Dual therapy based on a ritonavir-boosted protease inhibitor as a novel salvage strategy for HIV-1-infected patients on a failing antiretroviral regimen

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Received 20 November 2011; returned 10 January 2012; revised 18 January 2012; accepted 27 January 2012

Objectives: To assess the efficacy and safety of dual-antiretroviral therapy containing a ritonavir-boosted protease inhibitor (PI/r) in treatment-experienced patients failing a current antiretroviral regimen.

Methods: Retrospective analysis of 60 consecutive HIV-1-infected patients who started a dual-antiretroviral rescue regimen containing a PI/r, in three hospitals in Spain. Virological failure was defined as confirmed HIV RNA >50 copies/mL at treatment week 24 or later. The percentage of patients remaining free of therapeutic failure was estimated using the Kaplan–Meier method, by intent-to-treat analysis (missing, changes and virological failure = therapeutic failure).

Results: Median baseline characteristics of patients were: 13 years on antiretroviral therapy (four prior highly active antiretroviral therapy regimens and eight different drugs), 380 CD4 cells/mm3 and HIV RNA 3.04 log10 copies/mL. All patients had resistance mutations to at least two drug classes, although only 9.3% had specific mutations to darunavir. A darunavir-based regimen was started in 47 (78.4%) patients, combined with etravirine (26.7%), tenofovir (26.7%) or raltegravir (25%). Three (5%) patients discontinued treatment due to side effects. At the end of follow-up, 86.7% of patients remained free of therapeutic failure; the percentages of patients with no therapeutic failure at treatment weeks 24, 48 and 96 were 96.6% (95% CI, 91.9–101.3); 90.1% (95% CI, 81.9–98.3) and 79.8% (95% CI, 66.1–93.5), respectively.

Conclusions: Our results suggest that a dual-therapy rescue regimen including a PI/r is convenient, well tolerated and potent enough to achieve persistent viral suppression in selected pre-treated patients with low viral load and few PI resistance mutations.

Keywords: dual-antiretroviral therapy, salvage therapy, pre-treated HIV-infected patients

Introduction
The availability of newer antiretroviral drugs with novel mechanisms of action (as well as new-generation drugs within old classes) with a higher genetic barrier and different resistance profiles has expanded rescue treatment options for heavily pre-treated patients with multidrug-resistant HIV-1 infections. Phase III randomized clinical trials have evaluated the efficacy and safety of the new protease inhibitor (PI) darunavir, the new non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine, the integrase inhibitor raltegravir, and the CCR5 antagonist maraviroc, in combination with an optimized background regimen (OBR). The results show that patients treated with regimens including at least two fully active drugs achieved a high rate of complete viral suppression.1–4 The results of these studies led to the current guideline recommendations that salvage therapy in multi-experienced patients should include at least two, and preferably three, fully active agents and at least one from the new classes of antiretroviral, and that the treatment goal is suppression of HIV-1 RNA to <50 copies/mL, as for patients starting their first antiretroviral regimen.5,6

The advantage of a regimen including three rather than two active agents is not so evident in patients with less treatment experience and few accumulated resistance-associated mutations (RAMs).7 Furthermore, as the extended use of triple therapy has additional problems, such as complexity of the regimens and the...
elevated cost of the therapy, different strategies aimed at reduc-
ing the number of drugs have been attempted. Substantial data are now available showing that monotherapy with twice-daily
ritonavir-boosted lopinavir or once-daily ritonavir-boosted daru-
navir are valid treatment options, mainly to avoid nucleoside
reverse transcriptase inhibitor (NRTI)-related toxicity, in selected
patients with maintained virological suppression and no previous
PI failure.8–11

In this approach, a novel NRTI-sparing strategy using a
ritonavir-boosted PI (PI/r) in combination with new drugs is
now being evaluated in different studies in naive patients, and
preliminary data has shown that dual therapy based on PI/r
can be as effective as standard triple-drug therapy.12,13

To the best of our knowledge, very limited data are available
regarding the efficacy of dual therapy in the setting of
treatment-experienced patients. So far, only data from the
BIKS study have been reported.14 In that study, 21 patients,
treatment-experienced but naive to NNRTIs and with low PI re-
sistance (15 of 21 with no lopinavir-associated mutations),
received a combination of ritonavir-boosted lopinavir and efavir-
enz as rescue regimen, and 81% of them had <400 copies/mL at
treatment week 48.

