

# Immunovirological Response to Triple Nucleotide Reverse-Transcriptase Inhibitors and Ritonavir-Boosted Protease Inhibitors in Treatment-Naive HIV-2–Infected Patients: The ACHIEV<sub>2E</sub> Collaboration Study Group

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**Background.** Triple nucleoside reverse-transcriptase inhibitors (NRTIs) are recommended by the World Health Organization as first-line regimen in treatment-naïve HIV-2–infected patients. However, ritonavir-boosted protease inhibitor (PI/r)–containing regimens are frequently prescribed. In the absence of previous randomized trials, we retrospectively compared these regimens in observational cohorts.

**Methods.** HIV-2–infected patients from 7 European cohorts who started triple NRTI or PI/r since January 1998 were included. Piecewise linear models were used to estimate CD4 cell count and plasma HIV-2 RNA level slopes, differentiating an early phase (until end of month 3) and a second phase (months 4–12). On-treatment analyses censored data at major treatment modification and systematically at month 12.

**Results.** Forty-four patients started triple NRTI therapy and 126 started PI/r therapy. Overall, the median CD4 cell count was 191 cells/mm<sup>3</sup> and the median plasma HIV-2 RNA level was  $\geq 2.7$  log<sub>10</sub> copies/ml in 61% of the patients at combination antiretroviral therapy (cART) initiation; the median duration of the first cART was 20 months, not differing between groups. PI/r regimens were associated with better CD4 cell count and HIV-2 RNA level outcomes, compared with NRTI regimens. Estimated CD4 cell count slopes were +6 and +12 cells/mm<sup>3</sup>/month during the early phase ( $P = .22$ ), and  $-60$  cells/mm<sup>3</sup>/year versus  $+76$  cells/mm<sup>3</sup>/year during the second phase ( $P = .002$ ), for triple NRTI and PI/r, respectively. Estimated mean HIV-2 RNA levels at month 12 in patients with detectable viremia at cART initiation were 4.0 and 2.2 log<sub>10</sub> copies/ml, respectively ( $P = .005$ ).

**Conclusions.** In this observational study, PI/r-containing regimens showed superior efficacy over triple NRTI regimens as first-line therapy in HIV-2–infected patients.

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Although ultimately leading to AIDS and death, HIV-2 is associated with a slower T CD4<sup>+</sup> lymphocyte depletion [1, 2], a lower viral load at comparable CD4 cell counts [1, 3, 4], and a poorer CD4 cell recovery after treatment initiation in naïve patients [1, 5], compared with HIV-1.

Because of the limitation of the epidemic and the fewer treatment options because of natural resistance to enfuvirtide and nonnucleoside reverse-transcriptase

inhibitors (NNRTI) [6, 7], no randomized clinical trial has assessed the efficacy of specific combination antiretroviral therapies (cART) in treatment-naïve HIV-2-infected patients. Available data regarding nucleoside reverse-transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) are provided by small observational studies, evaluating first-generation antiretrovirals and showing no difference between drugs [1, 5, 8–10].

Current World Health Organization (WHO) treatment guidelines for HIV-2 infection recommend triple NRTI regimens as first-line cART [11]. PI in an initial treatment regimen would essentially rule out second-line options in areas with limited access to cART. This is important when considering that most HIV-2-infected individuals are living in sub-Saharan African countries, where tuberculosis is highly prevalent, with available rifamycin curative therapy limited to rifampicin, which interacts with PIs.

However, recent noncomparative studies have suggested better immunological and virological responses to ritonavir-boosted PI-containing cART in antiretroviral-naïve HIV-2-infected patients [12–14]. Furthermore, *in vitro* phenotypic susceptibility studies of HIV-2 to PI have shown similar half maximal inhibitory concentration, compared with those reported with HIV-1 for ritonavir-boosted darunavir, lopinavir, and saquinavir [15]. On the basis of these observations, we investigated whether PI/r-containing cART was associated with better immunological and virological responses, compared with triple NRTI regimens, as first-line therapy in HIV-2-infected patients, regardless of the level of immunodeficiency at treatment initiation, in a large European collaboration.

## METHODS

### Study Population

ACHIEV<sub>2E</sub> (<http://etudes.isped.u-bordeaux2.fr/achiev2e/>) was established in 2005 as a collaboration of 15 observational cohort studies in 10 European countries, Gambia, and North America.

Adult patients included in the analysis had a confirmed HIV-2 infection (HIV-1 and HIV-2 dually infected patients were not included) and started triple NRTI or PI/r (defined as  $\geq 3$  antiretrovirals) as their first-line regimen from 1 January 1998 through 20 June 2008 (when data were merged). For each individual, follow-up began on the date of cART initiation and ended on the date of the last recorded CD4 cell count.

