Role of Ritonavir in the Drug Interactions Between Telaprevir and Ritonavir-Boosted Atazanavir

Alicia Gutierrez-Valencia,1 Rosa Ruiz-Valderas,1 Almudena Torres-Cornejo,1 Pompeyo Viciana,1 Nuria Espinosa,1 Juan R. Castillo-Ferrando,2 and Luis F. Lopez-Cortes1

1Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, and 2Farmacología Clínica, Hospital Universitario Virgen del Rocío, Sevilla, Spain

Background. Detrimental bidirectional pharmacokinetic interactions have been observed when telaprevir (TVR) and ritonavir (RTV)-boosted human immunodeficiency virus (HIV) protease inhibitors are coadministered in healthy volunteers. Our aim was to evaluate the role of RTV in the bidirectional TVR and atazanavir (ATV) interactions.

Method. An open-label, sequential study was carried out in hepatitis C virus (HCV)/HIV–coinfected patients on a RTV-boosted ATV-based (ATVr) antiretroviral regimen (300/100 mg every 24 hours) and triple therapy for chronic C hepatitis genotype 1 (TVR, 1125 mg every 12 hours, pegylated interferon-alpha and ribavirin). Pharmacokinetic profiles were acquired before and after switching from ATVr to unboosted ATV (200 mg every 12 hours). The plasma levels of both drugs were determined by liquid chromatography coupled with mass spectrometry. Pharmacokinetic parameters were calculated by noncompartmental analysis and compared by geometric mean ratios and their 90% confidence intervals.

Results. Fourteen white HCV/HIV–coinfected males were enrolled in this study. After RTV was withdrawn, the TVR AUC0–12 (area under the concentration–time curve), maximum concentration (Cmax), and minimum concentration (Cmin) values increased by 19% (7%–30%), 12% (0.9%–29%), and 18% (2%–34%), respectively, without any changes in the TVR terminal half-life. The ATV AUC0–12, Cmax, and Cmin values were 39% (13%–66%), 19% (8%–59%), and 48% (1%–96%) higher, respectively, with a significantly shorter terminal half-life (22.6 hours vs 10.4 hours).

Conclusions. RTV is responsible for the adverse interactions that occur when TVR and ATVr are administered together, possibly by influencing either the absorption phase or first-pass metabolism of TVR. The boost effect of TVR on ATV exposure is higher than on RTV, despite its shorter terminal half-life. The coadministration of TVR and unboosted ATV results in increased exposure of both drugs compared with their coadministration with RTV.


Keywords. telaprevir; atazanavir; ritonavir; pharmacokinetics; drug interactions.

Telaprevir (TVR) and boceprevir (BOC) are peptidomimetic inhibitors of the hepatitis C virus (HCV) NS3-4A serine protease. These inhibitors have become the standard of care in combination with peginterferon and ribavirin when treating patients with HCV genotype 1 because of their excellent antiviral activity, both in vitro and in vivo [1,2]. TVR is primarily metabolized by the cytochrome P450 3A4 isofrom, acting as both a substrate and an inhibitor of the 3A4 isoenzyme, and is also a substrate for P-glycoprotein [3]. Therefore, drug–drug interactions are expected when TVR is coadministered with agents that either modulate the activities of...
or are metabolized by the CYP3A4. This is of particular importance for the treatment of individuals who are coinfected with chronic hepatitis C and human immunodeficiency virus (HIV), as the use of ritonavir (RTV)-boosted HIV protease inhibitors (HIV-PIr) is very common and, sometimes, indispensable. Contrary to the predicted results, data from phase 1 trials in healthy volunteers showed adverse bidirectional interactions when both direct-acting antiviral agents BOC and TVR were coadministered with HIV-PIr [4, 5]. Specifically, significant decreases in both TVR and RTV-boosted darunavir, fosamprenavir, and lopinavir concentrations were observed when they were administered twice a day in combination with TVR. These findings led to the recommendation against these combinations and to limitations of the therapeutic options for HCV/HIV–coinfected patients [3, 5].

Currently, the only HIV-PIr recommended for coadministration with TVR is RTV-boosted atazanavir (ATVr), as the effect for TVR exposure was minor (area under the concentration–time curve [AUC] reduced by approximately 20%) and an increase in the ATV minimum concentrations (C_{min}) was observed [3, 5].

