Pharmacokinetic Study of Raltegravir in HIV-Infected Patients With End-Stage Liver Disease: The LIVERAL-ANRS 148 Study

Caroline Barau,1,2 Joséphine Braun,2 Corine Vincent,3 Stéphanie Haim-Boukobza,2,4 Jean-Michel Molina,5 Patrick Miailhes,6 Isabelle Fournier,3 Jean-Pierre Aboulker,3 Daniel Vittecoq,2,7 Jean-Charles Duclos-Vallée,2,8 Anne-Marie Taburet,1,2 and Elina Teicher2,7; for the Agence Nationale de Recherche sur le Sida et les hépatites (ANRS) 148 Study Groupa

1Assistance Publique–Hôpitaux de Paris (AP-HP), Hôpital Bicêtre, Service de Pharmacie Clinique et Pharmacocinétique, Le Kremlin-Bicêtre; 2Département Hospitalo, Universitaire Hepatinov, 3INSERM SC10-US018, and 4AP-HP, Hôpital Paul Brousse, Service de Virologie, Villejuif; 5AP-HP, Hôpital Saint-Louis, Service des Maladies Infectieuses et Tropicales et INSERM U941, Université Paris VII Denis Diderot; 6Hospices Civils de Lyon, Service des Maladies Infectieuses et Tropicales, Hôpital de la Croix-Rousse and INSERM U1052; 7AP-HP, Hôpital Bicêtre, Service de Médecine Interne et Maladies Infectieuses, Le Kremlin-Bicêtre; and 8AP-HP, Hôpital Paul Brousse, Centre Hépato-Biliaire et INSERM UMR-S785 Villejuif, France

Background. The end-stage liver disease and RALtegravir-Agence Nationale de Recherche sur le Sida et les hépatites (LIVERAL-ANRS) 148 study aimed to evaluate the safety, efficacy, and pharmacokinetic parameters of raltegravir (RAL) in human immunodeficiency virus (HIV)–infected patients with end-stage liver disease (ESLD) (substudy 1) and to assess the lack of pharmacokinetic interaction between RAL and the immunosuppressive regimen introduced after liver transplant (substudy 2).

Methods. All patients received 400 mg RAL twice daily plus 2 nucleoside reverse transcriptase inhibitors. Liver function and immunovirological parameters were monitored throughout the study. Serial blood samples were drawn to explore RAL pharmacokinetics. Plasma concentrations of protein unbound, total RAL, and RAL glucuronide were determined by liquid chromatography–tandem mass spectrometry.

Results. Ten patients with ESLD were analyzed in substudy 1. Despite an increased RAL exposure, RAL was well tolerated in all patients and no patient had to stop RAL therapy because of adverse events. Four patients were analyzed in substudy 2. No pharmacokinetic interaction was observed between cyclosporine, mycophenolic acid, and RAL. RAL tolerability was excellent; there were no episodes of acute rejection or opportunistic infection. HIV-RNA levels remained controlled and CD4 cell counts remained stable in all patients throughout the study.

Conclusions. The results of the substudy 1 support RAL administration to patients with ESLD. Substudy 2 assesses the safety, tolerability, and efficacy of RAL therapy in HIV-infected patients after liver transplant. RAL might be recommended as a suitable antiretroviral therapy in HIV-infected patients undergoing liver transplant.

Keywords. end-stage liver disease; HIV; liver transplant; pharmacokinetics; raltegravir.

