Coadministration of Atazanavir-Ritonavir and Zinc Sulfate: Impact on Hyperbilirubinemia and Pharmacokinetics

Graeme Moyle,a Laura Else,b Akil Jackson,a David Back,b Manisha H. Yapa,a Natalia Seymour,a Lisa Ringner-Nackter,a Zeenat Karolia,a Brian Gazzard,a Marta Boffitob
St. Stephen’s Centre, Chelsea and Westminster Hospital, London, United Kingdoma; Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, United Kingdomb

Atazanavir (ATV) causes an elevation of unconjugated hyperbilirubinemia (HBR) as a result of UDP glucuronosyltransferase (UGT) 1A1 inhibition. Zinc sulfate (ZnSO₄) reduces unconjugated hyperbilirubinemia in individuals with Gilbert’s syndrome. We assessed the changes in total, conjugated, and unconjugated bilirubin and the effect on ATV pharmacokinetics (PK) after single and 14-day dosing of ZnSO₄. HIV patients, stable on ATV/ritonavir (ATV/r)-containing regimens with a total bilirubin level of >25mmol/liter received 125 mg daily of ZnSO₄ as Solvazinc tablets for 14 days. ATV/r and bilirubin concentrations were measured pre-ATV/r dose and 2, 4, 6, 8, and 24 h post-ATV/r dose; before ZnSO₄ initiation (phase 1), after a single dose (phase 2) and after 14 days (phase 3). Changes in bilirubin and ATV/r concentrations in the absence or presence of ZnSO₄ were evaluated by geometric mean ratios (GMRs) and 90% confidence intervals (CIs; we used phase 1 as a reference). Sixteen male patients completed the study maintaining virologic suppression; ZnSO₄ was well tolerated. Statistically significant declines in total bilirubin Cmax and AUC0–24 of 16 and 17% were seen in phase2 and 20% in phase 3. Although there were no significant changes in conjugated bilirubin, unconjugated bilirubin Cmax and AUC0–24 of were lower (17 and 19%, phase 2; 20 and 23% during phase 3). The ATV GMRs (90% CI) for Ctrough, Cmax, and AUC0–24 were 0.74 (0.62 to 0.89), 0.82 (0.70 to 0.97), and 0.78 (0.70 to 0.88). Intake of ZnSO₄ decreases total and unconjugated bilirubin and causes modest declines in ATV exposure. ZnSO₄ supplementation may be useful in management of ATV-related HBR in selected patients.

Atazanavir (ATV) is a commonly prescribed protease inhibitor (PI) approved for use in combination with other antiretroviral (ARV) agents in naive and treatment-experienced adults with HIV infection (1). ATV is a substrate of cytochrome P450 3A4 (CYP3A4) enzyme and coadministration with low doses of the CYP3A4 inhibitor ritonavir (r) increases ATV concentrations and ensures optimal plasma exposures (2). Most individuals on ATV/r-based regimens receive ATV/r at 300/100 mg once daily.

The most frequent symptomatic adverse events associated to ATV/r intake are scleral icterus and jaundice, leading to discontinuation in <1% of recipients in clinical trials, and the most frequent laboratory abnormality is isolated hyperbilirubinemia (HBR) (3, 4). This is consequent to elevations of unconjugated bilirubin due to inhibition of uridine 5’-diphospho-glucuronosyltransferase (UGT) 1A1 enzyme by ATV and leads to a Gilbert’s-like syndrome (3, 4). ATV absorption is stomach acid dependent; plasma concentrations vary within and between patients and correlate with increases in unconjugated bilirubin (5). Within the hepatocytes, UGT 1A1 is responsible for the conjugation of bilirubin to form the soluble glucuronide, which is then eliminated (6).

The increase in unconjugated HBR caused by ATV intake appears within the first week of treatment and resolves promptly when the drug is discontinued (4). However, although there are an increasing number of available ARVs, HIV-infected individuals may need to continue ATV/r-based ARV treatment because of the need of a PI/r-based therapy (i.e., second-line therapy in the presence of a resistant virus) (1) because of its favorable toxicity profile compared to other agents of the same class (i.e., limited hyperlipidemia) (7) or in case of local policies favoring less costly ARV combinations (8). Therefore, strategies to limit unconjugated bilirubin increases may benefit HIV-infected patients.

