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Immunovirological Response to Triple Nucleotide Reverse-Transcriptase Inhibitors and Ritonavir-Boosted Protease Inhibitors in Treatment-Naïve HIV-2–Infected Patients: The ACHIEV2E Collaboration Study Group

Antoine Benard,1,2 Ard van Sighem,3 Audrey Taieb,4 Emilia Valadas,5 Jean Ruelle,6 Vicente Soriano,7 Alexandra Calmy,8 Claudia Balotta,9 Florence Damond,3,4 Francoise Brun-Vezinet,3,4 Genevieve Chene,1,2 Sophie Matheron,4,5 and the ACHIEV2E Collaboration Study Group*

1INSERM, U897; 2University Bordeaux Segalen, Bordeaux; 3APHP, Hôpital Bichat – Claude Bernard, Laboratoire de Virologie; 4Paris VII Denis Diderot University; 5APHP, Hôpital Bichat-Claude Bernard, Service de Maladies infectieuses et Tropicales, Paris, France; 6Stichting HIV Monitoring, Amsterdam, the Netherlands; 7Hospital de Santa Maria, Clinica Universitaria de Doenças Infecciosas, Lisbon, Portugal; 8Université Catholique de Louvain, AIDS Reference Laboratory, Brussels, Belgium; 9Hospital Carlos III, Department of Infectious Diseases, Madrid, Spain; 10Hôpitaux Universitaires de Genève, Service de Maladies Infectieuses, Unite VIH/SIDA, Geneva, Switzerland; and 11University of Milan, Department of Clinical Sciences “L. Sacco”, Section of Infectious Diseases, Milan, Italy

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/mm³ and the median plasma HIV-2 RNA level was $2.7 \log_{10}$ 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 $16$ and $112$ cells/mm³/mo during the early phase ($P = .22$), and $-60$ cells/mm³/year versus $+76$ cells/mm³/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 $2.2 \log_{10}$ 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.

Although ultimately leading to AIDS and death, HIV-2 is associated with a slower T CD4⁺ 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-naive 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-naive 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

ACHIEV2E (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 ≥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 HIV2 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 (±1.5) was defined as an increase in CD4 cell count of ≥50 cells/mm°3 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°3. 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).
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 ($-0.002 \log_{10} \text{copies/mL/year}$) and increased in patients treated with 3 NRTIs ($+1.6 \log_{10} \text{copies/mL/year}$), 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 ($4.0 \text{ vs } 2.2 \log_{10} \text{copies/mL}; P = .005$).

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.

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### Table 1. Description of the First-Line cART Prescribed in Treatment-Naive HIV-2–Infected Patients: The ACHIEV2E Collaboration, 1998–2008

<table>
<thead>
<tr>
<th>cART</th>
<th>N (%)</th>
</tr>
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<tbody>
<tr>
<td>3 NRTI</td>
<td></td>
</tr>
<tr>
<td>abacavir + lamivudine + zidovudine</td>
<td>32 (73)</td>
</tr>
<tr>
<td>tenofovir + lamivudine + zidovudine</td>
<td>1 (2)</td>
</tr>
<tr>
<td>didanosine + lamivudine + zidovudine</td>
<td>3 (7)</td>
</tr>
<tr>
<td>didanosine + lamivudine + stavudine</td>
<td>3 (7)</td>
</tr>
<tr>
<td>abacavir + didanosine + stavudine</td>
<td>2 (5)</td>
</tr>
<tr>
<td>tenofovir + lamivudine + abacavir</td>
<td>1 (2)</td>
</tr>
<tr>
<td>tenofovir + lamivudine + stavudine</td>
<td>1 (2)</td>
</tr>
<tr>
<td>didanosine + lamivudine + tenofovir</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

**NOTE.** Bold: treatment recommended in antiretroviral-naive HIV-2–infected patients in current guidelines.
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$^3$/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$^3$; $P = .001$).