Seven cohorts participated in the present analysis: the Belgium and Luxemburg HIV-2 Database ( $n = 16$ ); the ANRS CO5 HIV-2 cohort, France ( $n = 145$ ); a cohort from the Section of Infectious Diseases at the “L. Sacco” Hospital in Milan, Italy ( $n = 3$ ); the ATHENA cohort in the Netherlands ( $n = 35$ ); the Santa Maria HIV<sub>2</sub> Cohort in Portugal ( $n = 29$ ); the Spanish

HIV-2 cohort ( $n = 9$ ); and the Swiss HIV Cohort Study ( $n = 5$ ). Each cohort submitted information, using a standardized data format (ie, the HIV Collaboration Data Exchange Protocol) [16], to the coordinating data center at the Bordeaux School of Public Health, France. Data collected included patient demographic characteristics, ART, CD4 cell counts and percentages, HIV-2 RNA level, AIDS, and deaths. The coordinating data center ensured adherence to strict quality-assurance guidelines and performed data quality checks.

### Markers and End Point Definition

In each of the 7 cohorts, CD4 cell counts were measured using flow cytometry, but different plasma HIV-2 RNA quantification assays were used [17]. Because each assay had a different threshold of detectability ( $1.7$ – $2.7 \log_{10}$  copies/mL), the highest threshold was taken into account. Furthermore, the best reproducibility was achieved for plasma RNA values above this threshold [17].

All CD4 cell count and plasma HIV-2 RNA level measurements between treatment initiation and month 12 were taken into account to estimate the immunovirological response. In addition, treatment success at month 12 ( $\pm 1.5$ ) was defined as an increase in CD4 cell count of  $\geq 50$  cells/mm<sup>3</sup> from treatment initiation, in conjunction with undetectable plasma RNA in the absence of progression to AIDS, death, or major treatment modification (ie, switch from triple NRTI or PI/r to another cART).

### Statistical Analysis

The changes in CD4 cell counts and plasma HIV-2 RNA level after cART initiation were studied using 2-phase linear mixed models in which data were censored for major treatment modification or after 12 months of treatment, whichever came first. The date of first cART initiation was considered as baseline. Plasma HIV-2 RNA level changes were estimated in patients with detectable values at baseline. Trends in the evolution of markers were fitted using 2 slopes: one for the early change (0–3 months, in unit/month) and a second for the long-term trend (4–12 months, in unit/year). The correlation between individual baseline value(s) and the subsequent slope(s) was handled through the unstructured covariance matrix of random effects. We performed a secondary analysis stratified by baseline CD4 cell count with use of a threshold of 200 cells/mm<sup>3</sup>. Left-censoring of plasma viral load because of undetectable values was taken into account by imputing half the value of the assay’s threshold of detectability. A sensitivity analysis was conducted among patients treated with currently recommended regimens: 3 NRTI (lamivudine [3TC], zidovudine [AZT], and abacavir or tenofovir) or PI/r (lopinavir, saquinavir, or darunavir) [11, 18, 19].

Comparisons of proportions were performed using Fisher’s exact tests. Data analyses were conducted using SAS, version 9.1 (SAS Institute).

## RESULTS

Overall, 242 HIV-2-infected adults were included in the database. Of these, 72 patients were excluded from subsequent analyses for the following reasons: 56 patients received a non-boosted PI-containing regimen, 15 received NNRTI-based cART, and 1 patient was treated with an enfuvirtide-containing regimen. Of the 170 patients included in the analysis, 44 (26%) received a triple NRTI regimen and 126 (74%) were treated with PI/r. The vast majority (72%) of patients treated with 3 NRTIs received a combination of abacavir, AZT and 3TC. In patients treated with PI/r, 61% received lopinavir, 14% received indinavir, and 13% received saquinavir (Table 1). Backbone regimens were a combination of AZT and 3TC in 79 patients (63%), whereas tenofovir was prescribed in 21 patients (17%; in association with emtricitabine in 11 patients [9%]). As shown in Table 1, 33 patients (75%) treated with 3 NRTIs and 93 (74%) treated with PI/r were selected for the sensitivity analysis including only currently recommended regimens.

Patients treated with 3 NRTIs did not differ from those receiving PI/r with regard to sex, age, mode of infection, and history of AIDS (Table 2). The proportion of patients originating from Africa was higher among those treated with PI/r than those treated with a triple NRTI regimen and patients treated with PI/r tended to have a more advanced infection at treatment initiation, as indicated by a higher proportion of plasma HIV-2 RNA values  $>2.7$  log<sub>10</sub> copies/mL and a lower median CD4 cell count, although these differences were not statistically significant.

