

A Randomized Study of Pharmacokinetics, Efficacy, and Safety of 2 Raltegravir Plus Atazanavir Strategies in ART-Treated Adults

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Background: New antiretroviral drug classes provide opportunities to explore novel regimens.

Methods: HIV+ adults (<50 copies/mL) receiving atazanavir (ATV) were randomized to raltegravir (RAL) 400 mg + ATV 300 mg twice daily (q12h) for 4 weeks followed by RAL 800 mg + ATV/ritonavir 300/100 mg once daily (q24h) for 4 weeks or vice versa. Validated assays quantitated RAL and ATV plasma concentrations. Primary endpoint was geometric mean ratio (GMR) of ATV minimum concentration (C_{min}) for q24h/q12h. Equivalence was 90% confidence interval (CI) of GMR lying between 0.80 and 1.25. Participants could consent to a total 48-week follow-up.

Results: Twenty-five men, mean age 45 (range, 35–57) years, were evaluated. ATV and RAL demonstrated considerable pharmacokinetic variability. There was no period or sequence effect for

pharmacokinetic parameters ($P > 0.1$ all measures). Ninety percent CIs of ATV GMR C_{min} [1.30 (90% CI: 1.08 to 1.58)] and RAL GMR C_{min} [0.48 (90% CI: 0.31 to 0.75)] demonstrated nonequivalence. Seventy-six percent consented to follow-up. There were no serious adverse events and no discontinuations due to adverse events over 48 weeks; HIV RNA remained undetectable.

Conclusions: In virologically suppressed adults, regimens comprising ATV plus RAL were efficacious and safe. ATV q12h troughs were lower than ritonavir-boosted atazanavir q24h; RAL q24h troughs were lower than q12h.

Key Words: HIV, raltegravir, atazanavir, antiretroviral therapy

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Conflicts of Interest: M. A. Boyd is on the board of Merck and a past board member for BMS. S. Emery has received research grants from BMS and Merck. D. A. Cooper has received honoraria for serving on advisory boards, speaker's fees, and funding for clinical research from BMS and Merck. S. L. Pett has received consultancy fees from Merck for education modules and travel expenses for education meetings.

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Author contributions: D. Carey participated in study design, study initiation, monitoring, and coordination; oversaw data monitoring; and drafted the article. S. L. Pett and M. Bloch participated in study design, patient enrollment, and article preparation. H. Wand undertook the statistical analyses and participated in article preparation. K. Beileiter and K. MacRae participated in patient enrollment and article preparation. M. A. Boyd participated in study design and article preparation. S. Emery participated in study design, overview of the project, analysis, and article preparation. D. A. Cooper conceived the study, participated in study design, patient enrollment, and article preparation.

No part of these data has been presented previously.

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INTRODUCTION

Antiretroviral therapy (ART)-related adverse effects and poor tolerability can complicate clinical management and compromise treatment benefits.^{1–6} The availability of new drug classes provides an opportunity to explore alternative therapeutic strategies. Raltegravir (RAL), an HIV-1 integrase strand transfer inhibitor, has demonstrated efficacy in both ART-naïve^{7,8} and ART-experienced populations.^{9,10} RAL is metabolized principally by uridine diphosphate–glucuronosyltransferase (UGT) 1A1–mediated glucuronidation and is not a cytochrome P450 (CYP) substrate.¹¹ RAL is a P-glycoprotein (P-gp) substrate but does not induce or inhibit CYP3A or other major CYP or UGT enzymes or P-gp.¹²

Atazanavir (ATV) and ritonavir-boosted atazanavir (ATV/RTV) have proven efficacy in treatment-naïve and treatment-experienced individuals.^{13–16} ATV is metabolized by CYP enzymes, predominantly CYP3A4, and an inhibitor of CYP3A and UGT1A1.¹⁷ Although ritonavir (RTV) coadministration increases ATV exposure,¹⁷ benefits may be counterbalanced by an increased risk of dyslipidemia.^{18,19} Therefore, novel regimens and/or dosing strategies that could increase ATV exposure without RTV boosting are attractive. A regimen comprising RAL plus ATV provides an attractive option given the favorable toxicity and tolerability profile of both agents.^{7,9,14,15} Healthy volunteer studies indicate that RAL and ATV coadministration increases RAL exposure consistent with UGT1A1 inhibition.^{20,21} Data from HIV-infected individuals who administered this combination confirm healthy

volunteer findings,^{22–24} indicating a clinically unimportant interaction without requirement for dosage adjustment.