Raltegravir (RAL) was the first human immunodeficiency virus type 1 (HIV-1) integrase inhibitor to be approved. It is orally administered at a dose of 400 mg twice daily, in combination with other antiretroviral agents. RAL is highly effective and well tolerated, with a favorable safety profile and low potential for drug–drug interactions [1–4]. The pharmacokinetic properties of RAL have been characterized [5]. It is rapidly absorbed, with maximum plasma concentration (Cmax) reached in a median time (Tmax) of about 3 hours in fasting conditions [6]. About 83% of the RAL is bound to plasma proteins, mostly albumin [7], and this drug is metabolized by the UDP-glucuronosyltransferase 1A1 (UGT1A1) isoenzyme [5, 8]. It is
commonly thought that glucuronidation remains unaltered in liver dysfunction. Some investigations have shown that, indeed, this is dependent on the isoenzymes involved. Although UGT1A9, UGT1A1, or UGT2B10 levels appear to be maintained during liver dysfunction, recent investigations evidenced a significant decrease in UGT1A6 [9, 10]. As end-stage liver disease (ESLD) is becoming an increasingly severe problem in HIV-infected patients, with a rise in the demand for liver transplant (LT), studies of the relevance of RAL-based therapy in a context of severe liver disease are crucial. Despite recent advances in the treatment of chronic hepatitis B and hepatitis C, LT remains the ultimate option for the treatment of patients with decompensated liver cirrhosis and can now be performed successfully in eligible HIV-infected patients [11]. In the period immediately following transplant, the immunosuppressive regimen generally includes calcineurin inhibitors, cyclosporine or tacrolimus, mycophenolic acid, and corticosteroids. One major problem is the occurrence of pharmacokinetic interactions between calcineurin inhibitors and many antiretroviral drugs that share the same metabolic pathway through cytochrome P450 3A4 (CYP3A4) [12]. Indeed, protease inhibitors are potent CYP3A4 inhibitors [12], whereas nonnucleoside reverse transcriptase inhibitors are CYP3A4 inducers [13]. RAL is not a CYP3A4 substrate; therefore, using an RAL-based regimen after LT may improve the management of the immunosuppressive treatment after antiretroviral introduction in the posttransplant period.

The aims of this study were to evaluate the safety, efficacy, and pharmacokinetic parameters of RAL in HIV-infected patients with ESLD and to assess the degree of pharmacokinetic interaction between RAL and the immunosuppressive regimen introduced after LT.

**PATIENTS AND METHODS**

**Study Design and Population**

The protocol of the multicenter end-stage LIVER disease and RALtegravir-Agence Nationale de Recherche sur le Sida et les hépatites (LIVERAL-ANRS) 148 study (EudraCT: 2009-014616-36) was reviewed and approved by an institutional review board (CPP-IDFVII, 2009) and competent health authorities. All patients gave written informed consent before participating in the study. For all patients, adverse events were graded according to the ANRS toxicity grading scale for adverse events in adults [14].

Patients were eligible in sub-study 1 if they had ESLD (defined as a Model for End-Stage Liver Disease [MELD] score of ≥15 and/or current or previous history of refractory ascites and/or current or previous history of repeated digestive hemorrhage and/or current or previous history of hepatic encephalopathy); had a plasma HIV RNA load (VL) on antiretroviral therapy <50 copies/mL for at least 6 months (Cobas TaqMan, Roche; limit of quantification 20 copies/mL); and had an HIV strain fully sensitive to at least 2 antiretroviral drugs according to cumulative genotypes carried out on viral RNA together with treatment history and no mutations related to RAL resistance on HIV DNA sequencing at enrollment.

Patients included in sub-study 1 were switched to a combined antiretroviral treatment with 400 mg RAL twice daily and a once-daily fixed dose of tenofovir/emtricitabine or abacavir/ lamivudine. Safety and tolerability were assessed by follow-up medical visits and laboratory measurements at screening (4 weeks before RAL introduction), day 0 (RAL introduction), and month 1 (M1), month 2 (M2), and month 3 (M3). Antiretroviral efficacy was assessed by determining VL and CD4 cell counts at screening, M1, and M3. Liver function, as assessed by the determination of MELD score, was monitored at screening and until M3 after RAL introduction. Blood samples were collected 1 month after RAL introduction before morning drug intake and 1, 2, 3, 5, 7, and 9 hours after intake to assess RAL pharmacokinetic parameters at steady state. Patients were asked to remain in a fasting state for 1 hour after RAL intake.

Liver transplant recipients for viral cirrhosis related to hepatitis C or B or another cause of cirrhosis were included in sub-study 2. The criteria for being registered on the French transplant list include decompensated cirrhosis with liver failure (ascites, prothrombin time <50%, or international normalized ratio >1.5), elevated serum conjugated bilirubin >50 µmol/L, hypoalbuminemia <30 g/L, and symptomatic portal hypertension (gastrointestinal bleeding).

