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Switch from a first virologically effective protease inhibitor-containing regimen to a regimen containing efavirenz, nevirapine or abacavir

Sophie Abgrall^{a,b}, Patrick G. Yeni^c, Olivier Bouchaud^b, Dominique Costagliola^a and the Clinical Epidemiology Group from the French Hospital Database on HIV*

Background: Treatment simplification in antiretroviral-experienced patients receiving protease inhibitor (PI)-containing antiretroviral regimens seems safe, but randomized trials have limited power to detect differences in virological rebound (VR) between different switch strategies.

Methods: From the French Hospital Database on HIV, we selected 2462 patients with undetectable viral load (VL) who switched from a first PI-containing antiretroviral combination (cART) to a combination containing efavirenz (EFV), nevirapine (NVP) or abacavir (ABC). Factors associated with VR and with immunological efficacy (gain of ≥ 50 CD4+ cells/ μ l) were identified by using Cox models.

Results: The 12-month Kaplan–Meier probabilities of VR were 6.8, 13.7 and 12.3% in patients switching to EFV-cART, NVP-cART and ABC-cART, respectively. Factors associated with VR were female sex, younger age, antiretroviral exposure before the first cART, time on first cART, higher VL at first cART initiation, a stavudine/didanosine backbone (rather than zidovudine/lamivudine) after the switch, and a switch to NVP or ABC [respective adjusted hazard ratio versus EFV: 1.53; 95% confidence interval (CI), 1.21–1.94; and 1.53; 95% CI, 1.12–2.08]. When the analyses were restricted to patients who were antiretroviral-naïve before their first cART, NVP (but not ABC) was associated with VR. Immunological outcomes did not differ among the three switch regimens.

Conclusion: When VL is undetectable on a first PI-cART regimen, switching to an EFV-containing regimen is more likely to avoid VR than switching to an ABC or NVP-containing regimen. ABC may be an alternative to EFV for patients who were not exposed to antiretroviral before their first cART regimen, after checking for ABC resistance mutations.

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Keywords: HIV/AIDS, undetectability, virological rebound, simplification therapy, efavirenz, nevirapine, abacavir, observational study, cohort study

Introduction

Combination antiretroviral therapy (cART) prolongs the survival of immunodeficient HIV-infected patients [1–3].

The potency, toxicity and interactions of available antiretroviral regimens are different [4], and the choice of initial cART is guided by the degree of immunodeficiency, likely adherence, and potential adverse effects

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and interactions. Randomized trials and cohort studies have examined virological outcomes in antiretroviral-naïve patients starting cART with efavirenz, nevirapine or triple-nucleoside regimens [5–11].

Even when virologically effective, a first protease inhibitor (PI)-containing cART regimen may have to be changed for reasons of toxicity or an excessive pill burden. Clinical trials suggest that simplification of PI-containing regimens is virologically safe, at least in patients who do not harbor archived resistance mutations [12]. However, randomized trials have limited power to detect differences in the risk of virological rebound between different switch strategies after a first PI-cART regimen.

Here we studied patients enrolled in the French Hospital Database on HIV (FHDH) who switched to a three-drug regimen containing efavirenz (EFV), nevirapine (NVP) or abacavir (ABC) at a time when their plasma viral load (pVL) was undetectable while on an initial PI-containing cART regimen. We focused on factors associated with subsequent virological rebound, and also analyzed mid-term immunological outcomes according to the switch regimen.

Methods

Patients

The FHDH is a large prospective cohort study of HIV-infected patients aged at least 15 years and treated in 68 French university hospitals. The only enrollment criteria are documented HIV-1 or HIV-2 infection and written informed consent. Trained research assistants use the French Ministry of Health DMI2 software to collect clinical and biological data prospectively at inclusion and at each visit or hospital admission for an HIV-related clinical event or a new treatment prescription, or at least every 6 months, on standardized forms.

