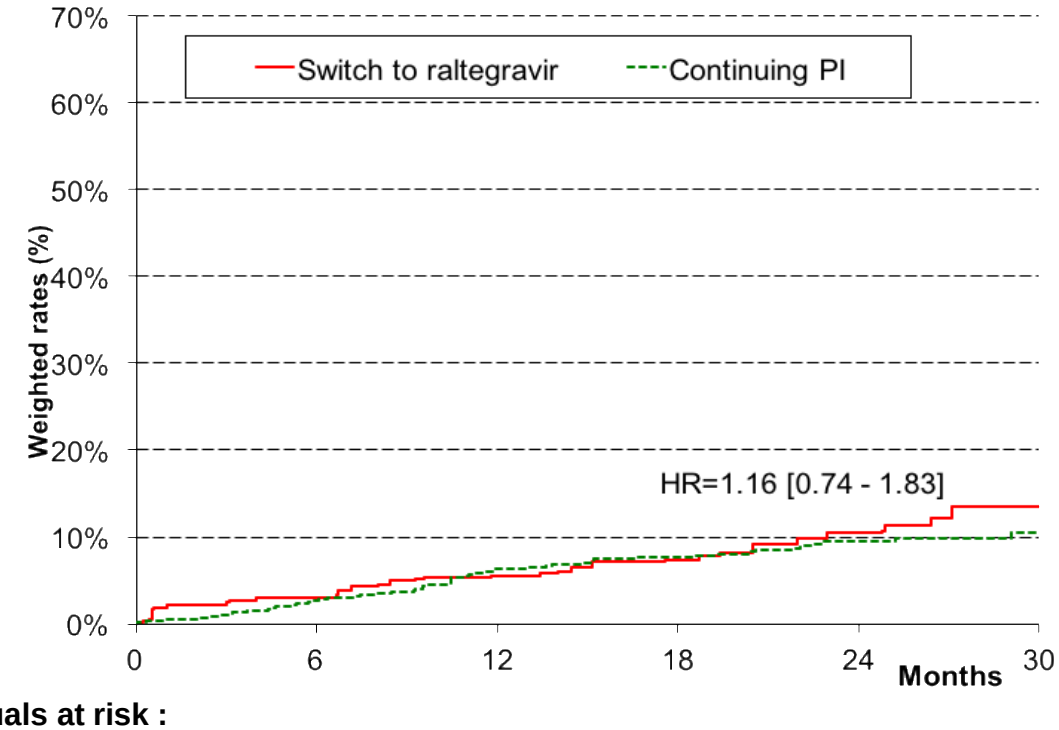


Figure 2. Weighted Kaplan-Meier plots according treatment strategy of times (a) to hospitalization or AIDS or death b) to 2 consecutive VL>50 copies/ml or 1 VL>50 copies/ml followed by a treatment switch prior to another VL measurement (c) to a gain of at least 100 CD4 cells/mm^3.