**Table 1. Description of the First-Line cART Prescribed in Treatment-Naive HIV-2-Infected Patients: The ACHIEVE Collaboration, 1998–2008**

cART	N	(%)
<b>3 NRTI</b>		
abacavir + lamivudine + zidovudine	32	(73)
tenofovir + lamivudine + zidovudine	1	(2)
didanosine + lamivudine + zidovudine	3	(7)
didanosine + lamivudine + stavudine	3	(7)
abacavir + didanosine + stavudine	2	(5)
tenofovir + lamivudine + abacavir	1	(2)
tenofovir + lamivudine + stavudine	1	(2)
didanosine + lamivudine + tenofovir	1	(2)
<b>Ritonavir-boosted PI</b>		
Lopinavir	76	(61)
Saquinavir	16	(13)
Darunavir	1	(1)
Indinavir	18	(14)
Atazanavir	8	(6)
fos-amprenavir	7	(5)

**NOTE.** Bold: treatment recommended in antiretroviral-naive HIV-2-infected patients in current guidelines.

The median duration of first-line cART was 19 months (interquartile interval [IQR], 7–40 months) in patients receiving 3 NRTIs and 20 months (IQR, 11–34 months) in patients treated with PI/r. A major treatment modification during the first 12 months of treatment was reported in 10 patients (23%) treated with 3 NRTIs and in 13 patients (10%) treated with PI/r. Reasons were unknown except for 2 patients treated with a triple NRTI regimen that experienced virological failure (threshold variable across participating centers) and 3 patients treated with PI/r, 2 of whom experienced toxicity issues and another who became pregnant.

### Virological Response

Sixty-seven patients with detectable plasma RNA values at baseline were included in the estimations of plasma HIV-2 RNA level changes (Figure 1). A total of 229 plasma HIV-2 RNA measurements were available, with a median number of 3 (IQR, 2–3) for patients treated with 3 NRTIs and 4 (IQR, 3–5) for patients treated with PI/r. During the first 3 months of treatment, the estimated decrease in HIV-2 RNA values did not differ in patients treated with 3 NRTIs and those treated with PI/r ( $P = .77$ ). From month 4 through month 12, plasma RNA values remained low in patients treated with PI/r ( $-0.002$  log<sub>10</sub> copies/mL/year) and increased in patients treated with 3 NRTIs ( $+1.6$  log<sub>10</sub> copies/mL/year), although the difference between slopes was not statistically significant ( $P = .12$ ). These changes resulted in estimated plasma HIV-2 RNA values at month 12 being higher in patients treated with 3 NRTIs than in those treated with PI/r (4.0 vs 2.2 log<sub>10</sub> copies/mL;  $P = .005$ ).

Only 9 patients treated with 3 NRTIs and 38 treated with PI/r in the subset with detectable plasma RNA values at baseline could be included in the sensitivity analysis restricted to patients given recommended regimens only, and too few RNA measurements were available to use a 2-phase linear mixed model. However, on the basis of observed data, 1 patient (11%) had sustained undetectable RNA values during months 3–12 among those who received 3 NRTIs, compared with 30 (79%) among those who received PI/r.

In patients with undetectable baseline plasma HIV-2 RNA, 1 (8%) of 12 treated with a triple NRTI regimen and 1 (3%) of 31 patients treated with PI/r had at least 1 subsequent detectable HIV-2 RNA value within the first 12 months of treatment.

### Immunological Response

Overall, 158 patients were included in the estimation of CD4 cell count changes (Figure 2); the other 12 patients had no CD4 cell count measurements available. A total of 669 CD4 cell count measurements were available, with a median number of 6 (IQR, 4–8) for patients treated with 3 NRTIs and 6 (IQR, 4–10) for patients treated with PI/r. During the first 3 months of treatment, the estimated CD4 cell count change did not differ significantly

**Table 2. Main Characteristics of Treatment-Naive HIV-2-Infected Patients Starting a First-Line Triple-NRTI Regimen or PI/r-Containing cART: The ACHIEVE Collaboration, 1998–2008**