Immunosuppressive treatment, including cyclosporine or tacrolimus, corticosteroids, and mycophenolate mofetil hydrolyzed to mycophenolic acid (MPA), the active moiety, was initiated in patients included in sub-study 2 the next day following LT. Doses were adapted according to the blood concentrations of cyclosporine (target: 100–400 ng/mL) and tacrolimus (target: 5–15 ng/mL) or plasma Area Under the Concentrations versus time curve during a 12-hour interval (AUC0–12) for MPA (target: 30–60 mg × h/L) [15, 16]. All antiretroviral drugs were discontinued on the day of transplant, and a RAL-based regimen associated with a combination of tenofovir/emtricitabine or abacavir/lamivudine was initiated as soon as the results of liver function tests normalized. Safety and tolerability were assessed at day 7 (D7; before RAL introduction), M1 (after RAL introduction), and M2 and M3 posttransplant. VL was measured on D7, M1, and M3. For analyses of RAL pharmacokinetic parameters, blood samples were collected as described for substudy 1, before (D7) and after (M1) RAL introduction, respectively.

**Drug Assays**

Concentrations of calcineurin inhibitors were determined by an immunoenzymatic chemiluminescent microparticle
immunoassay method in the same laboratory (Architect, Abbott). MPA and RAL assays were performed in a centralized laboratory. Plasma concentrations of total and unbound MPA were determined by validated reverse-phase high-performance liquid chromatography methods, after protein precipitation and centrifugation through Centrifree devices (Millipore), respectively [17]. Limits of quantification were 0.1 and 0.025 mg/L, respectively. Plasma concentrations of total RAL, unbound RAL and inactive RAL glucuronide were measured by liquid chromatography–tandem mass spectrometry (LC-MS/MS). Total RAL concentrations were determined after protein precipitation [18]. As we had no access to purified RAL glucuronide, this metabolite was hydrolyzed using β-glucuronidase (Helix pomatia, Sigma) during a 16-hour incubation at 37°C [19].

Values are expressed as median (range). Substudy 1: patients with end-stage liver disease; substudy 2: recipients of liver transplant.

### Table 1. Demographic Characteristics and Blood Parameters of Patients

<table>
<thead>
<tr>
<th>Demographic Parameters</th>
<th>Substudy 1 (n = 10)</th>
<th>Substudy 2 (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screening (n = 10)</td>
<td>M3 (n = 7)‡</td>
</tr>
<tr>
<td>Sex, female/male, No.</td>
<td>3/7</td>
<td>0/4</td>
</tr>
<tr>
<td>Age, y</td>
<td>50 (39–63)</td>
<td>47 (44–52)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>21 (16–28)</td>
<td>22 (18–30)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>60 (47–74)</td>
<td>60 (49–85)</td>
</tr>
<tr>
<td>Blood parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV/HCV coinfection</td>
<td>8/10</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes, cells/μL</td>
<td>763 (530–1640)</td>
<td>907 (520–1100)</td>
</tr>
<tr>
<td>CD4 count, cells/μL</td>
<td>259 (57–604)</td>
<td>260 (120–315)</td>
</tr>
<tr>
<td>CD4 %</td>
<td>25 (14–43)</td>
<td>27 (24–45)</td>
</tr>
<tr>
<td>MELD score</td>
<td>12 (5–26)</td>
<td>8 (3–18)</td>
</tr>
<tr>
<td>Child-Pugh score</td>
<td>10 (6–14)</td>
<td>. . .</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>65 (36–94)</td>
<td>68 (45–77)</td>
</tr>
<tr>
<td>Serum albumin, g/L</td>
<td>28 (22–42)</td>
<td>. . .</td>
</tr>
<tr>
<td>AST, IU/L</td>
<td>74 (25–150)</td>
<td>89 (38–120)</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>43 (6–104)</td>
<td>51 (43–121)</td>
</tr>
<tr>
<td>GGT, IU/L</td>
<td>70 (29–261)</td>
<td>68 (34–191)</td>
</tr>
<tr>
<td>ALP, IU/L</td>
<td>126 (56–273)</td>
<td>109 (52–173)</td>
</tr>
<tr>
<td>Total bilirubin, μmol/L</td>
<td>35 (14–397)</td>
<td>19 (12–32)</td>
</tr>
<tr>
<td>Prothrombin time, %</td>
<td>56 (32–78)</td>
<td>61 (30–80)</td>
</tr>
<tr>
<td>Factor V, %</td>
<td>52 (33–117)</td>
<td>59 (33–139)</td>
</tr>
<tr>
<td>INR</td>
<td>1.55 (1.20–2.59)</td>
<td>1.40 (1.17–2.71)</td>
</tr>
</tbody>
</table>