The aim of our study was to assess, in a real clinical setting,
the effectiveness and safety of an antiretroviral rescue regimen
containing only two drugs including a PI/r, in HIV pre-treated
patients failing a current antiretroviral treatment. This study
has special relevance considering that treatment adherence is
the main factor to achieve viral suppression and that, despite
the advances in drug development, treatment failures attribut-
able to suboptimal adherence continue to occur. Thus, more
convenient and better tolerable regimens are still needed for
the improvement of patient adherence and to maintain long-
term virological suppression.

Methods

Subjects and design

We conducted a multicentre observational study of all consecutive
treatment-experienced HIV-1-infected adult patients, on failing anti-
retroviral therapy (confirmed viral load >50 copies/mL) who started
a dual-therapy rescue regimen including a PI/r, between January 2005
and September 2011 in three university-affiliated hospitals in Barcelona,
Spain. Patients were identified through a systematic search of the HIV
database at each centre. The antiretroviral drug combinations were
selected by clinicians in charge of patients, on the basis of the cumulative
resistance profile, based on all available genotypic resistance tests for
each patient, the individual history of antiretroviral treatment and the
particular characteristics of adherence and tolerance of each patient.

Demographic data and HIV-related data (transmission risk factor,
prior AIDS-associated diseases, years of infection, previous antiretroviral
treatments and reason for discontinuation, as well as prior resistance
testing where performed) were recorded for each patient. HIV-1 RNA
measurements, CD4+ T cell counts, haematology, liver function tests,
hepatitis C virus (HCV) and hepatitis B virus serostatus, fasting blood
lipid and clinical evaluations were recorded at baseline and 12, 24, 48,
72 and 96 weeks thereafter. Adherence was evaluated according to
the information available in medical records.

Genotypic resistance tests were performed using the vircoTYPE HIV1
test (Virco BVBA, Beerse, Belgium). Drug RAMs were as defined by the
International AIDS Society–USA (IAS–USA) guidelines.15

The number of active drugs in each regimen (genotypic sensitivity
score (GSS)) was calculated according to the Stanford HIV Resistance
Database interpretation algorithm (HIVdb version 6.0.5): 1, 0.5 or
0 points were assigned to each drug in the regimen, depending on
whether it had low-level/zero resistance, intermediate resistance or high-
level resistance, respectively.16

Raltegravir was considered to be fully active in patients with no previ-
ous failure to this drug, and maraviroc was considered fully active in the
case of CCR5 tropism, as determined with the Enhanced sensitivity
phenotypic Trofile® assay (Monogram, San Francisco, CA, USA).

Efficacy and safety assessments

The efficacy was evaluated as the percentage of patients remaining free
of therapeutic failure as evaluated by a time-to-treatment failure algo-
rithm using intent-to-treat (ITT) analysis, in which virological failure,
missing values and discontinuation for any reason were recorded as
therapeutic failure.17 An on-treatment (OT) analysis was also conducted,
in which permanent interruptions of therapy, missing values or switches
were censored.

Virological failure was defined as never achieving a plasma viral load
<50 copies/mL or having two consecutive determinations of HIV RNA
>50 copies/mL at week 24 or later.

Safety and tolerability were assessed on the basis of clinical and la-
boratory adverse events. WHO toxicity grading scales were used to char-
acterize abnormalities in analytical results and physical examination.18

The number of adverse events leading to drug discontinuation was
recorded. Mean changes in CD4+ T cell counts and fasting blood lipids
over time were also evaluated.

Statistical analysis

SPSS software for Windows Version 15.0 (SPSS, Chicago, IL, USA)
was used for statistical analysis. Categorical variables are described
by number (proportion) and continuous variables, where not otherwise
specified, were evaluated as median and IQR. The time-to-loss-of-
therapeutic-response was estimated using the Kaplan–Meier
method. The Student’s t-test was used to compare related quantitative
variables. A last-observation-carried-forward approach was used for
missing CD4+ T cell and lipid data. All statistical tests were two-tailed
(statistical significance, 0.05).

Ethics

The study was approved by the Commission of Medical Ethics of Hospital
Vall d’Hebrón. Our institutions have an active programme for
HIV-infected patients (inpatient and outpatient care) that provides care
to most of the population in our reference areas. All HIV-infected patients
included gave written informed consent to use the information available
in the databases. No other consent was required due to the observational
design of the study.