		Overall (n = 170)		PI/r (n = 126)		3 NRTI (n = 44)		p <sup>b</sup>
At treatment initiation								
Male gender	N (%)	87	(51)	64	(51)	23	(52)	0.67
Age ≥ 45 years	N (%)	90	(53)	64	(51)	26	(59)	0.38
	Median [IQR]	45.6	[38.5–52.2]	45.3	[37.5–51.8]	46.9	[40.4–54.6]	0.45
Infection through heterosexual contact	N (%)	139	(82)	104	(83)	35	(80)	0.65
Originating from Africa	N (%)	128	(75)	100	(79)	28	(64)	0.04
AIDS before cART initiation	N (%)	36	(21)	28	(22)	8	(18)	0.67
Plasma HIV-2 RNA (log <sub>10</sub> copies/ml)	N (%) ≥2.7 <sup>a</sup>	67	(61)	56	(64)	11	(48)	0.16
(n = 110 with available data)	Median [IQR] for detectable values	4.0	[3.4–4.6]	4.0	[3.4–4.6]	4.0	[2.9–4.6]	0.64
CD4 count (cells/mm <sup>3</sup> ) (n = 134 with available data)	Median [IQR]	191	[90–275]	170	[72–275]	216	[150–287]	0.21
During follow-up								
Duration of first line cART	Median [IQR]	20	[8–36]	20	[11–34]	19	[7–40]	
Major treatment modifications	N (%)	23	(14)	15	(12)	8	(18)	

**NOTE.** IQR: Inter-quartile range.

<sup>a</sup> The highest threshold of detectability was taken into account to define detectable and undetectable RNA values.

<sup>b</sup> Comparison of patients treated with ritonavir-boosted PI based regimen and those receiving a 3-NRTI cART.

between patients treated with 3 NRTIs and those treated with PI/r ( $P = .24$ ). Beyond 3 months of treatment, the estimated CD4 cell count decreased in patients treated with 3 NRTIs and increased in those treated with PI/r ( $-60$  vs  $+76$  cells/mm<sup>3</sup>/year;  $P = .002$ ). These changes resulted in estimated CD4 cell counts at month 12 being lower in patients treated with 3 NRTIs than in patients treated with PI/r ( $191$  vs  $327$  cells/mm<sup>3</sup>;  $P = .001$ ).

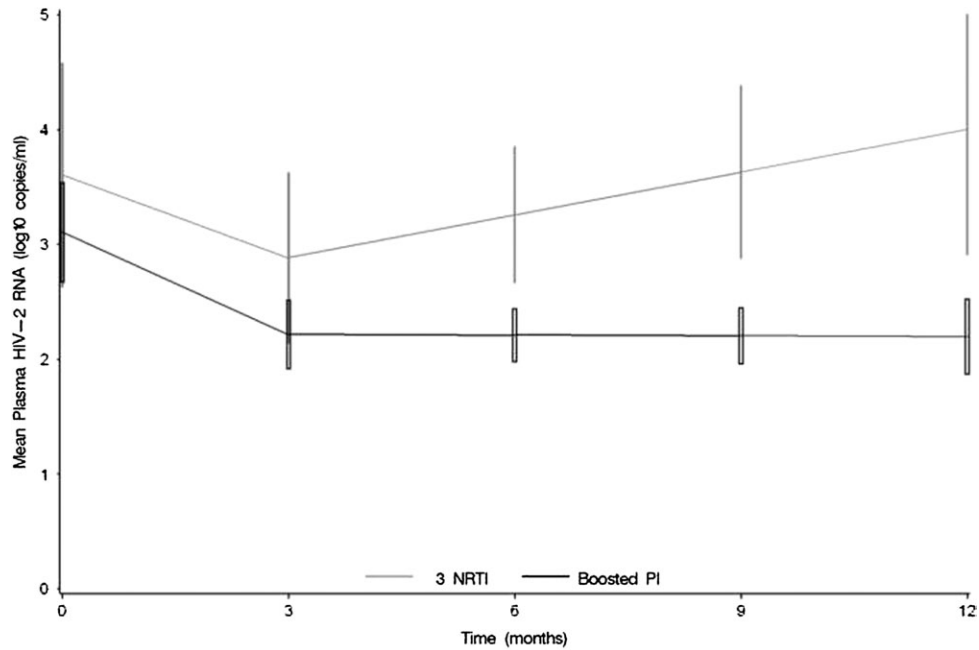
The difference in estimated CD4 cell counts at month 12 between patients treated with 3 NRTIs and those treated with PI/r remained statistically significant after adjustment for geographical origin ( $P = .0009$ ) or for baseline HIV-2 RNA level ( $P = .05$ ). Among patients originating from Africa, the estimated CD4 cell count at 12 months was  $320$  cells/mm<sup>3</sup> (3 NRTIs), compared with  $176$  cells/mm<sup>3</sup> (PI/r), and among patients with undetectable RNA value at treatment initiation, it was  $354$  cells/mm<sup>3</sup> (3 NRTIs), compared with  $242$  cells/mm<sup>3</sup> (PI/r).