ATV is a substrate and a weak inhibitor of CYP3A4 [6]; in contrast, RTV acts as an inhibitor of CYP3A4 but also induces the CYP3A4 transcription (mRNA) and CYP3A protein expression [7]. Based on the above-mentioned studies in which the HIV-PIr were dosed with 100 mg RTV twice daily except ATV, which was dosed with RTV 100 mg once daily, we hypothesized that the reduction in the TVR concentrations might be related to the RTV daily dose. Thus, our aim in this study was to evaluate the role of RTV in these interactions.

MATERIALS AND METHODS

Study Design

This study was an open-label, sequential study carried out at the Hospital Universitario Virgen del Rocio in Spain. Adult HCV/HIV-1–coinfected patients on stable antiretroviral therapy with ATVr (300/100 mg once daily) and either 2 nucleos(t)ide analogue reverse transcriptase inhibitors (NRTIs) or raltegravir plus triple therapy for chronic hepatitis C genotype 1 (TVR [1125 mg twice daily], pegylated interferon-α and ribavirin) for ≥2 weeks were enrolled in the study after providing written consent. The twice-daily TVR dosing was chosen because similar sustained virological response rates were observed regardless of TVR dosing frequency (twice or thrice daily) [8] and because this dosing regimen is easier to manage if the other drugs are also given twice daily.

Exclusion criteria were pregnancy, clinical history suggesting malabsorption, and concomitant use of drugs with potential interactions with the study drugs as described in their full prescribing information files. Liver stiffness was determined by hepatic transient elastography (FibroScan, Echosens, Paris) with values ≥14.6 kPa being indicative of cirrhosis [9].

The Spanish Agency for Medicine and Healthcare Products and Comité Autonómico de Ensayos Clínicos, Consejería de Salud, Junta de Andalucía (the central ethics committee) approved the study protocol. This study is registered at ClinicalTrials.gov, NCT01818856, and European Medicines Agency no. EudraCT: 2012-002515-25, and was conducted according to the Declaration of Helsinki guidelines.

Patients were admitted to the hospital in the morning. Blood samples for the measurement of TVR and ATV levels were obtained immediately before and at 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours after supervised drug intake following a standard breakfast. Additionally, blood samples were taken at 16, 20, and 24 hours to determine ATV levels. The following day, the ATV dose was switched to 200 mg every 12 hours (without RTV) while maintaining the NRTIs or raltegravir regimen. This ATV dose was selected based on the data from Bonora et al [10] and our own data, which showed that 200 mg ATV twice daily resulted in intermediate plasma concentrations between 300/100 mg ATVr and 400 mg ATV once daily in HIV-infected patients. After 8–10 days, 12-hour pharmacokinetic profiles were calculated using samples drawn before and at 1, 2, 3, 4, 6, 8, 10, and 12 hours after TVR and ATV intake.

Analytical Method

Within 1 hour after the collection of blood samples, the tubes were centrifuged at 1500 g for 20 minutes at room temperature. The plasma obtained was transferred to cryotubes and stored at −80°C until further analysis. Plasma concentrations were determined by liquid chromatography coupled with mass spectrometry. Drugs were extracted from the plasma samples with precipitation protein extraction using acetonitrile as the precipitation agent. TVR chromatographic separation was performed on a Luna C18 150 mm × 2.0 mm, 5 μm analytical column. The mobile phase A consisted of an ultrapure water/25% ammonia solution (100:0.05, v/v) and the mobile phase B consisted of a methanol/25% ammonia solution (100:0.05, v/v) with a chromatographic run time of 11 minutes, as previously reported [11]. Atazanavir chromatographic separation was performed on a 2.1 × 50 mm Waters Atlantis dC18 3 μm analytical column. Mobile phase A consisted of ultrapure water containing 0.05% formic acid; mobile phase B consisted of 0.05% formic acid in acetonitrile. The mobile phase was delivered using a gradient elution program with a flow rate of 0.3 mL/min at an analytical run time of 15 minutes [12]. Both the accuracy and precision for TVR and ATV were 100% ± 15%. The ATV standard curves were linear over the range of 20 to 15 000 ng/mL, whereas the TVR standard curves were linear over the range of 100 to 10 000 ng/mL. The assays were validated according to Food and Drug Administration guidelines.
Pharmacokinetic Analysis