Preliminary pharmacokinetic, safety, and tolerability data are important prerequisites to conducting adequately powered randomized trials of novel regimens. Hence, we conducted a randomized, crossover, open-label study to examine the pharmacokinetics, safety, and efficacy of 2 dosing strategies of RAL plus ATV in virologically suppressed HIV-infected adults receiving an ATV-containing regimen. The primary objective was to compare mean steady-state ATV trough plasma concentrations for the strategies. Other endpoints included steady-state ATV and RAL pharmacokinetic parameters, safety, and tolerability and short-term and long-term virologic efficacy. Optional components investigated steady-state ATV and RAL concentrations in cerebrospinal fluid (CSF) and seminal plasma.

MATERIALS AND METHODS

Participants

Participants were recruited at 2 clinical (1 primary care; 1 hospital outpatient) sites in Sydney, Australia. Eligibility included documented HIV-1 infection, age ≥ 18 years, and HIV RNA ≤ 50 copies per milliliter for ≥ 24 weeks on an unchanged ATV-containing regimen. Exclusion criteria included chronic active hepatitis B, any serious medical condition requiring hospitalization, malabsorption syndrome, current excessive alcohol or illicit substance use, breastfeeding, immunomodulating and other agents contraindicated for use with RAL or ATV, prior clinical or virologic failure on a protease inhibitor-containing regimen, any primary resistance mutation in the HIV-1 protease gene,²⁵ serum transaminases and bilirubin greater >5 times the upper limit of normal, hemoglobin ≤ 85 g/L, platelet count $\leq 50,000$ cells per milliliter, and neutrophil count <750 cells per milliliter.

All participants provided written informed consent after approval by the local human research ethics committee.

Study Design

This was a randomized, crossover, open-label study of 2 consecutive dosing strategies of RAL and ATV. Eligible patients were randomized in a 1:1 ratio to receive RAL 400 mg plus ATV 300 mg twice daily (q12h) for 4 weeks followed by RAL 800 mg plus ATV 300 mg plus RTV 100 mg once daily (q24h) (in the morning) for 4 weeks or vice versa. Randomization, using a RANUNI function, was performed by a single statistician at the Kirby Institute, Sydney, Australia, and stratified by current RTV boosting. Detailed pharmacokinetic visits were performed at the completion of each 4 weeks (28–35 days) of therapy. There was no washout period between strategies. Regimens did not include a nucleoside backbone. After the second pharmacokinetic/safety assessment, participants either continued a study regimen or recommenced pre-study therapy. Participants continuing a study regimen could consent to ongoing follow-up with visits at weeks 24 and 48 to assess long-term efficacy and safety.

Before pharmacokinetic assessments, participants completed 3-day medication diaries and abstained from alcohol for 24 hours; those with less than maximal adherence did

not participate. Participants presented after an overnight fast (minimum 10 hours) and received a standard breakfast (2562 kJ, 98 g carbohydrate, 14.5 g protein, and 16.5 g fat) after which study drugs were administered with 250 mL of water. Further food and fluid were prohibited for 1 hour. Serial blood samples were collected pre dose and 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours post dose for the q12h regimen and pre dose and 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, and 24 hours post dose for q24h for drug concentration assessment.

The study comprised 2 optional components, CSF and semen collection, designed to examine steady-state drug concentrations in these compartments. Participation involved separate written informed consent, and procedures were undertaken after day 14 of the q12h regimen. The CSF component involved a lumbar puncture for collection of a single CSF sample; a paired plasma sample was also collected. Participants in the seminal fluid component abstained from sexual activity for 72 hours before collection of single semen samples and paired plasma samples.

Analytical and Pharmacokinetic Measurements

Serial blood samples were collected into EDTA tubes. Plasma was separated by centrifugation within 4 hours of blood collection and stored at -20°C until analysis at a laboratory participating in an external quality control program for antiretroviral drug therapy monitoring.²⁶ CSF and seminal plasma were stored at -20°C until analysis. ATV and RTV plasma concentrations were determined using a validated high-performance liquid chromatography (HPLC) assay.²⁷ The method was adapted for analysis of ATV concentrations in seminal plasma.²⁸ The lower limit of quantification (50 ng/mL) of the assay was lowered and validated to 10 ng/mL for determination of ATV levels in CSF and semen.

RAL plasma, semen, and CSF concentrations were quantified using a validated HPLC assay. Plasma (0.5 mL), standards, and quality control samples were acidified with 0.2 M ammonium acetate (200 μL ; pH 4.0) and extracted with 6 mL hexane:dichloromethane (1:1 vol/vol). After mixing and centrifugation, the organic solvent was evaporated to dryness and the residue resuspended in mobile phase (200 μL acetonitrile: 25 mM sodium phosphate buffer pH 3.4; 42:58 vol/vol). The resuspended mobile phase (50 μL) was injected onto the HPLC. Separation was performed on a Zorbax Cyano column (150 \times 4.6 mm, 5- μm particle size) with fluorescence detection at 315 nm (excitation) and 430 nm (emission). RAL calibration standards ranged from 10 to 3000 ng/mL with lower quantitation limit of 10 ng/mL. Precision was better than 11% relative standard deviation and accuracy within 4% of expected assay values.