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$^3$ (3 NRTIs), compared with 176 cells/mm$^3$ (PI/r), and among patients with undetectable RNA value at treatment initiation, it was 354 cells/mm$^3$ (3 NRTIs), compared with 242 cells/mm$^3$ (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$^3$ (Figure 3A), the estimated change was $-99$ cells/mm$^3$/year (95% confidence interval [CI], $-201$ to 4) among patients receiving a triple NRTI regimen, compared with $+52$ cells/mm$^3$/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$^3$ (Figure 3B), although the difference according to treatment regimen 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$^3$; 95% CI, 163–291 cells/mm$^3$) and those treated with PI/r (238 cells/mm$^3$; 95% CI, 201–275 cells/mm$^3$; $P = .77$). 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$^3$/month; 95% CI, $-7$ to 13 cells/mm$^3$/month) and patients treated with PI/r (+13 cells/mm$^3$/month; 95% CI, 7–19 cells/mm$^3$/month; $P = .09$). Beyond 3 months of treatment, the estimated CD4 cell count slope was $-122$ cells/mm$^3$/year (95% CI, $-139$ to 51 cells/mm$^3$/year) in patients treated with 3 NRTIs and $+88$ cells/mm$^3$/year (95% CI, 43–134 cells/mm$^3$/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$^3$ (95% CI, 298–390 cells/mm$^3$) versus 204 cells/mm$^3$ (95% CI, 118–290 cells/mm$^3$; $P = .005$).

Only 106 patients (62%; 21 treated with 3 NRTIs and 85 with PI/r) had available data at month 12 (±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$^3$ 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 ACHI EV2E collaboration, 1998–2008. 1st slope (M0–M3): −0.3 log10 copies/mL/month in patients treated with a PI/r-containing cART; −0.2 log10 copies/mL/month in those treated with 3 NRTIs (P = .77). 2nd slope (M3–M12): −0.002 log10 copies/mL/month in patients treated with a PI/r-containing cART; +1.6 cells/mm³/month in those treated with 3 NRTIs (P = .12). M12 estimates: 2.2 log10 copies/mL in patients treated with a PI/r-containing cART; 4.0 log10 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 ACHI EV2E collaboration, 1998–2008. 1st slope (M0–M3): +12 cells/mm³/month in patients treated with a PI/r-containing cART; +6 cells/mm³/month in those treated with 3 NRTIs (P = .24). 2nd slope (M3–M12): −60 cells/mm³/year in patients treated with a PI/r-containing cART; +76 cells/mm³/month in those treated with 3 NRTIs (P = .002). M12 estimates: 327 cells/mm³ in patients treated with a PI/r-containing cART; 191 cells/mm³ 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 ≥200 CD4 cell/mm³ at treatment initiation (A, n = 71) or with <200 CD4 cell/mm³ at treatment initiation (B, n = 63). The ACHIEV2E collaboration, 1998–2008. A, ≥200 CD4 cell/mm³ at treatment initiation 1st slope (M0–M3): +9 cells/mm³/month in patients treated with a PI/r-containing cART; +5 cells/mm³/month in those treated with 3 NRTIs (P = .45). 2nd slope (M3–M12): +52 cells/mm³/year in patients treated with a PI/r-containing cART; −99 cells/mm³/month in those treated with 3 NRTIs (P = .02). M12 estimates: 451 cells/mm³ in patients treated with a PI/r-containing cART; 236 cells/mm³ in those treated with 3 NRTIs (P < .001). B, <200 CD4 cell/mm³ at treatment initiation 1st slope (M0–M3): +14 cells/mm³/month in patients treated with a PI/r-containing cART; +9 cells/mm³/month in those treated with 3 NRTIs (P = .56). 2nd slope (M3–M12): +80 cells/mm³/year in patients treated with a PI/r-containing cART; −12 cells/mm³/month in those treated with 3 NRTIs (P = .26). M12 estimates: 228 cells/mm³ in patients treated with a PI/r-containing cART; 156 cells/mm³ 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/mm³. 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-naive 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-naive 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/mm³.

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Potential conflicts of interest. A. B. received payment for development of educational presentations from Abbott. G. C. received payment for development of educational presentations from Bohringer Ingelheim and made punctual consultancy for Roche. J. R. received payment for lectures, including service on speakers, boards from Siemens Healthcare diagnostics. V. S. received payment for development of educational presentations from BMS, Gilead, and Merck Sharp and Dohme. F. B.-V. received payment for lectures, including service on speakers boards from Tibotec, and is board member at Gen Probe. S. M. made punctual consultancy for Bohringer ingelheim, Abbitt, and Gilead and received payment for development of educational presentations from MSD, Gilead, Abbott, Glaxo, Boringher Ingelheim, and BMS. All other authors: no conflicts.