A noncompartmental analysis was performed to determine the pharmacokinetic parameters for each individual. The maximum concentrations (C_{max}), time to reach C_{max} (T_{max}), and trough levels (C_{min}) at either 12 or 24 hours were obtained from direct observation of the plasma concentration curves as a function of time. The areas under the plasma concentration curves over the dosing interval (AUC_{0-\tau}) were calculated using the linear trapezoidal method for ascending concentrations and the logarithmic trapezoidal method for descending concentrations (WinNonlin software, Pharsight, Mountain View, CA). The elimination rate constant of the terminal phase (\lambda_z) was determined by linear regression of natural logarithms of the plasma concentrations during the elimination phase vs time as defined by the following equation:

$$\lambda_z = \ln C_t - \ln C_0/\Delta t.$$  

The half-life during the elimination phase (t_{1/2}^\beta) was calculated using the following equation:

$$t_{1/2}^\beta = 0.693/\lambda_z.$$  

For ATV, the terminal log-linear period (\beta) was defined by the data points from either 6 or 8 to 12 or 24 hours for the twice-daily and once-daily dosing regimens, respectively. For TVR, \beta was defined by the data points from 6 to 12 hours. The total clearance (Cl_T) was calculated as dose/AUC_{0-\tau}, assuming a value of 1 for the absorbed fraction of TVR (F). The results are expressed as micrograms per milliliter.

Statistical Analysis

The TVR and ATV pharmacokinetic parameters were described by the geometric means (GM) and compared between the first and second pharmacokinetic studies by their geometric mean ratios (GMRs) and their 90% confidence intervals (90% CIs) using the results of the first study as the reference group. The differences in the pharmacokinetic parameters between both studies were considered to be significant when the interval between the low and high 90% CI did not include the value 1.0 as compared by the Wilcoxon signed-rank test. Interindividual variability in drug concentrations was assessed by coefficient of variation (CV = standard deviation/mean × 100). The relationships between AUC_{0-\tau}, C_{max}, and C_{min} were analyzed by linear regression and Pearson coefficients after log_{10} transformation of the variables. Statistical calculations were performed with Statistical Product and Service Solutions for Windows (version 15.0, SPSS, Chicago, IL).

RESULTS

Fourteen white HCV/HIV–coinfected males (characteristics are shown in Table 1) were enrolled in the study. The median age was 47 years and the mean body mass index was 25.6 kg/m². All patients had normal renal function, and 11 were classified with cirrhosis Child–Pugh stage A with no clinical signs of liver impairment. Other than ATVr and TVR, patients were taking tenofovir plus emtricitabine (n = 6), abacavir plus lamivudine (n = 7), or raltegravir (n = 1). Both dosing regimens were well tolerated, and all patients successfully completed both pharmacokinetic profiles.

The GMs of the pharmacokinetic parameters of TVR coadministered with ATVr (300/100 mg once daily) and unboosted ATV (200 mg twice daily) and their ratios are shown in Table 1 and Figure 1. The AUC_{0-12}, C_{max}, and C_{min} values for TVR were 19% (90% CI, 1.07–1.30), 12% (90% CI, .96–1.29), and 18% (90% CI, 1.02–1.34) higher, respectively, when RTV was absent, though the difference in C_{max} was not statistically significant. Furthermore, the TVR t_{1/2}^\beta showed no change (12...
AUC0-24 was calculated as AUC0-12 × 2.

All patients had an increase in total bilirubinemia taking or not taking concomitant tenofovir during both periods were no differences in the ATV levels of patients who were

β 

t½

AUC0-

AUC0-

4.37; 

P

< .001) after 12 weeks on TVR.

With both ATV regimens, there were highly linear relationships between the TVR AUC0-12 and both Cmax and Cmin (r = 0.854 and r = 0.885, respectively; P < .001), as well as between TVR Cmax and Cmin (r = 0.639; P < .001). However, these correlations were lower for ATV (AUC0-1, with Cmax and Cmin, r = 0.726 and r = 0.592, respectively; P = .001).