Pharmacokinetic parameters were calculated using STATA 9.2. Parameters included plasma concentration at 12 hours ($C_{12\text{h}}$) and area under the concentration–time curve from 0 to 12 hours (AUC_{0-12}) for q12h, plasma concentration at 24 hours ($C_{24\text{h}}$), and area under the concentration–time curve from 0 to 24 hours (AUC_{0-24}) for q24h. RAL, ATV, and RTV maximal plasma concentration (C_{max}) and time to maximal plasma concentration (T_{max}) were calculated. AUC_{0-12}

and AUC_{0-24} values were calculated using the linear trapezoidal method. Values for C_{12h} and C_{24h} were assessed from concentrations determined for nominal sampling times at 12 and 24 hours post dose, respectively. Concentrations below the limit of quantification in CSF and semen, that is, <10 ng/mL, were replaced according to the following rules: no chromatographic peak detected, value = 0; chromatographic peak detected, value = 5 ng/mL.

HIV-1 RNA in plasma, CSF, and semen were measured using Roche 1.5 real-time polymerase chain reaction (PCR); lower detection limits were 50 copies per milliliter for plasma and CSF and 400 copies per milliliter for semen.

Assessments

Demographic characteristics, previous ART, and use of lipid-lowering and antidiabetic agents were recorded at screening. Participants were seen at weeks 0, 4, and 8. Safety assessments included clinical adverse events (AEs), physical examination, concomitant medication use, full blood count, biochemistry (electrolytes, urea, creatinine, creatinine kinase, amylase, and liver enzymes), fasting lipid and glycemic parameters, $CD4^+$ lymphocyte count, and plasma HIV RNA. Height was measured at baseline, and weight was recorded at all visits.

CSF component assessments included concentrations of albumin and HIV RNA in CSF and albumin concentration in plasma. Seminal fluid component assessments included HIV RNA in semen and urine PCR for *Chlamydia trachomatis* and *Neisseria gonorrhoea*. All testing was performed at one laboratory.

Statistical Analyses

Analyses were performed when all randomized participants had completed week 8 or had permanently withdrawn from follow-up. Baseline characteristics were summarized without formal between-group comparison. Pharmacokinetic parameter analysis was conducted separately for ATV and RAL by strategy. C_{12h} and C_{24h} values were renamed C_{min} to enable q12h and q24h comparison. Parameters C_{min} , C_{max} , AUC_{0-12} , and AUC_{0-24} were natural log transformed before analysis. Two-sided 90% confidence intervals (CIs) were constructed on the natural log scale and, apart from T_{max} , were based on an analysis of variance model with treatment as a fixed effect and participant as a random effect with compound systematic variance structure assumed. CIs were exponentiated before reporting. Parameters for drugs in each strategy were presented by separate listings and descriptive summary statistics.

Between-strategy mean difference in parameters was evaluated by calculating the geometric mean ratio (GMR). For this, AUC_{0-12} values were doubled to provide AUC_{0-24} . CIs for C_{min} , C_{max} , and AUC_{0-24} GMRs were back transformed; values were not rounded off. Changes in parameters were considered significant when GMR 90% CI did not cross 1. Equivalence was assessed as the 90% CIs of C_{min} GMR contained within the range 0.80–1.25.²⁹ Interindividual pharmacokinetic variability was expressed as the coefficient of variation [(SD/mean) \times 100]. Changes in interindividual variability between

strategies were assessed using analysis of variance. Mean plasma concentration–time curves were constructed for both dosages of RAL and ATV.

Secondary endpoints were analyzed on an intention-to-treat basis with a last value carried forward approach for participants lost to follow-up. Fasting lipid and glycemic parameters, $CD4^+$ counts, and plasma HIV RNA were analyzed using time-weighted change from baseline to week 8 and treatment arms compared using Kruskal–Wallis rank sum test. Mean change from baseline to weeks 4 and 8 was compared by strategy using *t* test for difference between means. Serious AEs, grade 3 or 4 clinical AEs, all AEs attributable to study treatment, and any AE leading to premature treatment cessation were summarized at each visit, overall and by strategy. *P* values were not adjusted for multiple comparisons. Plasma HIV RNA and $CD4^+$ counts at weeks 24 and 48 were summarized for participants continuing a study regimen after week 8.

Analysis of CSF and semen components was exploratory. ATV and RAL concentrations in CSF and semen were investigated as correlates with the concentration in matched plasma samples.