Results

Patients and baseline characteristics

Baseline characteristics of the 60 patients included in this study
are shown in Table 1. All patients had a long history of HIV infec-
tion and had been on an antiretroviral treatment for a median of
13 years; they had received a median of four highly active anti-
retroviral therapy regimens and eight different drugs, and had
failed a median of four regimens. The median plasma viral
load at baseline was 3.04 log10 HIV-1 RNA copies/mL, and 80%
Table 1. Demographic and HIV-related characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>45.5 (40–49.75)</td>
</tr>
<tr>
<td>Sex (male), n (%)</td>
<td>41 (68.3)</td>
</tr>
<tr>
<td>HCV positive, n (%)</td>
<td>29 (48)</td>
</tr>
<tr>
<td>Anti-HBsAg positive, n (%)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>HIV transmission route, n (%)</td>
<td></td>
</tr>
<tr>
<td>IDUs</td>
<td>24 (40)</td>
</tr>
<tr>
<td>MSM</td>
<td>11 (18.3)</td>
</tr>
<tr>
<td>heterosexual</td>
<td>19 (31.7)</td>
</tr>
<tr>
<td>CDC stage C, n (%)</td>
<td>16 (26.7)</td>
</tr>
<tr>
<td>Time since HIV diagnosis (years), median (IQR)</td>
<td>17 (12–20)</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm³), median (IQR)</td>
<td>380 (232–613)</td>
</tr>
<tr>
<td>&lt;200 CD4 cells/mm³, n (%)</td>
<td>12 (20)</td>
</tr>
<tr>
<td>200–350 CD4 cells/mm³, n (%)</td>
<td>13 (21.7)</td>
</tr>
<tr>
<td>&gt;350 CD4 cells/mm³, n (%)</td>
<td>35 (58.3)</td>
</tr>
<tr>
<td>HIV RNA (log₁₀ copies/mL), median (IQR)</td>
<td>3.04 (2.5–4)</td>
</tr>
<tr>
<td>Time on treatment (years), median (IQR)</td>
<td>13 (9–15)</td>
</tr>
<tr>
<td>Number of previous mono/dual therapies, median (range)</td>
<td>1 (0–3)</td>
</tr>
<tr>
<td>Number of previous highly active antiretroviral therapies, median (range)</td>
<td>4 (2–12)</td>
</tr>
<tr>
<td>Number of previous antiretroviral drugs, median (range)</td>
<td>8 (4–15)</td>
</tr>
<tr>
<td>NRTIs</td>
<td>5 (2–8)</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>1 (0–3)</td>
</tr>
<tr>
<td>PIs</td>
<td>2 (0–6)</td>
</tr>
</tbody>
</table>

Table 2. Previous treatment failures and RAMs at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous antiretroviral failure (n=60)</td>
<td></td>
</tr>
<tr>
<td>number of previous ART failures, median (range)</td>
<td>4 (1–10)</td>
</tr>
<tr>
<td>number of previous HAART failures, median (range)</td>
<td>4 (1–7)</td>
</tr>
<tr>
<td>3TC/FTC-containing regimen, n (%)</td>
<td>54 (90)</td>
</tr>
<tr>
<td>EFV/NVP-containing regimen, n (%)</td>
<td>38 (63.3)</td>
</tr>
<tr>
<td>TDF-containing regimen, n (%)</td>
<td>36 (60)</td>
</tr>
<tr>
<td>PI-containing regimen, n (%)</td>
<td>33 (55)</td>
</tr>
<tr>
<td>IAS-USA drug RAMs (n=54)</td>
<td></td>
</tr>
<tr>
<td>NRTI-associated mutations, median (range)</td>
<td>4 (1–11)</td>
</tr>
<tr>
<td>TAMS, median (range)</td>
<td>2 (0–7)</td>
</tr>
<tr>
<td>TAMs, n (%)</td>
<td>38 (70.4)</td>
</tr>
<tr>
<td>M184V, n (%)</td>
<td>41 (68.3)</td>
</tr>
<tr>
<td>K65R, n (%)</td>
<td>4 (6.7)</td>
</tr>
<tr>
<td>NNRTI-associated mutations, median (range)</td>
<td>2 (0–2)</td>
</tr>
<tr>
<td>any NNRTI-associated mutations, n (%)</td>
<td>34 (63)</td>
</tr>
<tr>
<td>K103N, n (%)</td>
<td>19 (31.7)</td>
</tr>
<tr>
<td>etravirine-associated mutations, n (%)</td>
<td>26 (48)</td>
</tr>
<tr>
<td>PI-associated mutations, median (range)</td>
<td>1 (0–8)</td>
</tr>
<tr>
<td>any PI-associated mutations, n (%)</td>
<td>29 (53.7)</td>
</tr>
<tr>
<td>major PI-associated mutations, n (%)</td>
<td>23 (42.5)</td>
</tr>
<tr>
<td>darunavir-related mutations, n (%)</td>
<td>5 (9.3)</td>
</tr>
<tr>
<td>Number of active drugs in the rescue regimen (GSS) (n=54)</td>
<td></td>
</tr>
<tr>
<td>GSS=1, n (%)</td>
<td>44 (81.5%)</td>
</tr>
<tr>
<td>GSS=2, n (%)</td>
<td>8 (14.8%)</td>
</tr>
</tbody>
</table>