**DISCUSSION**

The reduction in the plasma concentrations of both TVR and HIV-PIr when these drugs were co-dosed was somewhat unexpected. Earlier studies showed a positive interaction between TVR and HIV-PIr, as RTV strongly inhibited the metabolism of TVR in human liver microsomes and plasma concentrations above 15-fold were observed in rats in the presence of RTV [13]. By contrast, a 2-fold increase of TVR exposure was observed in healthy volunteers after a single 100-mg dose of RTV, but this boosting activity for TVR was lost following multiple doses despite an increase in the mean RTV plasma levels [14]. The mechanism of this effect remains to be elucidated. However, it has been suggested that TVR might have heterogeneous (inhibitory and activating) effects on CYP3A4, that both RTV and/or TVR might have autoinduction effects on CYP3A4, that both RTV and/or TVR might have autoinduction effects on CYP3A4, P-gp, or other transporters [4, 7, 15–20].

We have observed an increase in the TVR and ATV AUC0-1, Cmax and, to a lesser degree, Cmax after RTV withdrawal. This increase in TVR AUC0-1 appears to be primarily related to changes that occur during either the absorption phase or first-pass metabolism, as the curves are parallel after Tmax with similar TVR terminal elimination half-lives. These increases suggest a paradoxical or negative effect of RTV on TVR absorption, which might be due to a predominant induction effect of RTV on the intestinal CYP enzymes 3A, P-gp, or other transporters, as well as possible changes in metabolizing enzyme

---

**Table 2. Pharmacokinetic Parameters of TVR 1125 mg Twice Daily Together With 300/100 mg ATVr Once Daily and Unboosted ATV (200 mg Twice Daily).**

<table>
<thead>
<tr>
<th>TVR Pharmacokinetic Parameters (n= 14)</th>
<th>TVR + ATVr</th>
<th>CV (%)</th>
<th>TVR + ATV</th>
<th>CV (%)</th>
<th>GMR (90%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-12 (µg·h/mL), GM (range)</td>
<td>39.15 (22.30–59.09)</td>
<td>27.5</td>
<td>49.98 (25.49–79.98)</td>
<td>34.9</td>
<td>1.19 (1.07–1.30)</td>
<td>0.008</td>
</tr>
<tr>
<td>Cmax (µg/mL), GM (range)</td>
<td>5.06 (3.58–7.25)</td>
<td>23.1</td>
<td>5.69 (3.05–12)</td>
<td>41.9</td>
<td>1.12 (0.96–1.29)</td>
<td>0.198</td>
</tr>
<tr>
<td>Cmin (µg/mL), GM (range)</td>
<td>2.24 (1.37–3.93)</td>
<td>33.3</td>
<td>2.64 (1.15–5.51)</td>
<td>39.0</td>
<td>1.18 (1.02–1.34)</td>
<td>0.028</td>
</tr>
<tr>
<td>Tmax (h), GM (range)</td>
<td>2.7 (1–5)</td>
<td>46.4</td>
<td>3.2 (2–8)</td>
<td>47.8</td>
<td>1.19 (0.89–1.49)</td>
<td>0.458</td>
</tr>
<tr>
<td>μt½ β (h), (90%CI)</td>
<td>12.0 (7.4–16.6)</td>
<td>37.1</td>
<td>11.0 (7.0–15.0)</td>
<td>37.4</td>
<td>0.92 (0.74–1.10)</td>
<td>0.221</td>
</tr>
<tr>
<td>CIr (L/h), (90%CI)</td>
<td>28.7 (19.4–38.7)</td>
<td>31.2</td>
<td>24.4 (17.7–32.8)</td>
<td>33.4</td>
<td>0.84 (0.77–0.91)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Abbreviations: t½ β, TVR half-life for the elimination phase; ATV, atazanavir; ATVr, ritonavir-boosted atazanavir; CIr, total clearance; CV, coefficient of variation; GMR, geometric mean ratio and range; TVR, telaprevir.