Immunological response appeared to be different after 3 months, regardless of baseline CD4 cell counts. In patients with a baseline CD4 cell count  $\geq 200$  cells/mm<sup>3</sup> (Figure 3.A), the estimated change was  $-99$  cells/mm<sup>3</sup>/year (95% confidence interval [CI],  $-201$  to  $4$ ) among patients receiving a triple NRTI regimen, compared with  $+52$  cells/mm<sup>3</sup>/year in patients receiving PI/r (95% CI,  $-11$  to  $119$ ;  $P = .02$ ). The same trends were observed in patients with a baseline CD4 cell count  $< 200$  cells/mm<sup>3</sup> (Figure 3.B), although the difference according to treatment regimens was not statistically significant ( $P = .56$  for the months 0–3 and  $P = .26$  for months 4–12).

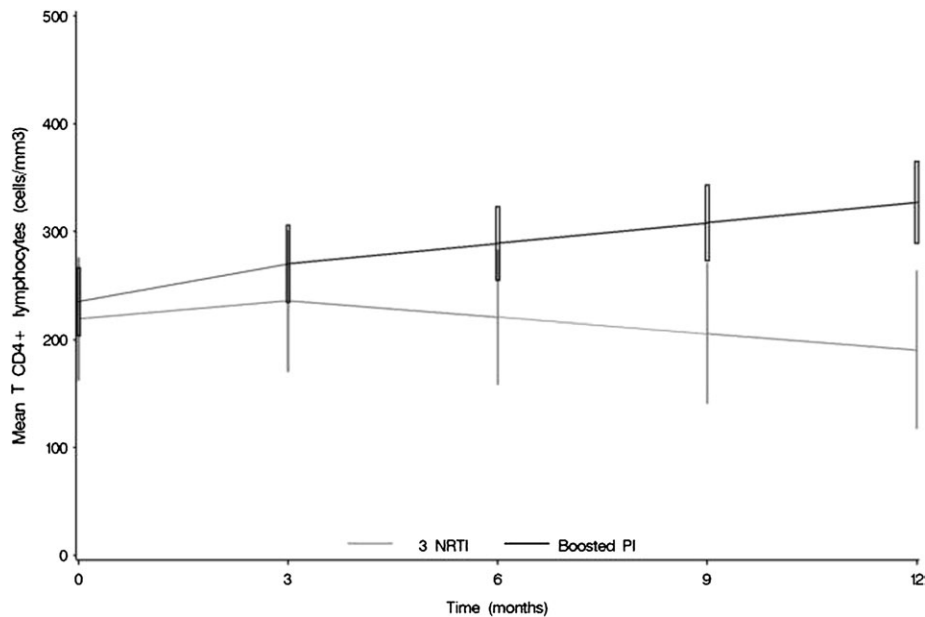
When the analysis was restricted to recommended regimens only (sensitivity analysis), the baseline estimated CD4 cell count did not differ between patients treated with 3 NRTIs ( $227$  cells/mm<sup>3</sup>; 95% CI,  $163$ – $291$  cells/mm<sup>3</sup>) and those treated with PI/r ( $238$  cells/mm<sup>3</sup>; 95% CI,  $201$ – $275$  cells/mm<sup>3</sup>;  $P = .77$ ). During the first 3 months of treatment, the estimated CD4 cell count change did not differ significantly between patients treated with 3 NRTIs ( $+3$  cells/mm<sup>3</sup>/month; 95% CI,  $-7$  to  $13$  cells/mm<sup>3</sup>/month) and patients treated with PI/r ( $+13$  cells/mm<sup>3</sup>/month; 95% CI,  $7$ – $19$  cells/mm<sup>3</sup>/month;  $P = .09$ ). Beyond 3 months of treatment, the estimated CD4 cell count slope was  $-122$  cells/mm<sup>3</sup>/year (95% CI,  $-139$  to  $51$  cells/mm<sup>3</sup>/year) in patients treated with 3 NRTIs and  $+88$  cells/mm<sup>3</sup>/year (95% CI,  $43$ – $134$  cells/mm<sup>3</sup>/year) in those treated with PI/r ( $P = .01$ ). This evolution resulted in lower estimated CD4 cell counts at month 12 in patients treated with 3 NRTIs, compared with those treated with PI/r:  $344$  cells/mm<sup>3</sup> (95% CI,  $298$ – $390$  cells/mm<sup>3</sup>) versus  $204$  cells/mm<sup>3</sup> (95% CI,  $118$ – $290$  cells/mm<sup>3</sup>;  $P = .005$ ).

Only 106 patients (62%; 21 treated with 3 NRTIs and 85 with PI/r) had available data at month 12 ( $\pm 1.5$ ). The observed success rate was 10% among patients treated with 3 NRTIs and 55% among those treated with PI/r ( $P < .001$ ). Five patients (26%) treated with 3 NRTIs and 50 (67%) treated with PI/r experienced an increase in CD4 cell count of at least 50 cells/mm<sup>3</sup> together with undetectable plasma RNA at month 12 ( $P = .003$ ).