Zinc sulfate (ZnSO₄) intake has been investigated in subjects with Gilbert’s syndrome, and it has shown to decrease unconjugated bilirubin levels significantly by inhibiting the enterohepatic cycling of unconjugated bilirubin (9). ZnSO₄ is a mineral used to treat or prevent zinc deficiency and can be purchased over the counter in most Western countries. Notably, although zinc therapy may shorten symptoms of common cold (10), chronic administration leading to zinc excess should be avoided since this can impair immune function and may contribute to other adverse experiences (11, 12).

The aim of the present study was to investigate the impact of ZnSO₄ acute and short-term administration on concentrations of unconjugated bilirubin in HIV-infected individuals with HBR secondary to ATV/r intake. Furthermore, the pharmacokinetics of ATV/r in the presence of ZnSO₄ was studied.

(Some of the results from this study were presented at the Eleventh International Congress on Drug Therapy in HIV Infection, 11 to 15 November 2012, Glasgow, United Kingdom.)

MATERIALS AND METHODS

Subjects. Adult male and nonpregnant, nonlactating female subjects, with confirmed HIV-1 antibody-positive status, were eligible for enrollment if they provided written informed consent and met the following...
criteria: (i) if they were between 18 and 65 years old, (ii) if they had a body mass index (BMI) between 18 and 35 kg/m², and (iii) if they were receiving ongoing treatment with tenofovir, emtricitabine, and ATV/r. Subjects were excluded based on the presence of any active clinically significant disease or AIDS-defining illness; evidence of uncontrolled HIV replication (viral load > 40 copies/ml) or the intake of disallowed concomitant therapies (including the use of zinc supplements for 1 month before screening). Approval for the study was obtained from the Riverside Research Ethics Committee, United Kingdom, and written informed consent was obtained from each subject before study procedures were conducted.

**Study design.** This was a 29-day, open-label, three-phase, randomized, crossover, pharmacokinetic study conducted at the Clinical Trial Unit of the St. Stephen’s Centre, Chelsea, United Kingdom, and Westminster Hospital, London, United Kingdom. The study was conducted in accordance with the Declaration of Helsinki and with the applicable regulatory requirements (EudraCT 2009-018055-16).

Patients underwent a clinical assessment, and routine laboratory investigations were performed at screening and throughout the study period. The safety and tolerability of the study medications were evaluated throughout the study using the NIAID Division of AIDS table for grading the severity of adult and pediatric adverse events to characterize abnormal findings (published December 2004), vital signs, physical examinations, and clinical laboratory investigations.

After successful screening, eligible subjects were instructed to continue atazanavir/ritonavir (ATV/r) for the whole study and underwent a full pharmacokinetic profile to assess ATV/r and total/conjugated bilirubin concentrations over 24 h in the absence of ZnSO₄ intake (day 1). They were then randomized to arm A (ZnSO₄ intake from days 2 to 15 and full pharmacokinetic profile on days 2, following a single dose of ZnSO₄ and 15, following 14 days of ZnSO₄ intake), or arm B (ZnSO₄ intake from days 15 to 28 and full pharmacokinetic profile on days 15, following a single dose of ZnSO₄ and 28, following 14 days of ZnSO₄ intake).

On the pharmacokinetic days, blood samples were drawn pre-ATV/r dose and (after a standard breakfast) 2, 4, 6, 8, and 24 h post dose. On days 2 and 15 for arm A and 15 and 28 for arm B, the ZnSO₄ intake was simultaneous to ATV/r intake.

**Analytical methods.** Plasma ATV and r concentrations were analyzed by liquid chromatography–mass spectrometry (13). The lower limits of quantification were 10 ng/ml for atazanavir and 5 ng/ml for ritonavir. Intra-assay and interassay coefficients of variation at the low-, medium-, and high-quality controls were <12%. Total and conjugated bilirubin levels were determined by Roche/Hitachi Cobas C systems (Roche Diagnostics GmbH, Mannheim, Germany).

**Pharmacokinetic and statistical analysis.** Unconjugated bilirubin values were obtained by subtracting the conjugated value from the total bilirubin value for each sampling time point. The calculated parameters for plasma ATV, r, total bilirubin, conjugated, and unconjugated bilirubin were the concentration measured 24 h after the observed ATV/r dose (C₂₄), the maximum observed concentration (Cₘₐₓ) according to the dose intake, and the area under the concentration–time curve (AUC) from 0 to 24 h. All of the parameters were calculated by using actual blood sampling times and noncompartamental modeling techniques (WinNonlin Phoenix [version 6.1; Pharsight Corp., Mountain View, CA]). Descriptive statistics, including the geometric mean and 90% confidence intervals (CIs), were calculated for all parameters.