The ACHIEV2E Collaboration Study Group

Clinical centres.

France: Clinical centres from the ANRS COS HIV-2 Cohort: Bichat-Claude Bernard Hospital, Paris (Sophie Matheron); Pitié-Salpêtrière Hospital, Paris (Roland Tubiana); Saint-Antoine Hospital, Paris (Marie-Caroline Meyohas); Cochin Hospital (Cornélia Bernasconi, Nicolas Dupin); Tenon Hospital, Paris (Laurence Slama); Saint-Louis Hospital, Paris (Diane Ponscarme, Caroline Lascoux-Combe, Françoise-Lélia Timsit); Delafontaine Hospital, Saint-Denis (Marie-Aude Khuong); Lariboisière Hospital, Paris (Agathe Rami); Paul Brousse Hospital, Villejuif (Elina Teichner); Villeneuve Saint Georges Hospital (Caroline Semaille); Bicêtre Hospital, Le Kremlin Bicêtre (Yann Quertantmont); Louis Mourier Hospital, Colombes (Martine Bloch); Lagney Hospital, Marne la Vallée (Eric Farguel); Victor Dupouy Hospital, Argenteuil (Philippe Genet); Simone Veil Hospital, Eaubonne (Annie Leprêtre); Foch Hospital, Suresnes (David Zucman); Georges Pompidou Hospital, Paris (Marina Karmochkine); René Dubos Hospital, Pontoise (Laurent Blum); Gilles de Corbeil Hospital, Corbeil Essones (Pierre Chevojon); Ambroise Paré Hospital, Boulogne Billancourt (Cyril Olivieri); Robert Ballanger Hospital, Aulnay sous Bois (Jean-Luc Delassus); Montsouris Hospital, Paris (Loïc Bodard); Bégin Hospital, Saint Mandé (Patrick Imbert); Antoine Béclère Hospital, Clamart (François Boué); Hôtel-Dieu Hospital, Nantes (Eric Billaud); Saint-Jacques Hospital, Besançon (Christine Drozacheff-Thiébaut); Hôtel-Dieu Hospital, Lyon (Laurent Cotte); Pays d’Aix Hospital, Aix en Provence (Thierry Allègre); Côte de Nacre Hospital, Caen (Claude Bazin); Bretonneau Hospital, Tours (Pascale Nau); Charles Nicolle Hospital, Rouen (Yasmine Debbab); Michallon Hospital, Grenoble (Pascale Leclercq); Pontchaillou Hospital, Rennes (Cédric Arvieux); Intercommunal Hospital, Toulon-La Seyne sur Mer (Alain Lefaullade); Hôpital Pellegrin Hospital, Bordeaux (Jean-Marie Ragnaud, Hervé Dutronc); La Roche sur Yon Hospital (Philippe Perré); Cannes Hospital (Nathalie Montagne); Guie de Chauliac Hospital, Montpellier (Jacques Reyes); Hôtel Dieu Hospital, Clermont Ferrand (Christiane Jacomet); Archet Hospital, Nice (Frédéric Sanderson); Civil Hospital, Strasbourg (David Rey); Saint André Hospital, Bordeaux (Maïté Longy-Boursier); Angers Hospital (Jean-Marie Chennebault); Dignes Bains Hospital (Patricia Granet).