For this study we selected HIV-1-infected patients starting a first PI-containing cART regimen (at least three antiretroviral drugs with at least two nucleoside reverse-transcriptase inhibitors (NRTI) and one PI) after 1 January 1997. We excluded patients with prior exposure to PI, non-nucleoside reverse-transcriptase inhibitors (NNRTI) or ABC, and patients previously included in a blinded clinical trial of antiretroviral therapy. We selected patients who subsequently switched to a regimen containing two NRTI plus one NNRTI or ABC while their pVL was undetectable (< 500 copies/ml) and who had received only one cART regimen before the switch. The date of inclusion in the study was the date of the switch. Patients were excluded if CD4 cell count or pVL values were unavailable within 3 months before the first cART and before the switch, and at least once during

subsequent follow-up. The cut-off date for database analysis was 31 December 2003. A total of 2462 patients met these criteria.

Statistical analysis

Three groups of patients were compared, based on whether their three-drug switch regimen contained efavirenz (EFV-cART), nevirapine (NVP-cART) or abacavir (ABC-cART). Follow-up data were censored at the date of any subsequent change in their antiretroviral therapy.

Factors associated with the risk of virological rebound, defined as the first of two consecutive pVL values of 500 copies/ml or more, were identified by using univariate and multivariable Cox proportional hazards models. Each variable associated with virological rebound in the univariate model ($P < 0.20$) was included in a multivariable model designed to evaluate the impact of the switch regimen on the risk of virological rebound, after adjustment for other risk factors. The influence of the dual-NRTI backbone was also assessed. Because of interactions between the antiretroviral treatment history and the switch regimen in terms of virological outcome, antiretroviral-experienced and antiretroviral-naïve patients were also examined separately.

Factors associated with immunological efficacy (gain of at least 50 CD4+ cells/ μ l from baseline) were also identified by using Cox regression models.

Results

Among the 2462 selected patients, 918 (37%) switched to EFV-cART, 947 (39%) to NVP-cART, and 597 (24%) to ABC-cART. The most frequently prescribed switch regimens were ABC-zidovudine-lamivudine in 522 cases (21%), NVP-zidovudine-lamivudine in 452 (18%), EFV-zidovudine-lamivudine in 369 (15%), NVP-stavudine-lamivudine in 330 (13%), EFV-stavudine-lamivudine in 277 (11%), EFV-stavudine-didanosine in 136 (6%), and NVP-stavudine-didanosine in 107 (4%).

The first cART regimen represented the first antiretroviral drug exposure in 1609 patients (65%). The other patients had received a median of two different antiretroviral drugs, for a median duration of 20 months [interquartile range (IQR), 10–35 months]. The first cART included lamivudine in 2052 cases (83%), stavudine in 1261 cases (51%), zidovudine in 1196 cases (49%), indinavir in 1240 cases (50%), and nelfinavir in 884 cases (36%). The protease inhibitor was boosted with ritonavir in 299 cases (12%).

The switch to a PI-free cART regimen took place a median of 19 months (IQR, 10–30 months) after the

beginning of the first PI-containing cART regimen. The characteristics of the patients are shown in Table 1. Median follow-up after the switch was 32 months (IQR, 16–45 months).

Virological outcome

A virological rebound occurred in 387 patients. The Kaplan–Meier 12-month probability of virological rebound was 10.7% overall [95% confidence interval (CI), 9.3–12.1%], 6.8% (95% CI, 5.0–8.7%) in patients switching to EFV-cART, 13.7% (95% CI, 11.2–16.3%) in patients switching to NVP-cART and 12.3% (95% CI, 9.8–15.4%) in patients switching to ABC-cART ($P < 0.01$) (Fig. 1). The 12-month probability of virological rebound was 13.4% (95% CI, 10.7–16.0%) among the 853 patients who had been exposed to antiretroviral before their first cART regimen, and 9.3% (95% CI, 7.9–10.9%) among the 1609 antiretroviral-naïve patients ($P < 0.01$).