Table 3. Dual-therapy rescue regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Value (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRV/r based etravirine</td>
<td>49 (81.7%)</td>
</tr>
<tr>
<td>etravirine</td>
<td>16 (26.7%)</td>
</tr>
<tr>
<td>tenofovir</td>
<td>16 (26.7%)</td>
</tr>
<tr>
<td>raltegravir</td>
<td>15 (25%)</td>
</tr>
<tr>
<td>other</td>
<td>2 (3.3%)</td>
</tr>
<tr>
<td>ATV/r based tenofovir</td>
<td>7 (11.7%)</td>
</tr>
<tr>
<td>raltegravir</td>
<td>4 (6.7%)</td>
</tr>
<tr>
<td>other</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>LPV/r based tenofovir</td>
<td>2 (3.3%)</td>
</tr>
<tr>
<td>raltegravir</td>
<td>2 (3.3%)</td>
</tr>
</tbody>
</table>

ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; 3TC, lamivudine; FTC, emtricitabine; EFV, efavirenz; NVP, nevirapine; TDF, tenofovir; TAMs, thymidine analogue-associated mutations.
Virological and immunological response

Patients were followed for a median time of 16 months (IQR, 9.25–25.5). By ITT analysis, the cumulative percentage of patients remaining free of therapeutic failure at the end of follow-up was 86.7% (52/60 patients). The corresponding data were 96.6% (95% CI, 91.9%–101.3%) at week 24, 90.1% (95% CI, 81.9%–98.3%) at week 48 and 79.8% (95% CI, 66.1%–93.5%) at week 96 (Figure 1). By OT analysis, the percentage of patients with therapeutic response was 98.2% (95% CI, 94.7%–101.7%) at week 24, 93.9% (95% CI, 87.3%–100.6%) at week 48 and 88.7% (95% CI, 76.9%–100.5%) at week 96.

True OT virological failure was observed in four patients. One of them had low grade virological failure with persistent viral load (100–200 copies/mL). This patient received treatment with ritonavir-boosted darunavir plus partially active etravirine (combination GS5=1.5). The other three patients with poor treatment adherence had viral load >10000 copies/mL, and two of these were lost to follow-up after confirmed virological failure. Two additional patients with single viral rebound (>50 copies/mL at week 24 or later) attained viral suppression without changing antiretroviral treatment. Regarding the immunological response, at week 48 of follow-up there was a significant mean increase of 83.6 cells/mm³ in CD4+ T cell counts (95% CI, 43.3–123.9; P<0.001).

Safety and tolerability

Overall, five (8.3%) patients prematurely discontinued treatment; of these, two were lost to follow-up and three discontinued due to intolerance or side effects. Of the latter, one virological failure had gastrointestinal intolerance to etravirine; another had a rash related to etravirine; the last was a haemophiliac who experienced bruising that worsened following the introduction of darunavir.

No patient interrupted treatment due to liver toxicity or any laboratory-related adverse event. There were no differences in fasting blood lipids after 48 weeks of treatment, with a mean decrease of 6.5 mg/dL (95% CI, –70.8 to 57.8, P=0.841) in total cholesterol levels and a mean increase of 36.9 mg/dL (95% CI, –10.6 to 84.5, P=0.125) in triglycerides.