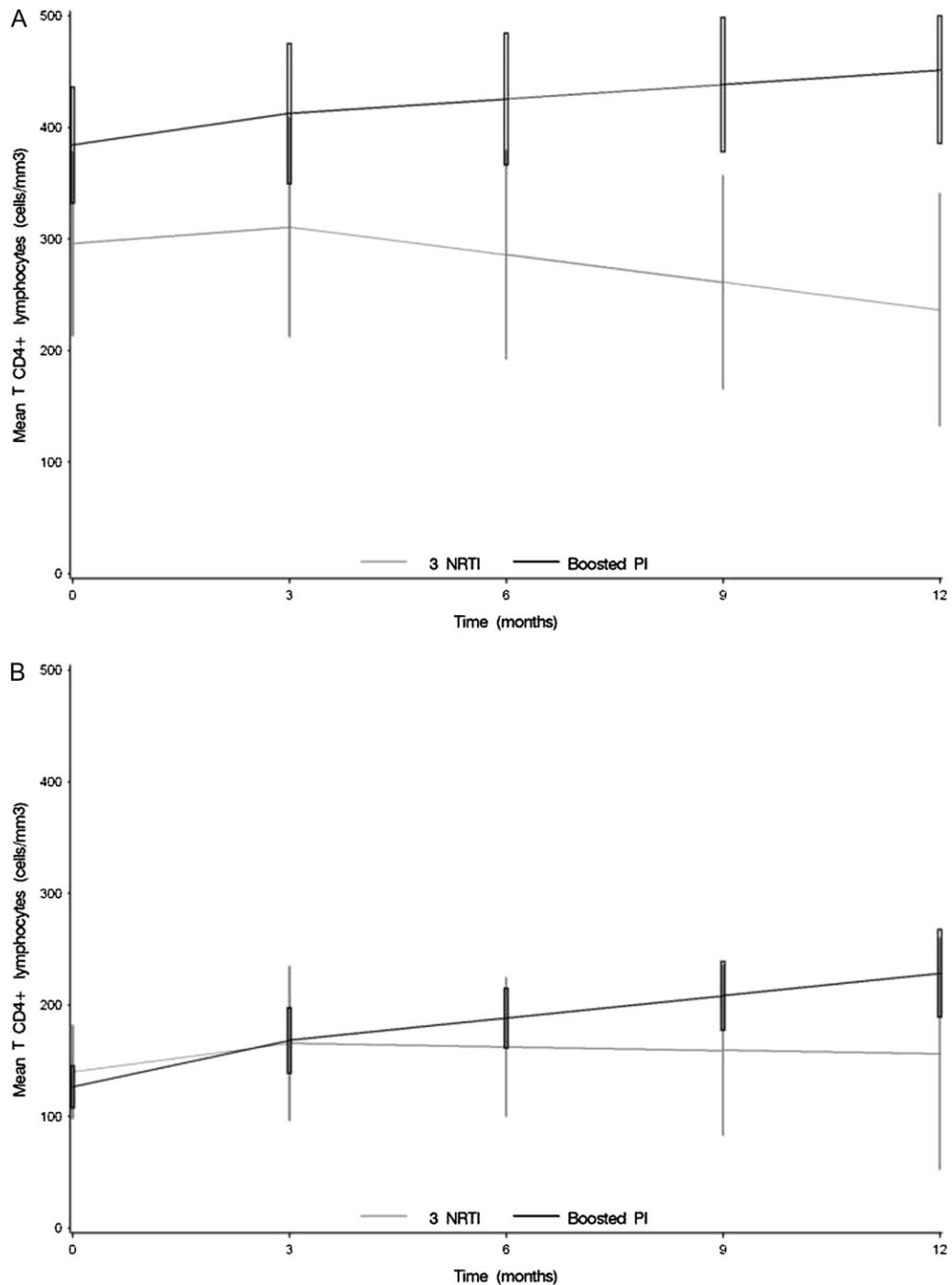
None of the patients died during the first 12 months of treatment. One patient (2%) receiving a triple-NRTI regimen experienced progression to AIDS (tuberculosis) 5 months after



**Figure 1.** Estimated HIV-2 RNA changes with 95% confidence interval in treatment-naive HIV-2-infected patients starting a first-line triple-NRTI regimen or PI/r-containing cART, with detectable values at treatment initiation ( $n = 67$ ). The ACHIEV<sub>2E</sub> collaboration, 1998–2008. 1st slope (M0–M3):  $-0.3 \log_{10}$  copies/mL/month in patients treated with a PI/r-containing cART;  $-0.2 \log_{10}$  copies/mL/month in those treated with 3 NRTIs ( $P = .77$ ). 2nd slope (M3–M12):  $-0.002 \log_{10}$  copies/mL/month in patients treated with a PI/r-containing cART;  $+1.6 \log_{10}$  copies/mL/month in those treated with 3 NRTIs ( $P = .12$ ). M12 estimates:  $2.2 \log_{10}$  copies/mL in patients treated with a PI/r-containing cART;  $4.0 \log_{10}$  copies/mL in those treated with 3 NRTIs ( $P = .005$ ).