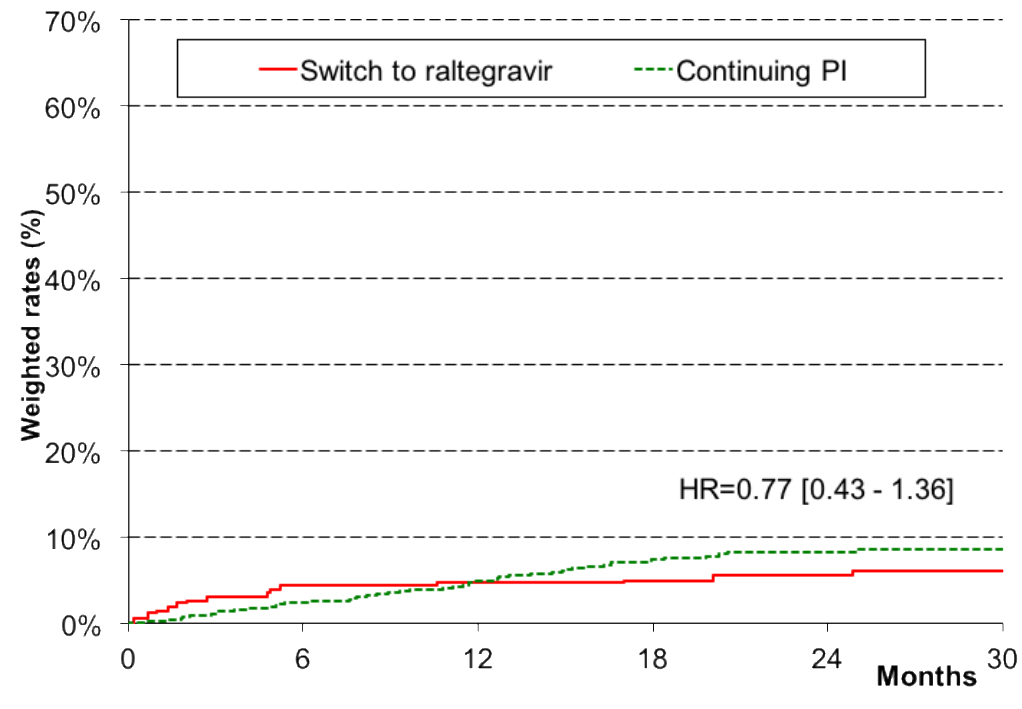
a. Hospitalization or AIDS or death



Individuals at risk :

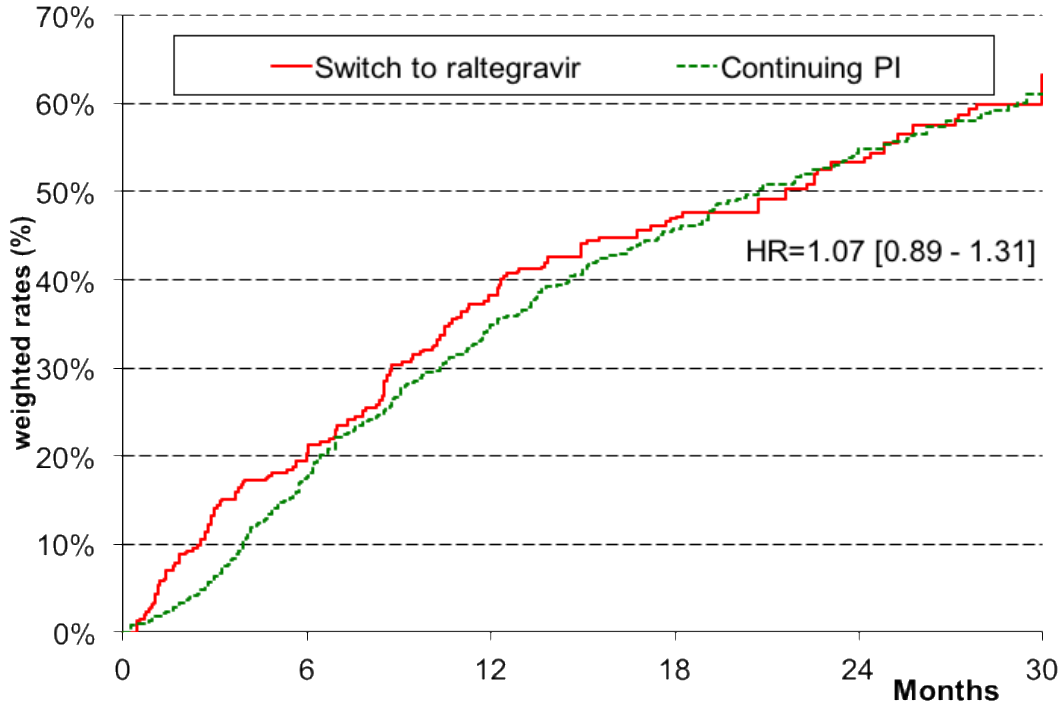
Boosted PI	847	769	628	434	284	147
Raltegravir	273	256	206	157	109	68