Within-subject changes of ATV concentrations and bilirubin levels (measured in the absence of supplemental zinc intake [the reference value] versus in the presence of ZnSO₄) were assessed by calculating the geometric mean ratios (GMRs) and 90% CIs. The CIs were first determined using logarithms of the individual GMR values and then expressed as linear values. The changes in parameters were considered significant when the CIs for the GMR did not exceed 1. The correlation between all measured ATV concentrations and all bilirubin levels was measured following log transformation of the data (since the latter were characterized by a non-normal distribution) by Pearson correlation.

**RESULTS**

**Demographic and clinical characteristics.** Sixteen male patients completed the study. The median (range) age, weight, BMI, and baseline CD4 cell count were: 46 (25 to 51) years, 80 (63 to 90) kg, 25 (18 to 28) kg/m², and 599 (317 to 777) cell/mm³. Twelve individuals were Caucasian, two were black, and two defined themselves as “other.” All individuals maintained an undetectable viral load throughout the study period. The study drugs were well tolerated, and no grade 3 or 4 adverse events were reported.

**Bilirubin concentrations.** Total bilirubin parameters in the absence and presence of ZnSO₄ are illustrated in Table 1. Total bilirubin concentrations are shown in Fig. 1. We observed a decline in total bilirubin Cₘₐₓ and AUC both after single (GMRs [90% CIs]) of 0.84 [0.77 to 0.92] and 0.83 [0.75 to 0.93], respectively) and multiple (GMRs [90% CIs]) of 0.80 [0.72 to 0.91] and 0.80 [0.71 to 0.91], respectively) doses of ZnSO₄.

Although no significant changes in conjugated bilirubin were observed (data not shown), a 28% decline in unconjugated bilirubin C₂₄ was observed after 14 days of ZnSO₄ intake. A decline in unconjugated Cₘₐₓ and AUC both after single (GMRs [90% CIs]) of 0.83 [0.75 to 0.92] and 0.81 [0.72 to 0.92], respectively) and multiple (GMRs [90% CIs]) of 0.80 [0.70 to 0.92] and 0.77 [0.66 to 0.80] doses of ZnSO₄. **TABLE 1** Total and unconjugated bilirubin parameters measured during ATV/r intake in the absence or presence of single and multiple (14 days) doses of zinc sulfate (ZnSO₄) (20). | Parameter | GM (90% CI) | GMR (90% CI) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C₂₄ (μmol/liter)</td>
<td>31 (28–38)</td>
<td>26 (24–32)</td>
</tr>
<tr>
<td>Cₘₐₓ (μmol/liter)</td>
<td>56 (51–64)</td>
<td>47 (43–54)</td>
</tr>
<tr>
<td>AUC₂₄–₂₄ (μmol - h/liter)</td>
<td>1,074 (983–1,248)</td>
<td>896 (817–1,055)</td>
</tr>
<tr>
<td>Unconjugated bilirubin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C₂₄ (μmol/liter)</td>
<td>24 (22–31)</td>
<td>18 (18–26)</td>
</tr>
<tr>
<td>Cₘₐₓ (μmol/liter)</td>
<td>47 (42–55)</td>
<td>39 (35–46)</td>
</tr>
<tr>
<td>AUC₂₄–₂₄ (μmol - h/liter)</td>
<td>887 (803–1,061)</td>
<td>721 (655–872)</td>
</tr>
</tbody>
</table>

**a** C₂₄, bilirubin concentration measured 24 h after atazanavir (without or with ZnSO₄); Cₘₐₓ, maximum bilirubin concentration measured 24 h after atazanavir (without or with ZnSO₄) intake; AUC₂₄–₂₄, AUC exposure to bilirubin measured over 24 h after atazanavir (without or with ZnSO₄) intake; GM, geometric mean; GMR, geometric mean ratio; CI, confidence interval.