After adjustment for other factors, male gender, older age, no antiretroviral exposure before the first cART regimen [adjusted hazard ratio (aHR), 0.68], and time on first cART (aHR, 0.90 per 6 months increment) were associated with a lower risk of virological rebound (Table 2). Type of first cART, namely with boosted or unboosted PI, did not influence risk of virological rebound in the univariate analysis and was not added to the multivariable model ($P = 0.89$ for the comparison between boosted and unboosted PI). Higher pVL values when starting the first cART regimen were associated

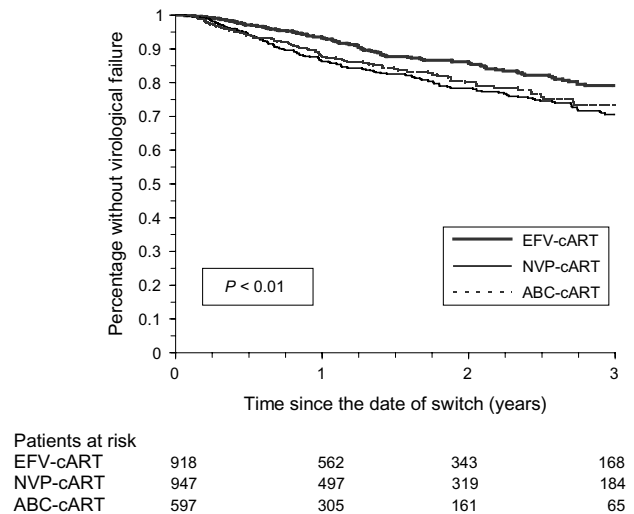


Fig. 1. Kaplan–Meier curves of the probabilities without virological failure according to the three categories of switch antiretroviral regimen. ABC, abacavir; cART, combination antiretroviral therapy; EFV, efavirenz; NVP, nevirapine.

with a higher risk of virological rebound (respective aHR, versus undetectable pVL: 1.56 for pVL between 2.70 and 4.00 \log_{10} copies/ml; and 1.44 for pVL above 4.00 \log_{10} copies/ml). The risk of virological rebound was 61% higher among patients with a stavudine/didanosine backbone at the time of switch than among patients with a zidovudine/lamivudine backbone. NVP-cART and ABC-cART were associated with a

Table 1. Characteristics of the patients with undetectable plasma viral load at switch according to the switch antiretroviral regimen.

	EFV ($n = 918$)	NVP ($n = 947$)	ABC ($n = 597$)
Sex (male) [n (%)]	693 (75.5)	686 (72.4)	429 (71.9)
Median (IQR) age (years)	39.3 (34.7–46.3)	38.6 (33.1–46.5)	39.1 (33.6–45.2)
Transmission group [n (%)]			
Men who have sex with men	374 (40.7)	391 (41.3)	199 (33.3)
Intravenous drug users	103 (11.2)	102 (10.8)	65 (10.9)
Heterosexual transmission	346 (37.7)	367 (38.8)	265 (44.4)
Other/unknown	95 (10.4)	87 (9.2)	68 (11.4)
At first cART initiation			
Antiretroviral drug-naïve [n (%)]	568 (61.9)	573 (60.5)	468 (78.4)
Boosted-PI [n (%)]	79 (8.6)	100 (10.6)	120 (20.1)
Median (IQR) CD4 cell count (cells/ μ l)	318 (180–479)	330 (193–490)	284 (166–436)
Median (IQR) plasma viral load (\log_{10} copies/ml)	4.20 (2.77–5.00)	4.14 (2.70–5.02)	4.55 (3.18–5.09)
At the date of switch			
Median (IQR) time on first cART (months)	20 (11–30)	16 (9–26)	19 (9–36)
Previous ADE [n (%)]	178 (19.4)	146 (15.4)	98 (16.4)
Median (IQR) CD4 cell count (cells/ μ l)	519 (349–732)	525 (345–701)	499 (322–704)
NRTI backbone			
Zidovudine–lamivudine	369 (40.2)	452 (47.7)	522 (87.4)
Stavudine–lamivudine	277 (30.2)	330 (34.9)	49 (8.2)
Stavudine–didanosine	136 (14.8)	107 (11.3)	16 (2.7)
Other	136 (14.8)	58 (6.1)	10 (1.7)
Calendar year			
1997–2000	618 (67.3)	703 (74.2)	198 (33.2)
2001–2003	300 (32.7)	244 (25.8)	399 (66.8)

ABC, abacavir; ADE, AIDS defining event; cART, combination antiretroviral therapy; EFV, efavirenz; IQR, interquartile range; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine.