**Figure 2.** Estimated CD4 cell count changes with 95% confidence interval in treatment-naive HIV-2-infected patients starting a first-line triple-NRTI regimen or PI/r-containing cART ( $n = 158$ ). The ACHIEV<sub>2E</sub> collaboration, 1998–2008. 1st slope (M0–M3):  $+12 \text{ cells/mm}^3$ /month in patients treated with a PI/r-containing cART;  $+6 \text{ cells/mm}^3$ /month in those treated with 3 NRTIs ( $P = .24$ ). 2nd slope (M3–M12):  $-60 \text{ cells/mm}^3$ /year in patients treated with a PI/r-containing cART;  $+76 \text{ cells/mm}^3$ /month in those treated with 3 NRTIs ( $P = .002$ ). M12 estimates:  $327 \text{ cells/mm}^3$  in patients treated with a PI/r-containing cART;  $191 \text{ cells/mm}^3$  in those treated with 3 NRTIs ( $P = .001$ ).



**Figure 3.** Estimated CD4 cell count changes with 95% confidence interval in treatment-naive HIV-2-infected patients starting a first-line triple-NRTI regimen or PI/r-containing cART, with  $\geq 200$  CD4 cell/mm<sup>3</sup> at treatment initiation (A,  $n = 71$ ) or with  $< 200$  CD4 cell/mm<sup>3</sup> at treatment initiation (B,  $n = 63$ ). The ACHIEVE collaboration, 1998–2008. A,  $\geq 200$  CD4 cell/mm<sup>3</sup> at treatment initiation 1st slope (M0–M3): +9 cells/mm<sup>3</sup>/month in patients treated with a PI/r-containing cART; +5 cells/mm<sup>3</sup>/month in those treated with 3 NRTIs ( $P = .45$ ). 2nd slope (M3–M12): +52 cells/mm<sup>3</sup>/year in patients treated with a PI/r-containing cART; -99 cells/mm<sup>3</sup>/month in those treated with 3 NRTIs ( $P = .02$ ). M12 estimates: 451 cells/mm<sup>3</sup> in patients treated with a PI/r-containing cART; 236 cells/mm<sup>3</sup> in those treated with 3 NRTIs ( $P < .001$ ). B,  $< 200$  CD4 cell/mm<sup>3</sup> at treatment initiation 1st slope (M0–M3): +14 cells/mm<sup>3</sup>/month in patients treated with a PI/r-containing cART; +9 cells/mm<sup>3</sup>/month in those treated with 3 NRTIs ( $P = .56$ ). 2nd slope (M3–M12): +80 cells/mm<sup>3</sup>/year in patients treated with a PI/r-containing cART; -12 cells/mm<sup>3</sup>/month in those treated with 3 NRTIs ( $P = .26$ ). M12 estimates: 228 cells/mm<sup>3</sup> in patients treated with a PI/r-containing cART; 156 cells/mm<sup>3</sup> in those treated with 3 NRTIs ( $P = .2$ ).

treatment initiation. Patients who progressed to AIDS were 9 (7%) in those treated with PI/r (cytomegalovirus infections [2], recurrent bacterial pneumonia [1], candidiasis [1], toxoplasmosis [1], cryptococcosis [1], pneumocystosis [1], HIV wasting syndrome [1], and unknown [1]) within a median delay of 2 months (range, 0.5–7.5 months) after treatment initiation.

## DISCUSSION

In this large collaborative analysis comparing the immunological and virological response to PI/r with that to triple NRTI regimens among ART-naive HIV-2-infected patients followed up in developed countries, we showed better viral suppression and higher CD4 cell recovery associated with PI/r than with a triple NRTI regimen. This result was observed regardless of geographical origin or baseline HIV-2 RNA values and even in patients with baseline CD4 cell counts  $>200$  cells/mm<sup>3</sup>. A subgroup analysis including only patients treated with currently recommended cART (126; 74%) yielded the same favorable trend for those initially treated with PI/r regimens. A combined end point reflecting successful clinical, therapeutic, virological, and immunological measurements at month 12 showed superiority of PI/r over triple NRTI regimens.