Netherlands: The ATHENA database was set up and is maintained by the Stichting HIV Monitoring. The physicians and data analysts include (*site coordinating physicians): Prof. dr. F. de Wolf (director), Dr D. O. Bezem, Drs L. A. J. Gras, Drs A. M. Kesselring, Dr. A. I. van Sighem, Dr C. Smit, Drs S. Zhang (data analysis group), Drs S. Zaheri (data collection); Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam: Prof. dr. J. M. Prins*, Prof. dr. T. W. Kuipers, Dr H. J. Scherpber, Dr K. Boer, Dr J. T. M. van der Meer, Dr F. W. M. N. Wit, Dr M. H. Godfried, Prof. dr. P. Reiss, Drs M. E. Havercort, Prof. dr. T. van der Poll, Dr F. J. B. Nellen, Prof. dr. J. M. A. Lange, Dr S. E. Geerlings, Dr M. van Vugt, Drs S. M. E. Vrouenraets, Drs D. Pajkrt, Drs J. C. Bos, Drs M. van der Valk; Academisch Ziekenhuis Maastricht, Maastricht: Dr G. Schreij*, Dr S. Lowe, Dr A. Oude Lashof; Catharina Ziekenhuis, Eindhoven: Drs M. J. H. Pronk*, Dr B. Bravenboer, Erasmus Medisch Centrum, Dr M. E. van der Ende*, Drs T. E. M. S. de Vries-Slujs, Dr C. A. M. Schurink, Drs M. van der Feltz, Dr J. L. Nouwen, Dr L. B. S. Gelinck, Dr A. Verbon, Drs B. J. A. Rijnders, Drs E. D. van de Ven-De Ruiter, Dr L. Slobbe, Erasmus Medisch Centrum-Sophia, Rotterdam: Dr N. G. Hartwig, Dr G. J. A. Driessen, Feleovo ziekenhuis, Almere: Dr J. Branger*. HagaZiekenhuis, Den Haag: Dr R. H. Kauffmann*, Dr E. F. Schippers, Isala Klinieken, Zwolle: Dr P. H. P. Groeneveld*, Dr M. A. Alleman, Drs J. W. Bouwhuis, Kennemer Gasthuis, Haarlem: Prof. dr. R. W. ten Kate*, Dr R. Soetekouw, Leids Universitair Medisch Centrum, Leiden: Dr F. P. Kroon*, Dr P. J. van den Broek, Prof. dr. J. T. van Dissel, Drs S. M. Arend, Drs M. E. van der Ende, Drs C. van Nieuwkoop, Drs M. G. J. de Boer, Drs H. Jolink; Prof. dr. F. de Wolf (director), Dr D. O. Bezem, Drs L. A. J. Gras, Drs A. M. Kesselring, Dr. A. I. van Sighem, Dr C. Smit, Drs S. Zhang (data analysis group), Drs S. Zaheri (data collection); Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam: Prof. dr. J. M. Prins*, Prof. dr. T. W. Kuipers, Dr H. J. Scherpber, Dr K. Boer, Dr J. T. M. van der Meer, Dr F. W. M. N. Wit, Dr M. H. Godfried, Prof. dr. P. Reiss, Drs M. E. Havercort, Prof. dr. T. van der Poll, Dr F. J. B. Nellen, Prof. dr. J. M. A. Lange, Dr S. E. Geerlings, Dr M. van Vugt, Drs S. M. E. Vrouenraets, Drs D. Pajkrt, Drs J. C. Bos, Drs M. van der Valk; Academisch Ziekenhuis Maastricht, Maastricht: Dr G. Schreij*, Dr S. Lowe, Dr A. Oude Lashof; Catharina Ziekenhuis, Eindhoven: Drs M. J. H. Pronk*, Dr B. Bravenboer, Erasmus Medisch Centrum, Dr M. E. van der Ende*, Drs T. E. M. S. de Vries-Slujs, Dr C. A. M. Schurink, Drs M. van der Feltz, Dr J. L. Nouwen, Dr L. B. S. Gelinck, Dr A. Verbon, Drs B. J. A. Rijnders, Drs E. D. van de Ven-De Ruiter, Dr L. Slobbe, Erasmus Medisch Centrum-Sophia, Rotterdam: Dr N. G. Hartwig, Dr G. J. A. Driessen, Feleovo ziekenhuis, Almere: Dr J. Branger*. HagaZiekenhuis, Den