Table 2. Relative hazards of virological rebound in patients with undetectable plasma viral load (pVL) at switch (2462 patients, 387 events), results of the multivariable Cox's proportional hazards analysis.

	N	Rebound n	Virological rebound ^a in patients with undetectable switch pVL		
			HR	(95%CI)	P value
Sex:					
Female	654	125	1.00		
Male	1808	262	0.69	(0.53–0.89)	< 0.01
Age ^b					
			0.87	(0.78–0.98)	0.02
Transmission group					
Homosexual men	964	143	1.00		
Intravenous drug	270	49	1.32	(0.94–1.86)	0.12
Heterosexual transmission	978	158	0.99	(0.75–1.30)	0.94
Other/unknown	250	37	1.08	(0.73–1.59)	0.70
At first cART initiation					
Antiretroviral history					
Antiretroviral drug-experienced	853	165	1.00		
Antiretroviral drug-naïve	1609	222	0.62	(0.49–0.79)	< 0.01
CD4 cell count (/μl)					
0 ≤ CD4 < 50	216	26	1.00		
50 ≤ CD4 < 200	480	61	0.83	(0.51–1.36)	0.47
200 ≤ CD4 < 350	694	96	0.85	(0.50–1.44)	0.54
CD4 ≥ 350	1072	204	1.08	(0.63–1.84)	0.79
Plasma viral load (log ₁₀ copies/ml)					
pVL < 2.70	588	76	1.00		
2.70 ≤ pVL < 4.00	472	97	1.56	(1.15–2.12)	< 0.01
pVL ≥ 4.00	1402	214	1.44	(1.09–1.90)	0.01
At the date of switch					
Time on first cART ^c					
			0.90	(0.85–0.95)	< 0.01
HIV status:					
A–B	2040	334	1.00		
C	422	53	1.21	(0.87–1.69)	0.27
CD4 count (/μl)					
0 ≤ CD4 < 50	25	2	1.00		
50 ≤ CD4 < 200	198	26	1.83	(0.43–7.81)	0.42
200 ≤ CD4 < 350	424	54	1.88	(0.45–7.96)	0.39
CD4 ≥ 350	1815	305	2.14	(0.50–9.05)	0.30
NRTI backbone					
Zidovudine–lamivudine	1343	201	1.00		
Stavudine–lamivudine	656	109	0.99	(0.76–1.30)	0.95
Stavudine–didanosine	259	55	1.61	(1.16–2.22)	< 0.01
Other	204	22	1.03	(0.65–1.63)	0.89
Calendar year:					
1997–2000	1519	284	1.00		
2001–2003	943	103	1.47	(1.13–1.92)	< 0.01
Switch antiretroviral regimen					
Efavirenz-containing regimen	918	120	1.00		
Nevirapine-containing regimen	947	178	1.53	(1.21–1.94)	< 0.01
Abacavir-containing regimen	597	89	1.53	(1.12–2.08)	< 0.01

cART, combination antiretroviral therapy; CI, confidence interval; HR, hazard ratio; pVL, plasma viral load

^aFirst of two plasma viral load ≥ 500 copies/ml (2.70 log₁₀ copies/ml).

^bHR is estimated for increments of 10 years.

^cHR is estimated for increments of 6 months.

significantly higher risk of virological rebound than EFV-cART (respective aHR, 1.53; 95% CI, 1.21–1.94; and 1.53; 95% CI, 1.12–2.08).

Among patients who had been exposed to antiretroviral drugs before starting their first cART regimen, NVP-cART and ABC-cART were associated with a significantly higher risk of virological rebound than EFV-cART (respective aHR, 1.80; 95% CI, 1.26–2.59; and 2.70; 95% CI, 1.56–4.67). Among patients who were antiretroviral-naïve before starting their first cART, NVP-cART (but not ABC-cART) was associated with

a significantly higher risk of virological rebound than EFV-cART (respective aHR, 1.51; 95% CI, 1.09–2.09; and 1.29; 95% CI, 0.88–1.89).