b. Virological failure



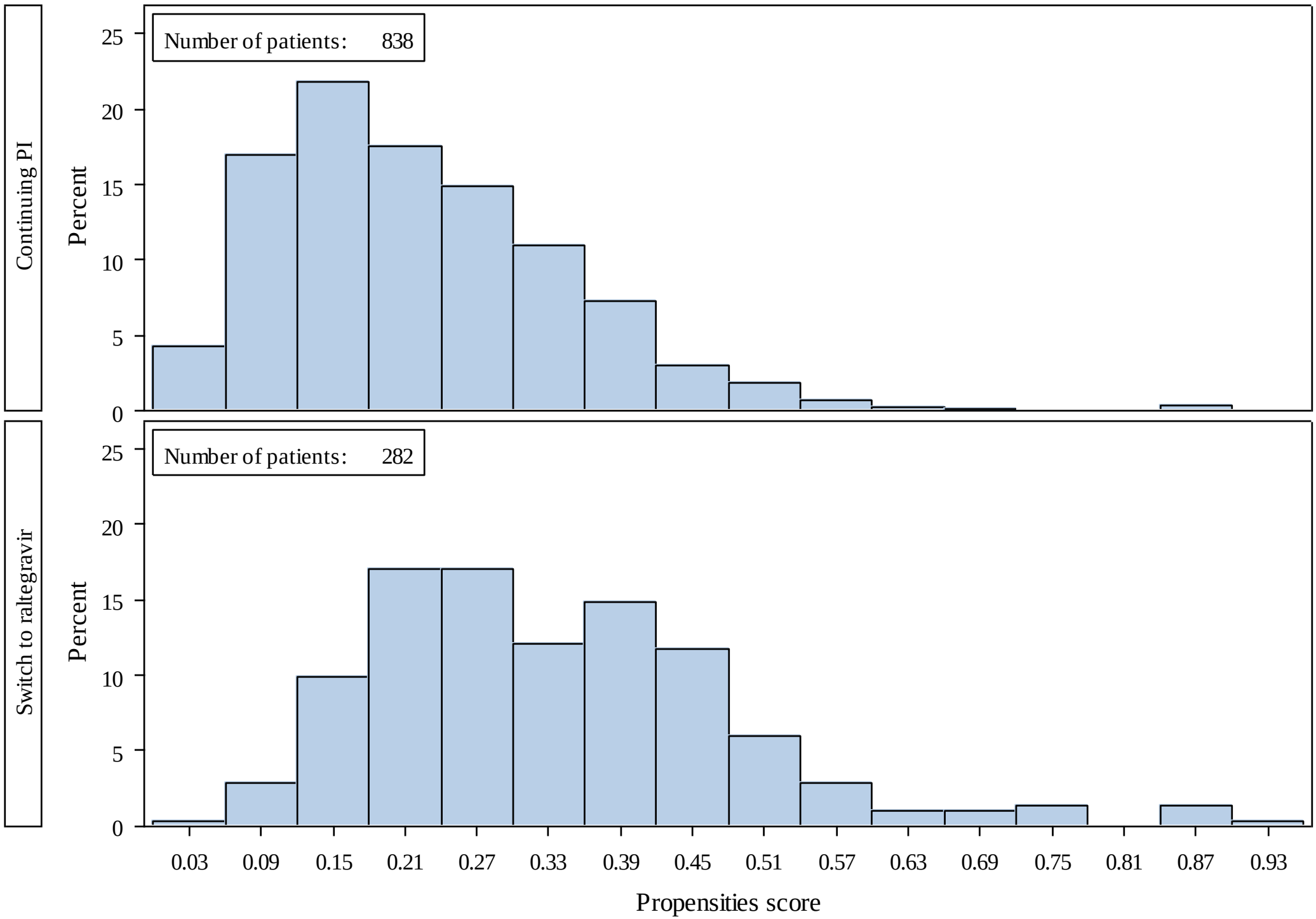
	847	766	630	424	282	149
	273	251	205	159	113	71