**GM and GMR (90% CI)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single dose</th>
<th>Multiple dose</th>
<th>Single dose</th>
<th>Multiple dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ZnSO₄</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C₂₄ (μmol/liter)</td>
<td>31 (28–38)</td>
<td>26 (24–32)</td>
<td>26 (23–32)</td>
<td>0.85 (0.71–1.02)</td>
</tr>
<tr>
<td>Cₘₐₓ (μmol/liter)</td>
<td>56 (51–64)</td>
<td>47 (43–54)</td>
<td>45 (41–53)</td>
<td>0.84 (0.77–0.92)</td>
</tr>
<tr>
<td>AUC₂₄–₂₄ (μmol - h/liter)</td>
<td>1,074 (983–1,248)</td>
<td>896 (817–1,055)</td>
<td>864 (782–1,032)</td>
<td>0.83 (0.75–0.93)</td>
</tr>
<tr>
<td>Single dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C₂₄ (μmol/liter)</td>
<td>24 (22–31)</td>
<td>18 (18–26)</td>
<td>17 (16–25)</td>
<td>0.76 (0.55–1.04)</td>
</tr>
<tr>
<td>Cₘₐₓ (μmol/liter)</td>
<td>47 (42–55)</td>
<td>39 (35–46)</td>
<td>37 (34–45)</td>
<td>0.83 (0.75–0.92)</td>
</tr>
<tr>
<td>AUC₂₄–₂₄ (μmol - h/liter)</td>
<td>887 (803–1,061)</td>
<td>721 (655–872)</td>
<td>684 (615–856)</td>
<td>0.81 (0.72–0.92)</td>
</tr>
</tbody>
</table>
ZnSO₄ may affect ATV/r absorption.

and ritonavir concentrations was also observed, suggesting that leads to a decrease in both total and unconjugated bilirubin concentrations in subjects with Gilbert’s syndrome. The authors of that suggested a role for zinc in inhibiting the enterohepatic circulation of unconjugated bilirubin and therefore discussed the potential usefulness of ZnSO₄ in the treatment of different conditions associated with hyperbilirubinemia (9).

Our data, showing an average 20% reduction in bilirubin due to ZnSO₄, would support this theory. However, the chronic use of ZnSO₄ in patients without zinc depletion requires further evaluation to ensure the lack of unwanted side effects (11, 12). Furthermore, we observed an effect of zinc intake on the pharmacokinetics of ATV/r. This is unlikely to be due to a metabolic drug interaction mechanism. Interestingly, ritonavir Cmax was decreased by ca. 20% by ZnSO₄, suggesting a role of the latter in affecting ritonavir absorption. Zinc was already shown to affect ciprofloxacin exposure and cause a similar decrease (20%) in its absorption (16). Importantly, the chelating effect of zinc that leads to the lower ciprofloxacin exposures is minimized by separating the doses of zinc and ciprofloxacin by at least 2 h. However, in our study ZnSO₄ and ATV/r were administered simultaneously. This suggests that the chelating effect of zinc may be extended to lipophilic drugs in the gastrointestinal tract, causing the formation of complexes between the salt substance and the therapeutic drug (in this case ATV or r), and limiting the absorption of the latter. Further study is needed to understand if the benefit of zinc on bilirubin levels can be observed without a parallel impact on ATV concentrations.

ATV absorption seemed to be less affected after a single dose administration of ZnSO₄, but Cmax was decreased by 18% after 14 days of ZnSO₄ intake. ATV total exposure and C_\text{trough} were also decreased by 18 and 26%, respectively. Whether the effect on ATV PK was due to ZnSO₄ intake per se or secondary to the decrease in r absorption is unclear. When looking at the correlation between ATV concentrations and bilirubin, this seems stronger in the presence of zinc without a parallel impact on ATV concentrations.

Because of the need for lifelong ARV intake, strategies on how to manage ARV therapy-related adverse effects are often investigated in order to improve the quality of life for HIV-infected individuals. Unconjugated HBR is the most commonly described laboratory abnormality associated with ATV and ATV/r intake, occasionally leading to icterus, jaundice, and treatment discontinuation (4). In our study, 14-day intake of ZnSO₄ has shown to decrease unconjugated bilirubin exposure measured over 24 h by 23%. This is probably a consequence of ZnSO₄ chelating unconjugated bilirubin after biliary elimination (15).

A previous study showed that acute and chronic administration of oral ZnSO₄ is able to decrease unconjugated bilirubin concentrations in subjects with Gilbert’s syndrome. The authors of that suggested a role for zinc in inhibiting the enterohepatic circulation of unconjugated bilirubin and therefore discussed the potential usefulness of ZnSO₄ in the treatment of different conditions associated with hyperbilirubinemia (9).