Immunological outcome

Among patients switching to EFV-cART, the median (IQR) CD4 cell counts at the switch and 24 months later were 519 cells/μl (IQR, 349–732 cells/μl) and 575 cells/μl (IQR, 398–782 cells/μl). The respective values were 525 cells/μl (IQR, 345–701 cells/μl) and 556 cells/μl (IQR, 406–784 cells/μl) among patients switching to NVP-cART, and 499 cells/μl (IQR, 322–704 cells/μl)

and 483 cells/ μl (IQR, 358–615 cells/ μl) among patients switching to ABC-cART.

During follow-up, 613 patients who switched to EFV-cART, 607 patients who switched to NVP-cART and 364 patients who switched to ABC-cART gained at least 50 CD4+ cells/ μl . The respective 24-month probabilities of gaining ≥ 50 CD4+ cells/ μl were 81.5% (95%CI, 78.4–84.7%), 81.6% (95%CI, 78.4–84.9%) and 79.8% (95%CI, 75.2–84.3%) ($P = 0.41$). After adjustment for other variables, immunological outcomes on the different switch regimens did not differ (data not shown).

Discussion

Among 2462 patients with undetectable pVL while on a first PI-containing cART regimen, switching to NVP-cART or ABC-cART was associated with a higher risk of virological rebound than switching to EFV-cART. Switching to NVP-cART was also significantly associated with virological rebound among patients who had not been exposed to antiretroviral drugs before their first cART regimen, whereas switching to ABC-cART was not. No differences in immunological efficacy were observed among the three switch regimens.

Rate of virological rebound in naive patients [12-month probability of 9.3% corresponding to an incidence rate of 8.9 per 100 person-years of follow-up (PYFU)] was higher than rates previously estimated in other cohort studies (4.8 per 100 PYFU and 6.3 per 100 PYFU) [13,14]. However, lower threshold values (50 to 80 copies/ml) were used to define undetectability in these studies than in ours (500 copies/ml). These studies also included patients at the time of first undetectable pVL on cART whereas, in our study, patients were included at the time they switched from a first PI-containing cART to a cART without PI while their pVL was undetectable. Some of these patients may have experienced a low level of viral replication before their switch with acquisition of resistance mutations further compromising virological outcome.

Relative to efavirenz, nevirapine was associated with a higher risk of virological rebound in our study, in both antiretroviral-experienced and antiretroviral-naive patients. Some reasons of this poorer outcome may be due to the higher rate of adverse events and/or higher daily pill burden owing to lower adherence. Previous undeclared use of nevirapine as part of a prevention of mother to child HIV transmission (PMTCT) regimen could explain a higher risk of virological rebound among women who switched to NVP-cART. However, French recommendations on PMTCT have been successively the use of zidovudine, then zidovudine plus lamivudine, and now cART including PI for several years. Nevirapine

monotherapy has rarely been used for this indication in France. A randomized study of antiretroviral-naive patients showed no significant difference between NVP and EFV-containing first-line cART regimens with regard to the risk of virological failure, although the latter was slightly higher in patients who received NVP than in patients who received EFV when CD4 cell counts were low [15]. NVP was also associated with more virological failures than EFV in an observational study of antiretroviral-experienced patients, independently of pVL at the outset of NNRTI therapy [16]. Similar results were obtained in a cohort of patients with undetectable pVL at the time of switch, independently of the antiretroviral treatment history [17]. Our results are similar to those of the EuroSIDA study, although the latter failed to show a significant difference between NVP and EFV in naive patients, probably owing to a lack of power (fewer patients switched to NVP than in our study) [18].

We found that, compared to EFV, ABC was only significantly associated with virological rebound in antiretroviral-experienced patients. However, with a hazards ratio of 1.29 and a 95%CI of 0.88–1.89, we cannot rule out a similar difference in naive patients.