Values are expressed as median (range). Substudy 1: patients with end-stage liver disease; substudy 2: recipients of liver transplant. Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, γ-glutamyltransferase; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international normalized ratio; M1, month 1; M3, month 3; MELD, Model for End-Stage Liver Disease.

* Two patients were transplanted before the M3 visit, and 1 patient did not take his visit at M3 but rather at M6.
Characteristics of the Study Population
The main demographic characteristics and laboratory parameters are shown in Table 1. Ten patients were analyzed in substudy 1. The causes of ESLD were hepatitis C cirrhosis (8/10), hepatitis B cirrhosis (1/10) and nodular regenerative hyperplasia (1/10). Eight of the 10 patients had a history of ascites before their inclusion, and only 1 patient exhibited reoccurrence of ascites after improvement. Median follow-up was 11 weeks (range, 4–14 weeks).

Five LT recipients were included in substudy 2, of whom 2 also consented to participate in substudy 1. Four were analyzed. The indications for LT were hepatitis B cirrhosis (1/5) and hepatitis C cirrhosis (4/5). Daily doses of cyclosporine and MPA ranged from 175 to 550 mg twice daily and from 500 to 1000 mg twice daily, respectively. No modifications of cyclosporine or MPA dosage were made between D7 and M1. In this substudy, median follow-up was 12 weeks (range, 1–14 weeks).

One patient in substudy 1 and 2 patients in substudy 2 received RAL concomitantly with a proton pump inhibitor. None of the other concomitant medication taken in either substudy was expected to have a clinically meaningful effect on RAL metabolism. Five of the 13 viral transcriptase gene sequences analyzed included resistance-associated mutations (RAMs): 1 each displayed the 41L, 67N, 69D, M184V, and 215Y mutations; 3 displayed the M184V or I RAM; and 1 displayed the 69T/S RAM. None of the 6 integrase gene sequences analyzed presented any RAM likely to confer resistance to RAL.

Pharmacokinetic Parameters of RAL
The median pharmacokinetic parameters for RAL are summarized in Table 2 and are in the same range for both substudies. The concentration of unbound RAL varied considerably between individuals in both populations (Figure 1). Whatever the substudy, the unbound fraction of RAL was stable over the dosing interval and was not correlated with albumin concentration.

In patients with ESLD, median RAL AUC seemed to be unchanged whether measured in the presence or absence of ascites (33 451 [range, 5163–54 830] ng × h/mL, n = 8 or 13 247 and 65 972 ng × h/mL, n = 2). Plasma concentration–time profiles for total RAL and RAL glucuronide were similar (Figure 1). In LT recipients, RAL glucuronide concentrations were slightly higher than total RAL concentrations (Figure 2). The 3 patients who received RAL concomitantly with a proton pump inhibitor had the highest AUC0–9 values for total RAL (65 972, 42 189, and 52 653 ng.h/mL).

Pharmacokinetic Parameters of Mycophenolic Acid and Cyclosporine
All patients in substudy 2 received immunosuppressant therapy including cyclosporine, MPA, and corticosteroids. The median

### Table 2. Pharmacokinetic Parameters of Total and Unbound Raltegravir and Raltegravir Glucuronide in Substudy 1 and Substudy 2