Haag: Dr R. H. Kauffmann*, Dr E. F. Schippers, Isala Klinieken, Zwolle: Dr P. H. P. Groeneveld*, Dr M. A. Alleman, Drs J. W. Bouwhuis, Kennemer Gasthuis, Haarlem: Prof. dr. R. W. ten Kate*, Dr R. Soetekouw, Leids Universitair Medisch Centrum, Leiden: Dr F. P. Kroon*, Dr P. J. van den Broek, Prof. dr. J. T. van Dissel, Dr S. M. Arend, Drs C. van Nieuwkoop, Drs M. G. J. de Boer, Drs H. Jolink; Maasstad Ziekenhuis, Rotterdam: Dr J. G. van den Jong, Dr K. Pogany; Medisch Centrum Alkmaar, Alkmaar: Drs W. Kortmann, Drs G. van Twillert*; Medisch Centrum Haaglanden, Den Haag: Dr R. Vriesendorp*, Dr E. M. S. Leyten; Medisch Spectrum Twente, Enschede: Dr C. H. H. ten Napel*, Drs G. J. Kootstra. Onze Lieve Vrouwe Gasthuis, Amsterdam:
Prof. dr. K. Brinkman*, Dr W. L. Blok, Dr P. H. J. Frissen, Drs W. E. M. Schouten, Drs G. E. L. van den Berk; St. Elisabeth Ziekenhuis, Tilburg; Dr J. R. Juttmann*, Dr M. E. E. van Kasteren, Drs A. E. Brouwer; Sint Lucas Andreas Ziekenhuis, Amsterdam: Dr J. Veenstra*, Dr K. D. Lettinga; Slotervaart Ziekenhuis, Amsterdam: Dr J. W. Mulder*, Dr E. C. M. van Gorp, Drs P. M. Smit, S. Wiemer; Stichting Medisch Centrum Jan van Goyen, Amsterdam: Drs A. van Eeden*, Dr D. W. M. Verhagen*; Universitair Medisch Centrum Groningen; Groningen: Dr H. G. Sprenger*, Dr R. Doedens, Dr E. H. Scholvinck, Drs S. van Assen, C. J. Stek; Universitair Medisch Centrum Sint Radboud, Nijmegen: Dr P. F. Koopmans*, Prof. dr. R. de Groot, Dr M. Keuter, Dr A. J. A. M. van der Ven, Dr H. J. M. ter Hofste, Dr M. van der Flier, Drs A. M. Brouwer, Dr A. S. M. Dofferhoff; Universitair Medisch Centrum Utrecht, Utrecht: Prof. dr. A. I. M. Hoepelman*, Dr T. Mudrikova, Dr M. M. E. Schneider, Drs C. A. J. J. Jaspers, Dr P. M. Ellerbroek, Dr E. J. G. Peters, Dr L. J. Maarschalk-Ellerbroek, Dr J. J. Oosterheert, Dr J. E. Arends, Dr M. W. M. Wassenberg, Dr J. C. H. van der Hilst; VU Medisch Centrum, Amsterdam: Prof. dr. S. A. Danner*, Dr M. A. van Agtmael, Drs Wassenberg, Dr J. C. H. van der Hilst. VU Medisch Centrum, Amsterdam: Prof. dr. J. J. Oosterheert, Dr J. E. Arends, Dr M. W. M. Ellerbroek, Dr E. J. G. Peters, Dr L. J. Maarschalk-Ellerbroek, Dr J. J. Oosterheert, Dr J. E. Arends, Dr M. W. M. Ellerbroek; Universitair Medisch Centrum, Utrecht: Prof. dr. A. I. M. Hoepelman*, Dr T. Mudrikova, Dr M. M. E. Schneider, Drs C. A. J. J. Jaspers, Dr P. M. Ellerbroek, Dr E. J. G. Peters, Dr L. J. Maarschalk-Ellerbroek, Dr J. J. Oosterheert, Dr J. E. Arends, Dr M. W. M. Wassenberg, Dr J. C. H. van der Hilst; Universitair Medisch Centrum, Amsterdam: Prof. dr. S. A. Danner*, Dr M. A. van Agtmael, Drs Wassenberg, Dr J. C. H. van der Hilst.

Portugal: Hospital Egas Moniz, Lisbon (Ricardo Camacho, Perpetua Gomes).


Coordinating center.

France: ANRS Clinical Trials Unit INSERM U897 (Antoine Bénard, Marie Bertoncello, Geneviève Chêne, Audrey Taieb).

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