Our data, showing an average 20% reduction in bilirubin due to ZnSO₄, would support this theory. However, the chronic use of ZnSO₄ in patients without zinc depletion requires further evaluation to ensure the lack of unwanted side effects (11, 12). Furthermore, we observed an effect of zinc intake on the pharmacokinetics of ATV/r. This is unlikely to be due to a metabolic drug interaction mechanism. Interestingly, ritonavir Cmax was decreased by ca. 20% by ZnSO₄, suggesting a role of the latter in affecting ritonavir absorption. Zinc was already shown to affect ciprofloxacin exposure and cause a similar decrease (20%) in its absorption (16). Importantly, the chelating effect of zinc that leads to the lower ciprofloxacin exposures is minimized by separating the doses of zinc and ciprofloxacin by at least 2 h. However, in our study ZnSO₄ and ATV/r were administered simultaneously. This suggests that the chelating effect of zinc may be extended to lipophilic drugs in the gastrointestinal tract, causing the formation of complexes between the salt substance and the therapeutic drug (in this case ATV or r), and limiting the absorption of the latter. Further study is needed to understand if the benefit of zinc on bilirubin levels can be observed without a parallel impact on ATV concentrations.

ATV absorption seemed to be less affected after a single dose administration of ZnSO₄, but Cmax was decreased by 18% after 14 days of ZnSO₄ intake. ATV total exposure and C_\text{trough} were also decreased by 18 and 26%, respectively. Whether the effect on ATV PK was due to ZnSO₄ intake per se or secondary to the decrease in r absorption is unclear. When looking at the correlation between ATV concentrations and bilirubin, this seems stronger in the presence of zinc without a parallel impact on ATV concentrations.

The administration of both single and multiple doses of ZnSO₄ to HIV-infected individuals stable on ATV/r-based ARV therapy leads to a decrease in both total and unconjugated bilirubin consistent with data in Gilbert’s syndrome. A modest decrease in ATV and ritonavir concentrations was also observed, suggesting that ZnSO₄ may affect ATV/r absorption.

Because of the need for lifelong ARV intake, strategies on how to manage ARV therapy-related adverse effects are often investigated in order to improve the quality of life for HIV-infected individuals. Unconjugated HBR is the most commonly described laboratory abnormality associated with ATV and ATV/r intake, occasionally leading to icterus, jaundice, and treatment discontinuation (4). In our study, 14-day intake of ZnSO₄ has shown to decrease unconjugated bilirubin exposure measured over 24 h by 23%. This is probably a consequence of ZnSO₄ chelating unconjugated bilirubin after biliary elimination (15).

A previous study showed that acute and chronic administration of oral ZnSO₄ is able to decrease unconjugated bilirubin concentrations in subjects with Gilbert’s syndrome. The authors of that suggested a role for zinc in inhibiting the enterohepatic circulation of unconjugated bilirubin and therefore discussed the potential usefulness of ZnSO₄ in the treatment of different conditions associated with hyperbilirubinemia (9).

Our data, showing an average 20% reduction in bilirubin due to ZnSO₄, would support this theory. However, the chronic use of ZnSO₄ in patients without zinc depletion requires further evaluation to ensure the lack of unwanted side effects (11, 12). Furthermore, we observed an effect of zinc intake on the pharmacokinetics of ATV/r. This is unlikely to be due to a metabolic drug interaction mechanism. Interestingly, ritonavir Cmax was decreased by ca. 20% by ZnSO₄, suggesting a role of the latter in affecting ritonavir absorption. Zinc was already shown to affect ciprofloxacin exposure and cause a similar decrease (20%) in its absorption (16). Importantly, the chelating effect of zinc that leads to the lower ciprofloxacin exposures is minimized by separating the doses of zinc and ciprofloxacin by at least 2 h. However, in our study ZnSO₄ and ATV/r were administered simultaneously. This suggests that the chelating effect of zinc may be extended to lipophilic drugs in the gastrointestinal tract, causing the formation of complexes between the salt substance and the therapeutic drug (in this case ATV or r), and limiting the absorption of the latter. Further study is needed to understand if the benefit of zinc on bilirubin levels can be observed without a parallel impact on ATV concentrations.