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Substudy 1 (n = 10)</th>
<th>Interpatient CV, %</th>
<th>Substudy 2 (n = 4)</th>
<th>Interpatient CV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total raltegravir</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmin, ng/mL</td>
<td>421 (36–8148)</td>
<td>65</td>
<td>460 (167–1927)</td>
<td>106</td>
</tr>
<tr>
<td>Cmax, ng/mL</td>
<td>8759 (889–16 203)</td>
<td>82</td>
<td>6953 (5454–14 812)</td>
<td>51</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>2.0 (1.0–7.0)</td>
<td>62</td>
<td>2.5 (1.0–4.9)</td>
<td>61</td>
</tr>
<tr>
<td>AUC0–9, ng × h/mL</td>
<td>33 451 (5163–65 972)</td>
<td>95</td>
<td>32 373 (16 230–52 653)</td>
<td>51</td>
</tr>
<tr>
<td><strong>Unbound raltegravir</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmin, ng/mL</td>
<td>81 (11–1314)</td>
<td>83</td>
<td>82 (29–295)</td>
<td>99</td>
</tr>
<tr>
<td>Cmax, ng/mL</td>
<td>1574 (176–2638)</td>
<td>88</td>
<td>866 (831–2576)</td>
<td>67</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>2.0 (1.0–7.0)</td>
<td>62</td>
<td>2.5 (1.0–4.9)</td>
<td>61</td>
</tr>
<tr>
<td>AUC0–9, ng × h/mL</td>
<td>6110 (903–9863)</td>
<td>91</td>
<td>4190 (2533–6737)</td>
<td>42</td>
</tr>
<tr>
<td>Unbound fraction, %</td>
<td>18.6 (12.3–32.3)</td>
<td>17</td>
<td>13.9 (11.8–15.6)</td>
<td>13</td>
</tr>
<tr>
<td><strong>Raltegravir glucuronide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmin, ng/mL</td>
<td>720 (82–18 440)</td>
<td>112</td>
<td>4341 (506–8322)</td>
<td>73</td>
</tr>
<tr>
<td>Cmax, ng/mL</td>
<td>5072 (606–25 378)</td>
<td>71</td>
<td>11 088 (5424–17 567)</td>
<td>55</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>3.0 (2.0–7.2)</td>
<td>47</td>
<td>5.1 (2.0–9.3)</td>
<td>56</td>
</tr>
<tr>
<td>AUC0–9, ng × h/mL</td>
<td>20 801 (4483–163 907)</td>
<td>75</td>
<td>48 762 (35 515–113 696)</td>
<td>57</td>
</tr>
<tr>
<td>Metabolic ratio</td>
<td>0.9 (0.3–2.5)</td>
<td>71</td>
<td>2.1 (0.9–3.1)</td>
<td>49</td>
</tr>
</tbody>
</table>

Values are expressed as median (range).
Abbreviations: AUC0–9, area under the concentration–time curve during a 9-hour time interval; Cmax, concentration of the peak; Cmin, predose concentration; CV, coefficient of variation; Tmax, time to reach concentration peak.
pharmacokinetic parameters for cyclosporine and MPA are summarized in Table 3 and are in the same range between D7 and M1 posttransplant.

Safety and Tolerability
In substudy 1, VL remained <50 copies/mL and median CD4 cell count was 259 cells/µL (range, 57–604 cells/µL) and 260 cells/µL (range, 120–315 cells/µL) at screening and M3, respectively. Median MELD score was 12 (range, 5–26) at screening and 8 (range, 3–18) at M3.

In substudy 2, after a median follow-up of 3 months, 4 of the 5 patients were still alive, with good graft function and no acute rejection or opportunistic infection. One patient died immediately after LT, due to bacterial sepsis without being able to participate in the pharmacokinetic sampling. Viral replication was <50 copies/mL throughout the study, and the median percentages of CD4 cells were 38% (range, 10%–42%) at D7 posttransplant and 22% (range, 11%–25%) at M3 of follow-up.

DISCUSSION
In this study, we determined the pharmacokinetic parameters of RAL in patients with ESLD and in LT recipients. This information is important because the target population for RAL treatment includes HIV/hepatitis C virus (HCV)–coinfected patients with hepatic impairment. Our findings suggest that despite an increased RAL exposure in patients with ESLD, RAL was well tolerated. Our study therefore supports the administration of RAL to patients with ESLD. This study also demonstrated the absence of pharmacokinetic interaction between RAL and cyclosporine and MPA after LT. RAL may therefore be considered a suitable antiretroviral treatment for HIV-infected patients undergoing LT.