Discussion

In this study, a dual-therapy rescue regimen containing PI/r was highly effective and well tolerated in treatment-experienced patients. Of all patients, 90% had <50 copies/mL at week 48 of treatment (ITT analysis) and almost 85% remained free of therapeutic failure after a median follow-up of 16 months. Furthermore, a significant increase in CD4+ T cell count was observed during the first 48 weeks of treatment, similar to that observed in other studies.19,20

Although cross-study comparisons must be undertaken with caution, the efficacy results seen in our study are consistent with previously reported data from trials conducted in similar settings.5,20 In the TMC114-C214 (TITAN) study,7 the efficacy and safety of ritonavir-boosted darunavir and ritonavir-boosted lopinavir, both in combination with an OBR, were compared in 595 pre-treated patients on viral failure. At treatment week 48, 71% of subjects in the darunavir arm and 60% in the lopinavir arm achieved virological suppression to <50 copies/mL (ITT analysis, P=0.005). Overall, 33% of these patients had, at most, one active drug in the OBR. In a stratified analysis of patients treated with darunavir, 80% (44/55) with one active drug in the OBR, and 68% (142/209) with at least two active drugs, had <50 copies/mL at week 48 [risk ratio (RR) for viral response, 1.18; 95% CI, 1.0–1.38; P=0.082]. Corresponding data in the lopinavir arm were 57% (43/75) and 61% (110/181) (RR, 0.94; 95% CI, 0.75–1.18; P=0.610).7

The high efficacy of darunavir plus one additional fully active drug was also observed in the context of heavily pre-treated patients. In a pooled subgroup analysis of data from the POWER trials, no differences were seen in the percentage of patients with less than 50 copies/mL at week 48 of treatment, with ritonavir-boosted darunavir among patients with one active drug in the OBR (50%; 17/34) compared with those with at least two active drugs in the OBR (56%; 27/48) (RR, 0.89; 95% CI, 0.58–1.35; P=0.578).1

Even though it is not powered to show significant effects within a subgroup, stratified analysis of salvage trials provides relevant information regarding which factors are associated with viral response, and could contribute to explaining the results of this study.

In the POWER trials, 80% of patients with viral load <20000 copies/mL achieved viral suppression, compared with 29% of those with >20000 copies/mL at baseline (RR, 2.72; 95% CI, 1.85–4.02).1 A lower pre-treatment viral load was also independently associated with higher rates of viral response to salvage regimens containing new drugs in other clinical trials.21–23 In our study, median viral load at baseline was low (3.04 log₁₀ copies/mL) and was probably an important determinant of the high viral response.

Another factor associated with the likelihood of achieving viral suppression with a darunavir-containing salvage regimen is the number of RAMs in the protease gene, and in particular the number of specific darunavir-associated mutations. A loss of response to darunavir occurs with the first mutation, increasing linearly with additional mutations, and beyond three mutations the response is greatly reduced.1,24,25 The low number of PI-related mutations and in particular the low percentage of patients with darunavir-associated mutations (all remaining fully susceptible to darunavir) may contribute to explaining the high efficacy
observed in our study. Other factors, such as the preserved immune status of patients evaluated in the present study, could also contribute to explaining the excellent treatment outcome.7,21–23

These data taken together suggest that in selected patients with predictors of viral response (high CD4+ T cell counts, low basal viral load and absence of or few PI-associated resistance mutations) a PI/r-based rescue regimen employing only two active drugs might be as effective as standard triple therapy.

Regarding the most suitable drugs to construct an effective dual regimen, data from salvage trials highlight the pivotal role of ritonavir-boosted darunavir in rescue regimens. Because of its potency, high genetic barrier and resistance profile, darunavir was a main component of salvage therapy both in heavily pre-treated patients and in those with less advanced disease.3,7 Furthermore, once-daily darunavir dosing has proven to be as effective as twice-daily dosing in selected patients with no darunavir-associated mutations, which may facilitate the construction of a more convenient once-daily regimen.20

Concerning selection of the second drug, etravirine in combination with darunavir has shown an impressive efficacy in pooled analysis from DUET studies (63% of patients who received only these two active drugs achieved <50 copies/mL at week 48 in ITT analysis).26 Furthermore, etravirine is generally well tolerated with few side effects, and allows the construction of a once-daily regimen.26 However, it should be borne in mind that in patients previously failing a first-generation NNRTI-based regimen, minority resistant variants, which might have a negative impact on etravirine activity, are common and not detected by population sequencing.27