There are several limitations to our analysis. Patients were not randomized to receive one regimen or the other; thus, there were differences between the 2 patient groups at baseline. Although we adjusted for geographical origin and baseline plasma HIV-2 RNA level, a bias due to unmeasured confounding might still remain. Nevertheless, because patients receiving a PI/r regimen had markers of more advanced disease at baseline, this bias would lead to underestimate rather than overestimate the difference between both regimens. No data on adverse events were available. Reasons for major treatment modifications could have provided reasonable information on this matter, but we were not able to collect this information from the participating cohorts. However, major treatment modifications were rather uncommon during the 12-month study period, and we believe that the benefit-to-risk ratio remained in favor of PI/r over 3 NRTI regimens in HIV-2-infected patients. No data on adherence were available in this retrospective study. A higher pill burden ( $>10$  per day) has been associated with a poorer adherence [20, 21]. Because PI/r regimens involve a higher pill burden than triple NRTI regimens used in our study, lack of adherence is expected to occur more frequently with PI/r and to jeopardize the response mainly in that group, again reinforcing our conclusion. Of note, none of the antiretroviral regimens considered in our study necessitated  $>10$  pills per day. Another limitation is the lack of a longer follow-up period and sufficient power to investigate clinical outcomes. However, CD4 cell counts and plasma HIV-2 RNA levels are recognized as major predictors of clinical progression in HIV-2 infection

[3, 22, 23], and we may rely on our conclusion showing a superiority of PI/r over triple NRTI regimens based on these surrogate markers.

To our knowledge, our study was the first to evaluate the efficacy of PI/r in comparison with triple NRTI regimens, since the latter regimens have been recommended by 2010 WHO guidelines as first-line cART in HIV-2-infected patients [11]. Our results are in line with previous noncomparative observational studies in treatment-naive HIV-2-infected patients: poor immunological and virological responses to triple NRTI regimens [8, 14] and good immunological and virological responses to PI/r-containing cART [12, 14].

A large proportion of HIV-2-infected patients in our study had undetectable plasma RNA at treatment initiation, even with low CD4 cell counts. This highlights the importance of taking into account CD4 cell count changes and plasma HIV-2 RNA levels to adequately evaluate treatment responses in HIV-2-infected patients [24]. In our study, the coherence between virological and immunological responses is in favor of a higher effectiveness of PI/r, compared with triple NRTI regimens, in treatment-naive HIV-2-infected patients. Indeed, in patients receiving a triple NRTI regimen, the poor immunological response beyond 3 months of treatment was often observed together with an increase in plasma HIV-2 RNA values during the same period. In contrast, in patients treated with PI/r, the sustained CD4 cell count increase was generally supported by sustained viral suppression.

In vitro phenotypic susceptibility studies have reported a full activity of all NRTIs (including zidovudine, lamivudine, and abacavir) against wild-type ROD and EHO HIV-2 isolates [25]. The difference in viro-immunological response observed between patients receiving a triple-NRTI regimen and those treated with PI/r might be explained by the resistance mutation profile of HIV-2. Indeed, HIV-2 displays NRTI-resistance pathways different from those in HIV-1 [26, 27]. Mutations Q151M (+/-V111I) and K65R develop more frequently in HIV-2 than in HIV-1 and are the main NRTI resistance pathways [28–30]. The Q151M mutation, together with K65R or M184V, is sufficient to confer high-level resistance to both lamivudine and zidovudine, the most frequently prescribed NRTIs in our study. Furthermore, the combination of K65R, Q151M, and M184V mutations confers classwide NRTI resistance [27]. M184V/I appears at treatment failure in patients treated with lamivudine-emtricitabine and has been reported to occur in vitro within 6 weeks [31]. Our results are consistent with these observations even if no resistance data are available yet to establish the role of resistance mutations in response to both triple NRTI regimens and PI/r. A recent study has also increased concerns about the risk of transmission of drug-resistant HIV-2 strains [14], further emphasizing the need for prescribing the most potent first-line ART in HIV-2-infected patients [32].

The vast majority (61%) of patients treated with a PI/r-containing cART in our study received lopinavir, and very few were treated with other potent PI/r regimens that have shown promising results in vitro against HIV-2, such as saquinavir or darunavir [15]. Further research is needed to evaluate the optimal cART regimen for treatment-naïve patients with earlier HIV-2-infection, at best through a randomized clinical trial [24, 33].

In the mean time, our results represent the best evidence to date for the treatment of ART-naïve HIV-2-infected patients and suggest that PI/r-containing cART should be considered as first-line ART, even when CD4 cell counts are  $>200$  cells/mm<sup>3</sup>.

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