RAL Cmin, Cmax, and AUC reported in substudy 1 in patients with ESLD (Cmin range, 36–8148 ng/mL) were higher than those observed in patients with normal liver function (Cmin range, 15–2223 ng/mL) [20]. We confirmed the high variability of RAL parameters, showed by the high interpatient coefficient of variation. This result is in line with previous findings [21]. Many factors potentially impacting the variability of RAL pharmacokinetics have been identified, such as food intake and the coadministration of proton pump inhibitors [6, 22] accounting for the high intersubject variability. In our study, RAL pharmacokinetic parameters were measured in the fasting state, which may account for the higher concentrations reported in subjects with normal liver function and no food restriction [20, 23]. We obtained higher RAL Cmax and AUC values than those reported

![Figure 1](image1.png)

Figure 1. Plasma concentrations of total raltegravir (circles), unbound raltegravir (triangles), and raltegravir glucuronide (squares) in the 10 patients with end-stage liver disease enrolled in substudy 1, one month after raltegravir introduction.

![Figure 2](image2.png)

Figure 2. Plasma concentrations of total raltegravir (circles), unbound raltegravir (triangles), and raltegravir glucuronide (squares) in the 4 surviving liver transplant patients enrolled in substudy 2, one month after raltegravir introduction.

<table>
<thead>
<tr>
<th>Table 3. Pharmacokinetic Parameters of Cyclosporine and Mycophenolic Acid in Substudy 2, at Day 7 and Month 1 After Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacokinetic Parameters</strong></td>
</tr>
<tr>
<td>Total MPA</td>
</tr>
<tr>
<td>Unbound MPA</td>
</tr>
<tr>
<td>Unbound fraction, %</td>
</tr>
<tr>
<td>Cyclosporine</td>
</tr>
</tbody>
</table>

Values are expressed as median (range). Abbreviations: AUC<sub>0–12</sub>, area under the concentration–time curve during a 12-hour time interval; M1, month 1; MPA, mycophenolic acid.
latent enzymes during liver injury [28, 29]. It was demonstrated
lism, particularly in the kidney, or the release or activation of
completely elucidated, but may involve extrahepatic metabo-

In transplant recipients, the range of the RAL metabolic
index was close to that reported in patients with normal liver
function included in the ANRS 139 TRIO study (0.9–3.1 vs
0.4–3.3; C. Barau, personal unpublished work), indicating that
the liver grafts had metabolizing capacity. No interaction was
observed between cyclosporine, MPA, and RAL. Exposure to
cyclosporine and MPA was not modified by the introduction of
RAL, as expected, given the different metabolic pathways of
these molecules. Virological efficacy was maintained in patients
switching from a ritonavir-boosted protease inhibitor regimen
to a regimen based on RAL associated with 2 nucleoside reverse
transcriptase inhibitors, despite the low genetic barrier of
resistance of RAL. We observed 1 case of diabetes mellitus
among the LT recipients, induced by the combination of ste-
roids and immunosuppressive agents. The small decrease in
CD4 cell counts observed following LT could be related to
immunosuppression. One patient, who exhibited leukopenia
probably due to MPA treatment, died immediately after LT
from bacterial sepsis. Cytolysis, cholestasis, and an increase in
bilirubin events after LT were related to the recurrence of
HCV infection on the graft, which represents the main severe
complication after LT for HIV/HCV-coinfected patients. The
absence of clinically relevant drug–drug interactions and the
good tolerance makes RAL a very attractive candidate for HIV
treatment in patients undergoing LT, confirming the findings of
Tricot et al [31].

This study was subject to several limitations. First, although
RAL pharmacokinetic parameters were not directly compared
between the patients and healthy controls, we can compare
pharmacokinetic parameters in ESLD with those observed in
LT patients who have a prompt graft recovery. Second, following
the initiation of this study, Iwamoto et al [22] reported that pro-
ton pump inhibitors induced a 3- to 4-fold increase in RAL
AUC and C_{max} in healthy subjects. However, in HIV-infected
patients, the increase in RAL concentrations was lower than
what was observed in healthy subjects, probably because these
patients often have achlorhydria or hypochlorhydria [6]. In this
study, although high AUC_{0-\infty} values for total RAL were noticed
in the 3 patients taking proton pump inhibitors, the safety pro-
file of RAL was similar overall to that of patients not using such
drugs. Third, this study was conducted in a small number of pa-
ients, but our safety and pharmacokinetic data nevertheless
support the use of RAL in patients with liver disease before
and after LT. Finally, our strategy is applicable only to patients
undergoing very close monitoring that will detect early virolo-
gical failure and prompt a switch to a rescue antiretroviral regi-
men as needed.