First line antiretroviral therapy with zidovudine, lamivudine and abacavir is virologically less effective than zidovudine, lamivudine and efavirenz, whatever the pretreatment viral load level [9]. Combinations of lamivudine, tenofovir and abacavir or didanosine [19,20], and stavudine, didanosine and abacavir [21] are associated with higher virological failure rates than the zidovudine, lamivudine and abacavir combination. When we restricted our analysis to this latter combination, we obtained results similar to those obtained with all combinations including ABC (data not shown). To ensure a better quality of information collection, a limited number of variables are included in the FHDH database, among which data on resistance mutations are not collected. Although data on resistance mutations were lacking in our study, our results are consistent with those of reports showing that a switch from a PI-containing regimen to an ABC-containing NRTI combination is associated with an increased risk of virological rebound, possibly restricted to NRTI-experienced patients [18,22]. Indeed, in a randomized switch study [12], cross-resistance between ABC and other NRTIs was forwarded to explain, in part, the higher rate of virological failure in patients switching to ABC-containing regimens rather than to NNRTI-containing regimens [23], as most virological failures occurred in patients with prior suboptimal NRTI therapy. This could be an indication for analyzing proviral DNA in peripheral blood mononuclear cells in patients with undetectable pVL before the switch, as several resistance mutations found at the time of virological failure may already be present at baseline [24]. Viral DNA genotyping can detect subclinical resistance mutations that may undermine virological efficacy after the switch.

The stavudine/didanosine backbone was associated with a higher risk of virological rebound than the zidovudine/lamivudine backbone, whereas stavudine/lamivudine was not, in keeping with the results of previous studies [8,18]. One possible reason is poor tolerance of this regimen, leading to incomplete adherence and higher rates of NRTI resistance mutations [25]. Interactions between an NRTI backbone and the third drug could also explain differences in the risk of acquiring NRTI resistance mutations according to the third drug [25]. However, we found no significant interactions between the NRTI backbone and the switch drugs.

Female gender was associated with virological rebound after the switch. A recent analysis on the FHDH database has shown no differences in immunological and virological responses to a first cART between men and women within each HIV transmission group [26]. After a switch for intolerance, differences in virological outcome between men and women may be explained by adherence differences. Adherence data are not available in the FHDH database. However, antiretroviral treatment is fully reimbursed in France and adherence was not influenced by different medical insurance cover [27]. Since women are 1.4 time more likely than men to interrupt at least one drug because of toxicity [28], drug toxicity may have lowered adherence and increased virological rebound among women in our study.

This was an observational study, and the different switch regimens were not randomly allocated, meaning that a selection bias cannot be ruled out. However, cohort studies have the potential to identify effects that cannot be shown in clinical trials. Moreover, we used multivariable analysis to adjust for numerous potential confounding factors, and the study was restricted to the period between the switch and a subsequent change in antiretroviral therapy. The study was also restricted to patients with undetectable pVL before the switch, and it is likely that adherence before the switch was similar among patients in the three switch regimens. The impact of residual indication biases is probably weak in this setting. The absence of any difference in immunological outcome among the three switch regimens, despite the different virological outcomes was probably due to the relatively short follow-up. PIs used in the first cART are no longer commonly used and only few patients received a boosted PI in our study. If patients treated with unboosted PIs theoretically had a higher risk of achieved NRTI-resistance mutations, it is not a major limitation of the study since type of first PI did not influence virological and immunological outcome after the date of switch.

A switch from an initial effective PI-containing regimen may be necessary because of elevated blood lipid levels, an increased risk of cardiovascular morbidity, or a large daily pill burden [29]. Switching from PI-containing cART to simplified therapy with efavirenz, nevirapine or abacavir

can improve the lipid profile [30]. Some studies [22,31] but not others [30] have shown a trend towards a larger decline in total cholesterol and low-density lipoprotein-cholesterol levels after a switch to nevirapine or abacavir than to efavirenz. However, switching from a PI-containing regimen to an NNRTI-containing regimen is less effective, in terms of lipid profile improvement, than simply adding pravastatin or bezafibrate to an ongoing PI regimen [32]. Treatment simplification and a lower pill burden may nonetheless improve adherence and postpone the virological rebound, often associated with the emergence of detectable mutation resistance [33].

In conclusion, when a switch from a first, virologically effective PI-containing cART is envisaged, EFV-cART appears to be the regimen with the lowest risk of virological rebound. For patients who were not exposed to antiretroviral drugs before their first PI-containing regimen, ABC-cART may be an alternative to EFV-cART, after careful screening for NRTI resistance mutations.

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Appendix

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