---

**Table 3. Pharmacokinetic Parameters of 300/100 mg ATVr Once Daily and Unboosted ATV (200 mg Twice Daily).**

<table>
<thead>
<tr>
<th>ATV pharmacokinetic parameters (n= 14)</th>
<th>ATVr + TVR</th>
<th>CV (%)</th>
<th>ATV + TVR</th>
<th>CV (%)</th>
<th>GMR (90%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-1 (µg·h/mL), GM (range)</td>
<td>46.12 (21.92–99.80)</td>
<td>42.6</td>
<td>64.24 (46.72–119.4) *</td>
<td>32.2</td>
<td>1.39 (1.13–1.66)</td>
<td>0.004</td>
</tr>
<tr>
<td>Cmax (µg/mL), GM (range)</td>
<td>3.49 (1.55–8.29)</td>
<td>45.8</td>
<td>4.16 (2.60–6.80)</td>
<td>33.1</td>
<td>1.19 (0.80–1.59)</td>
<td>0.286</td>
</tr>
<tr>
<td>Cmin (µg/mL), GM (range)</td>
<td>1.23 (0.43–2.74)</td>
<td>47.9</td>
<td>1.83 (1.06–4.09)</td>
<td>40.9</td>
<td>1.48 (1.01–1.96)</td>
<td>0.019</td>
</tr>
<tr>
<td>Tmax (h), GM (range)</td>
<td>2.8 (1–5)</td>
<td>41.1</td>
<td>2.7 (2–3)</td>
<td>39.0</td>
<td>0.94 (0.63–1.26)</td>
<td>0.587</td>
</tr>
<tr>
<td>μt½ β (h), (90%CI)</td>
<td>22.6 (19.9–25.4)</td>
<td>26.6</td>
<td>10.4 (8.5–12.3)</td>
<td>42.1</td>
<td>0.46 (0.36–0.46)</td>
<td>0.002</td>
</tr>
<tr>
<td>CIr (L/h), (90%CI)</td>
<td>6.2 (5.0–7.4)</td>
<td>42.5</td>
<td>6.2 (5.52–6.94)</td>
<td>25.1</td>
<td>1.00 (0.85–1.15)</td>
<td>0.972</td>
</tr>
</tbody>
</table>

Abbreviations: t½ β, ATV half-life for the elimination phase; ATV, atazanavir; ATVr, ritonavir-boosted atazanavir; CIr, total clearance; CV, coefficient of variation; GMR, geometric mean ratio and range.

*; AUC0-24 was calculated as AUC0-12 × 2.
function when coadministered with TVR [16]. However, it is known that TVR is displaced from its binding site by human α-1-acid glycoprotein and albumin in the presence of RTV, yielding an approximately 30% increase in the free fraction of TVR [4, 21], but this would not justify our results.

In the absence of RTV, TVR has a more pronounced boosting effect on the ATV absorption phase or first-pass metabolism than RTV. Thus, increased AUC₀₋₁ and Cmin values were observed despite a shorter ATV terminal elimination half-life, which may be due to the lack of the RTV inhibitory effect on the ATV metabolism by hepatic CYP3A4 activity [21].

To our knowledge, this is the first pharmacokinetic study of TVR in HCV/HIV–coinfected patients to address these interactions. Additionally, this study also investigated the pharmacokinetic interactions when ATV was administered twice daily. With both ATV regimens, the TVR exposure after doses of 1125 mg twice daily were similar or higher (particularly the Cmax) than those described in other studies in HCV-infected patients on either a 750-mg thrice daily or a 1125-mg twice daily regimen [4, 8, 22, 23], as well as in the study of interactions between HIV-PIr and TVR in healthy volunteers [5].

Our results have several clinical implications. First, in several TVR clinical trials (PROVE 1, 2, and 3; ADVANCE; and REALICE), the TVR Cmin, Cavg, or AUC values were predictors of virological responses. Given the TVR levels observed in our study, a maximal TVR efficacy would be warranted in HCV/HIV–coinfected patients regardless of the coadministration of either ATVr or unboosted ATV. Also, compared with healthy volunteers, lower overall CYP3A activity has been reported among HIV-infected patients [24], and this could explain some of the differences between the results in healthy volunteers and HIV-infected patients.

Second, these studies showed that the TVR Cmin value was significantly associated with increased risk of severe anemia [5]. Accordingly, TVR would be a good candidate for therapeutic drug monitoring if its best therapeutic range were known. In this regard, the highly linear relationship observed between TVR AUC₀₋₁ and Cmin would facilitate subsequent human pharmacokinetic studies. Finally, these results justify new studies on the interactions between telaprevir and HIV-PIr because darunavir and fosamprenavir are frequently administered with lower doses of RTV than those used in the above-mentioned trial (100 mg once daily instead of 100 mg twice daily) [25].