In conclusion, despite high exposure, RAL was well tolerated
by patients with ESLD. Our study supports the administration
of RAL to patients with ESLD at the approved dosing. Our re-
results also assess the safety, tolerability, and efficacy of RAL

by Iwamoto et al [24] for patients with moderate hepatic insuffi-
ciency, but our results are consistent with those recently pub-
lished by Hernandez-Novoa et al [25], who demonstrated
higher levels of RAL exposure in patients with advanced cirrhosis,
with no increase in toxicity, in 10 HIV/HCV-coinfected patients.

An increase in the unbound fraction of drugs that normally
bind strongly to albumin has been reported in patients with se-
vere liver disease [26]. In our study, the unbound fraction of
RAL was 18.6% (range, 12.3%–32.3%), consistent with the
mean unbound fraction of 17% previously reported for patients
with normal liver function [5]. The change in unbound RAL
concentration over time seems to parallel that of total RAL con-
centration, indicating a lack of change in protein binding over
the dosing interval. No correlation with albumin concentration
was observed, in contrast to previous findings [7], probably be-
cause all the patients presented hypoalbuminemia, with albu-
min concentrations <35.0 g/L and falling within a narrow
range (23.7–35.0 g/L). We analyzed, for the first time, the phar-
cmakinetiic parameters of RAL glucuronide and RAL meta-

In transplant recipients, the range of the RAL metabolic
index was close to that reported in patients with normal liver
function included in the ANRS 139 TRIO study (0.9
[range, 0.3–2.5] vs 1.2 [range, 0.4–3.3]; C. Barau, personal un-
published work), suggesting weak and not clinically signi-
ficant impairment of liver metabolism of RAL in patients with
ESLD. Indeed, unlike cytochrome-based metabolism, the glucuronida-
tion of various drugs has been shown to be unaffected by severe
liver disease [9,27,28]. The underlying mechanism has not been
completely elucidated, but may involve extrahepatic metabo-
lism, particularly in the kidney, or the release or activation of
latent enzymes during liver injury [28,29]. It was demonstrated
that liver diseases have no significant effect on UGT1A1 protein
levels [10], confirming the little potential for altered gluco-
ronidation of RAL observed in vivo in this study.

RAL was previously demonstrated to be a safe option for
HIV/HCV-coinfected patients with fibrosis stage ≥2 or cirrho-
sis [30]. Our study confirms these results, because despite the
high RAL concentrations observed in the patients with ESLD,
RAL was well tolerated with no aggravation or flare-up of ala-
nine aminotransferase/aspartate aminotransferase activity and
no VL breakthrough. Bilirubin concentration and MELD
score decreased in 4 patients who switched from atazanavir, a
UGT1A1 inhibitor, to RAL. MELD score remained stable
throughout the study, and no clinical events were observed.
No adjustment of the dose of RAL was required in this popula-
tion, and no risk of subtherapeutic concentrations is to be ex-
pected in case of ascites.

In conclusion, despite high exposure, RAL was well tolerated
by patients with ESLD. Our study supports the administration
of RAL to patients with ESLD at the approved dosing. Our re-
results also assess the safety, tolerability, and efficacy of RAL

In transplant recipients, the range of the RAL metabolic
index was close to that reported in patients with normal liver

...
therapy in HIV-infected patients after LT. Moreover, cyclosporine and MPA exposure remained unchanged after the introduction of RAL, avoiding the need to manage drug–drug interactions during the immediate post-LT period. RAL might be recommended as a suitable antiretroviral therapy in HIV-infected patients undergoing LT.

Notes

Acknowledgments. We express our gratitude to all the patients who participated in this study.

Financial support. This trial was conducted with the support of Merck Sharp & Dohme-Chibret.

Potential conflicts of interest. All authors: No reported 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


APPENDIX

The members of LIVERAL-ANRS 148 Study Team were as follows: Chair, E. Teicher; Co-chair, J.-C. Duclos-Vallee; Methodology, J.-P. Aboulker; Project managers, J. Braun and