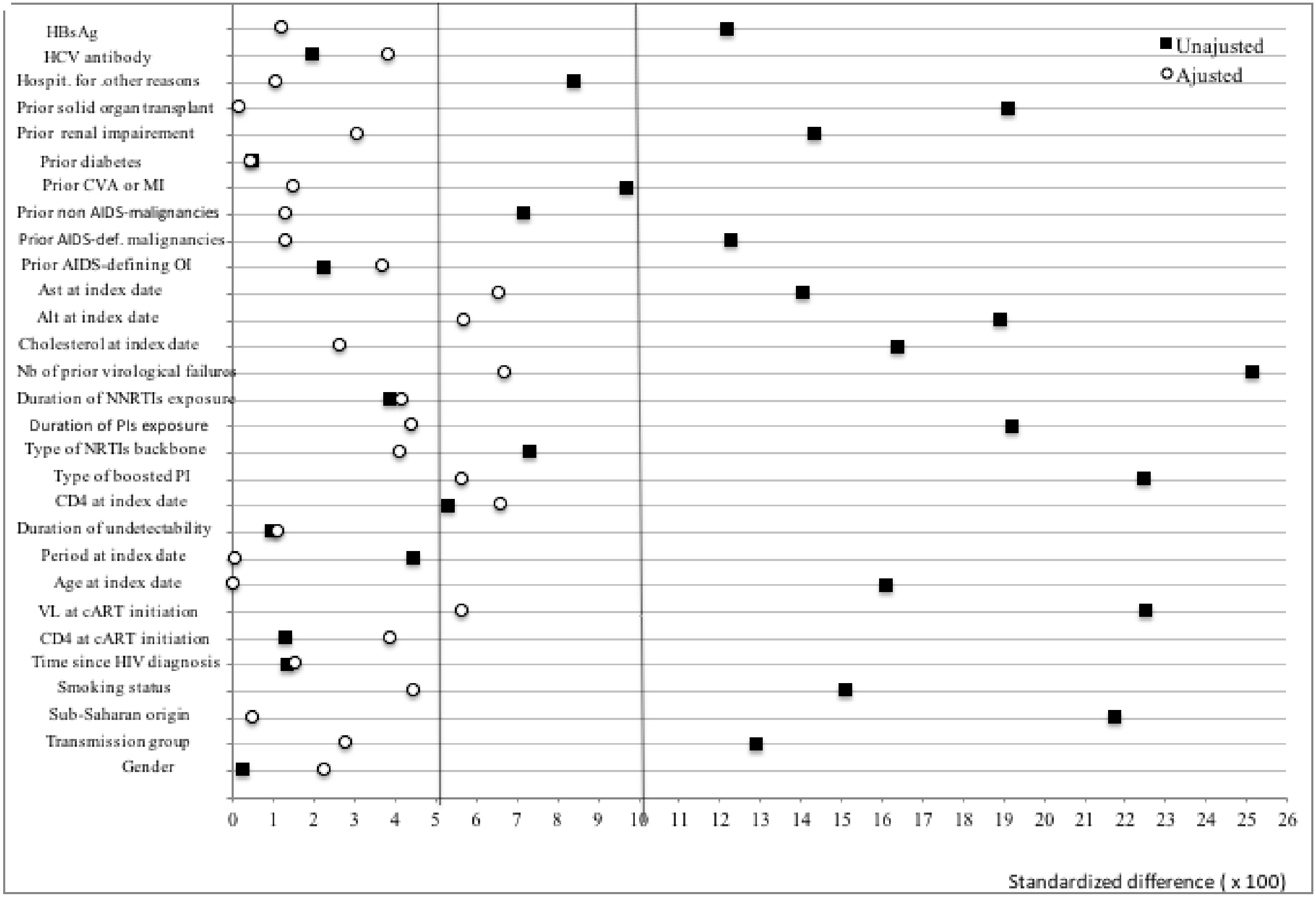
c. Immunological success



Individuals at risk :

Boosted PI	847	647	441	264	154	74
Raltegravir	273	210	138	96	63	32


Continuing PI
Number of patients: 838
Percent
25
20
15
10
5
0
Switch to raltegravir
Number of patients: 282
Percent
25
20
15
10
5
0
0.03
0.09
0.15
0.21
0.27
0.33
0.39
0.45
0.51
0.57
0.63
0.69
0.75
0.81
0.87
0.93
Propensities score


HBsAg
HCV antibody
Hospit. for .other reasons
Prior solid organ transplant
Prior renal impairement
Prior diabetes
Prior CVA or MI
Prior non AIDS-malignancies
Prior AIDS-def. malignancies
Prior AIDS-defining OI
Ast at index date
Alt at index date
Cholesterol at index date
Nb of prior virological failures
Duration of NNRTIs exposure
Duration of PIs exposure
Type of NRTIs backbone
Type of boosted PI
CD4 at index date
Duration of undetectability
Period at index date
Age at index date
VL at cART initiation
CD4 at cART initiation
Time since HIV diagnosis
Smoking status
Sub-Saharan origin
Transmission group
Gender
Unajusted
Ajusted
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
Standardized difference (x 100)