Tenofovir, when full activity is preserved, can be an attractive option considering its potency, simple dosage, long experience in use and moderate cost. In patients with CCR5 tropism, maraviroc may be useful to construct a potent and convenient once-daily regimen in combination with darunavir.21 Raltegravir, in spite of its high price and twice-daily dosing, is a potent and very well tolerated antiretroviral drug that may be very useful to construct an effective dual regimen in combination with PI/r.28

In our study, dual therapy was well tolerated and improved treatment convenience, compared with the failing regimen in 40% of patients. In contrast, construction of a triple standard therapy in this population would have to use more complex regimens,29,30 which might have a negative impact on adherence and treatment outcome. In fact, therapeutic failure was mainly due to intolerance or lack of adherence, and a true OT viral failure due to insufficient antiviral potency was observed in just one patient. These data highlight the importance of efforts to improve treatment adherence and reinforce the idea of an individually based approach—taking into account not only cumulative resistance mutations and historical treatment but also the patient’s needs and tolerances to previous regimens—as the best strategy to optimize treatment outcome in pre-treated patients on failing antiretroviral therapy.

The present study has some potential limitations. The first is the lack of a control group to compare with this new strategy; however, the rate of viral response was very high and similar to that observed with standard triple therapy.7,21 Secondly, the heterogeneity of the rescue regimens might hinder the interpretation and extrapolation of the results. Nevertheless, almost 80% of patients received darunavir as a pivotal drug, in combination with etravirine, tenofovir or raltegravir. Consequently, although a two-component fully active regimen based on ritonavir-boosted atazanavir32 or lopinavir33,34 can achieve and maintain viral suppression in patients with no PI-related mutations, the results of our study apply mainly to dual therapy based on ritonavir-boosted darunavir plus a second active drug. Thirdly, we must note the small number of patients analysed, and the inherent limitations of the observational design.

Despite these limitations, this study provides novel and clinically relevant data on salvage antiretroviral therapy. Our results suggest that a regimen with two fully active drugs, including a ritonavir-boosted PI, might improve convenience and tolerance and provide enough potency to achieve persistent viral suppression in selected pre-treated patients with low viral load and no or few PI resistance-associated mutations. Properly designed randomized control trials are necessary to ascertain whether these treatment-experienced patients benefit from two or three fully active antiretroviral regimens.

**Funding**

This work was supported by Red Temática de Investigación en SIDA (RIS G03/173-RETIC RD06/0006/0039).

**Transparency declarations**

J. B. has received honoraria and speakers’ fees from Bristol-Myers Squibb, GlaxoSmithKline, Janssen-Cilag, Pfizer and ViIV Healthcare. M. C. has received honoraria and speakers’ fees from Abbott, Bristol-Myers Squibb, Gilead, GlaxoSmithKline and Janssen-Cilag. V. F. has received honoraria and speakers’ fees from Bristol-Myers Squibb. A. C. has received honoraria, speakers’ fees and funds for research from Abbott, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Janssen-Cilag, MSD and ViIV Healthcare. A. I. has received honoraria and speakers’ fees from Abbott, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Janssen-Cilag, Merk, MSD, Pfizer and ViIV Healthcare. P. D. has received honoraria, speakers’ fees and funds for research from Abbott, Bristol-Myers Squibb, Boehringer Ingelheim, Ferrer Internacional, Janssen-Cilag, Merck Sharp and Dohme, Theratechnologies and ViIV Healthcare. D. P. has received honoraria and speakers’ fees from Abbott, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Janssen-Cilag, Merck, Pfizer, Janssen and ViIV Healthcare. M. G. M. has received honoraria and speakers’ fees from Abbott, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Janssen-Cilag, Merck, Pfizer, Janssen and ViIV Healthcare. E. R. has received honoraria, speakers’ fees, consultant fees and funds for research from Abbott, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Janssen-Cilag, Merck, Pfizer, Roche Farma and Schering-Plough. S. V.: none to declare.

**Author contributions**

J. B. and M. C. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: J. B. and M. C. Acquisition of data: J. B., A. C., A. I. and M. G. M. Analysis and interpretation of data: J. B., M. C., V. F. and A. C. Drafting of the manuscript: J. B. and M. C. Critical revision of the manuscript for important intellectual content: V. F., A. C., A. I., P. D., D. P., E. V. d. E., S. V. and E. R. Statistical expertise: J. B. and M. C. Study supervision: M. C. and E. R. All authors approved the final version of the manuscript.
References