In summary, RTV is responsible for the detrimental interactions that occur between TVR and ATVr when administered together, likely by influencing either the absorption phase or first-pass metabolism of TVR. The boosting effect of TVR on ATV exposure is higher than RTV despite having a shorter terminal half-life. The coadministration of TVR and unboosted ATV gives rise to increased exposure to both drugs compared with their coadministration with RTV. Additional in vitro and in vivo studies are necessary to clarify the underlying mechanism.

### Table 4. Pharmacokinetic Parameters of Ritonavir-Boosted ATVr 300/100 mg qd and Unboosted ATV (200 mg q12h) With (+) and Without the Concomitant Administration of TDF.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ATV + TDF (n= 6)</th>
<th>ATV without TDF (n= 8)</th>
<th>p</th>
<th>ATV + TDF (n= 6)</th>
<th>ATV without TDF (n= 8)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀₋₁ (μg·h/mL), GM (range)</td>
<td>47.02 (37.60–81.50)</td>
<td>40.90 (22.60–99.80)</td>
<td>0.414</td>
<td>29.25 (26.80–59.50)</td>
<td>29.75 (23.30–51.40)</td>
<td>0.491</td>
</tr>
<tr>
<td>Cmax (μg/mL), GM (range)</td>
<td>4.00 (2.70–5.80)</td>
<td>3.40 (1.60–8.30)</td>
<td>0.282</td>
<td>3.85 (2.90–6.80)</td>
<td>4.05 (2.60–6.60)</td>
<td>0.950</td>
</tr>
<tr>
<td>Cmin (μg/mL), GM (range)</td>
<td>1.27 (0.43–2.81)</td>
<td>1.19 (0.55–2.74)</td>
<td>0.950</td>
<td>1.83 (1.06–4.09)</td>
<td>1.83 (1.06–4.09)</td>
<td>0.573</td>
</tr>
<tr>
<td>Tₘₕ (h), GM (range)</td>
<td>3.0 (1–5)</td>
<td>3.0 (2.0–5.0)</td>
<td>0.755</td>
<td>3.0 (2–4)</td>
<td>3.0 (1–5)</td>
<td>0.950</td>
</tr>
<tr>
<td>t½ (h), (90%CI)</td>
<td>20.5 (15.3–25.6)</td>
<td>24.1 (21.4–27.4)</td>
<td>0.662</td>
<td>11.5 (8.2–14.9)</td>
<td>9.6 (7.4–11.7)</td>
<td>0.414</td>
</tr>
<tr>
<td>ClT (L/h), (90%CI)</td>
<td>5.7 (4.6–6.7)</td>
<td>6.8 (4.7–7.1)</td>
<td>0.284</td>
<td>5.8 (4.7–6.9)</td>
<td>6.5 (5.6–7.5)</td>
<td>0.491</td>
</tr>
</tbody>
</table>

Abbreviations: t½, ATV half-life for the elimination phase; ATV, atazanavir; ATVr, ritonavir-boosted atazanavir; ClT, total clearance; GMR: geometric mean ratio and range; TDF, tenofovir.
Notes

Acknowledgments. We acknowledge the participation of patients in this study. We thank the collaboration of Pilar Marquez, Antonio Cervera, and Rocío Cidoncha.

Financial support. This work was supported by an unrestricted grant from Bristol-Myers Squibb Company (BMS) through a contractual agreement between BMS and our center foundation (Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla - Hospital Universitario Virgen del Rocío). BMS had no access to data from this study and no participation during the analysis or publication.

Potential conflicts of interest. L. F. L.-C. and P. V. have received honoraria for speaking at symposia organized on behalf of Abbott Laboratories (Spain), Bristol-Myers Squibb, GlaxoSmithKline, Gilead Sciences, Janssen-Cilag España, Merck Sharp & Dohme España, Roche Pharma SA, and ViIV Healthcare. These authors also received unrestricted funds for research from Abbott Laboratories (Spain), Bristol-Myers Squibb, GlaxoSmithKline, Gilead Sciences, GlaxoSmithKline, Roche Pharma S.A., and ViIV Healthcare. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References