ATV absorption seemed to be less affected after a single dose administration of ZnSO₄, but Cmax was decreased by 18% after 14 days of ZnSO₄ intake. ATV total exposure and C_\text{trough} were also decreased by 18 and 26%, respectively. Whether the effect on ATV PK was due to ZnSO₄ intake per se or secondary to the decrease in r absorption is unclear. When looking at the correlation between ATV concentrations and bilirubin, this seems stronger in the presence of zinc without a parallel impact on ATV concentrations.

The administration of both single and multiple doses of ZnSO₄ to HIV-infected individuals stable on ATV/r-based ARV therapy leads to a decrease in both total and unconjugated bilirubin consistent with data in Gilbert’s syndrome. A modest decrease in ATV and ritonavir concentrations was also observed, suggesting that ZnSO₄ may affect ATV/r absorption.

**TABLE 2** Pharmacokinetic parameters of ATV and ritonavir measured in the absence or presence of ZnSO₄ (zinc sulfate, single and multiple dose)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GM (90% CI)</th>
<th>Single dose</th>
<th>Multiple dose</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATv</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{max}</td>
<td>538 (485–842)</td>
<td>454 (419–598)</td>
<td>400 (377–532)</td>
<td>0.84 (0.67–1.06)</td>
</tr>
<tr>
<td>AUC_{0–24} (ng · h/ml)</td>
<td>35,340 (31,603–46,551)</td>
<td>31,014 (28,475–37,687)</td>
<td>27,726 (25,770–34,331)</td>
<td>0.88 (0.77–1.01)</td>
</tr>
</tbody>
</table>

| RTV       |             |             |               |              |
| C_{max}   | 46 (41–80) | 43 (38–67) | 39 (35–64) | 0.93 (0.78–1.12) |
| AUC_{0–24} (ng · h/ml) | 8,702 (7,980–12,178) | 7,341 (6,777–9,820) | 7,312 (6,526–9,847) | 0.84 (0.77–0.92) |

**a** ATV, atazanavir; C_{max}, atazanavir/ritonavir concentration measured 24 h after drug intake; C_{0–24}, maximum concentration measured over 24 h after atazanavir/ritonavir intake; AUC, area under the curve; GM, geometric mean; GMR, geometric mean ratio; CI, confidence interval.
ence of ZnSO₄, suggesting that ZnSO₄ may drive a parallel reduction in both ATV and bilirubin.

Importantly, all individuals, with the exception of one patient, maintained concentrations above the suggested MEC of ATV of 150 ng/ml (14) throughout the study. This patient had lower than expected ATV concentrations both in the presence and in the absence of ZnSO₄. Whether the limited decrease in ATV exposure is significant in HIV-infected individuals long term, especially in those with an extensive history of ARV intake and limited future treatment options due to infection by resistant viruses, remains unclear.

Furthermore, one of the limitations of our study was that we investigated the effect of ZnSO₄ intake over a short period of 14 days only. Therefore, data on the impact of chronic ZnSO₄ intake are warranted. We have not measured the plasma exposure of the other components of the ARV regimen (the NRTIs tenofovir and emtricitabine), since it is unlikely that zinc intake affects their efficacy, because the efficacy of these hydrophilic prodrugs is determined by their intracellular anabolite concentrations (14). The long-term use of metal ions known to bind to the bile and cholate drugs in the gastrointestinal tract to form complexes that are poorly absorbed should be undertaken with caution, and its benefits carefully weighed against its risks.

In conclusion, this is the first study to investigate a novel potential means of managing ATV-associated HBR in HIV-infected individuals. We observed a meaningful decrease in unconjugated and total bilirubin following ZnSO₄ intake and a limited decrease in ATV/r plasma exposure. ZnSO₄ supplementation may present a useful tool in the short-term management of ATV-related HBR in selected patients.

ACKNOWLEDGMENTS

We thank the St. Stephen’s AIDS Trust Research Team for their hard work and the volunteers who took part in the study.

A.J., G.M., D.B., B.G., and M.B. received travel and research grants from and have been advisers for Tibotec, Roche, Pfizer, GlaxoSmithKline, Bristol-Myers Squibb, Merck Sharp & Dohme, Abbott, and Boehringer Ingelheim.

This study was supported in part by a research grant from Bristol-Myers-Squibb. Funding support was also provided by the St. Stephen’s AIDS Trust.

REFERENCES