RESULTS

Participant Disposition

Twenty-six men were screened and randomized. One participant withdrew consent (patient choice) after randomization and was excluded from analysis. Twenty-five completed week 4 and 8 visits and were included in the final analysis. Participants had mean age 45 years (range 35–57 years), mean weight 76.7 ± 11.7 kg (Table 1). Median ATV therapy duration was 4.0 (interquartile range, 1.4–5.2) years; 21 (84%) participants were receiving ATV/RTV at baseline. All participants were RAL naive with undetectable (<50 copies/mL) plasma HIV RNA; 7 were receiving lipid-lowering therapy. Twelve participants were randomized to the q12h strategy and the remainder to q24h.

Pharmacokinetics

Mean steady-state plasma concentration–time profiles are shown in Figure 1. Pharmacokinetic parameters are summarized in Table 2. There was no period or sequence effect for any ATV parameter (AUC_{0-24} , $P = 0.25$; C_{max} , $P = 0.46$; C_{min} , $P = 0.91$; T_{max} , $P = 0.84$) or RAL parameter (AUC_{0-24} , $P = 0.12$; C_{max} , $P = 0.35$; C_{min} , $P = 0.19$; T_{max} , $P = 0.47$). Both ATV and RAL demonstrated considerable pharmacokinetic variability (Table 2). The 90% CIs of C_{min} GMR (q24h/q12h) for both ATV and RAL were outside the pre-specified equivalence interval of 0.80–1.25 [1.30 (90% CI: 1.08 to 1.58) and 0.48 (90% CI: 0.31 to 0.75), respectively], demonstrating nonequivalence between q12h and q24h dosages. We observed significant between-strategy differences for ATV AUC_{0-24} [GMR 0.76 (90% CI: 0.59 to 0.98)] and RAL C_{max} [GMR 1.99 (90% CI: 1.50 to 2.63)]. RTV pharmacokinetic parameters are summarized in Table 2; there was no period effect for any parameter (AUC_{0-12} , $P = 0.10$; C_{min} , $P = 0.31$; C_{max} , $P = 0.45$; T_{max} , $P = 0.86$).

TABLE 1. Participant Baseline Characteristics

Characteristics	Value
Age, mean (range), y	45 (35–57)
Gender (male)	25 (100)
White race	25 (100)
Body mass index, kg/m ² *	24.7 (3.3)
CDC category	
A	13 (52)
B	11 (44)
HIV RNA, % <50 copies/mL	100
CD4 ⁺ lymphocyte count, cells/mm ³ *	554 (247)
Total duration ART, y†	9.0 (3.3–12.7)
Duration ATV therapy, y†	4.0 (1.4–5.2)
Triglycerides, mmol/L*	1.8 (1.1)
Total cholesterol, mmol/L*	4.7 (1.0)
LDL cholesterol, mmol/L*	2.9 (0.8)
HDL cholesterol, mmol/L*	1.2 (0.2)
Serum bilirubin, μmol/L*	37.0 (21.0)

Data are n (%) unless otherwise stated.

*Values are mean (SD).

†Median (interquartile range).

CDC, Centers for Disease Control and Prevention; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Safety

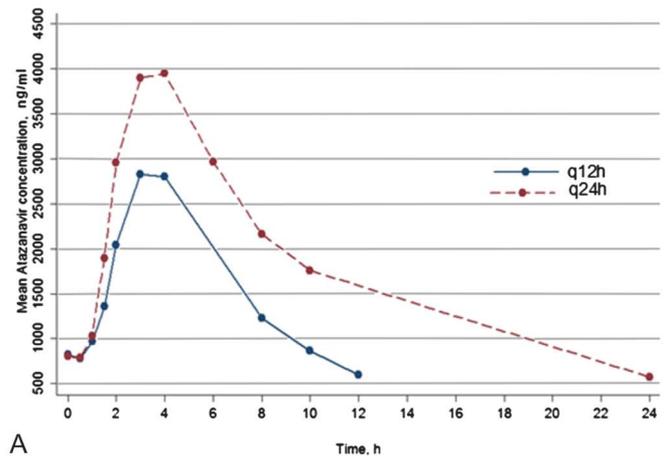
There were no serious AEs during the study. Regimens were well tolerated, and there were no study discontinuations due to AEs. Two participants experienced grade 4 hyperbilirubinemia, one during q12h and the other during q24h. There was no jaundice or scleral icterus. We found no association between change from baseline in total bilirubin and ATV AUC_{0–24} ($P = 0.65$). Four participants experienced mild transaminase elevations, 3 during the q12h strategy and one during q24h. Triglycerides increased significantly from baseline to week 4 in participants randomized to the q24h strategy (mean change, 0.63 mmol/L; $P = 0.034$). There were no on-study changes to lipid-lowering therapy.

Efficacy

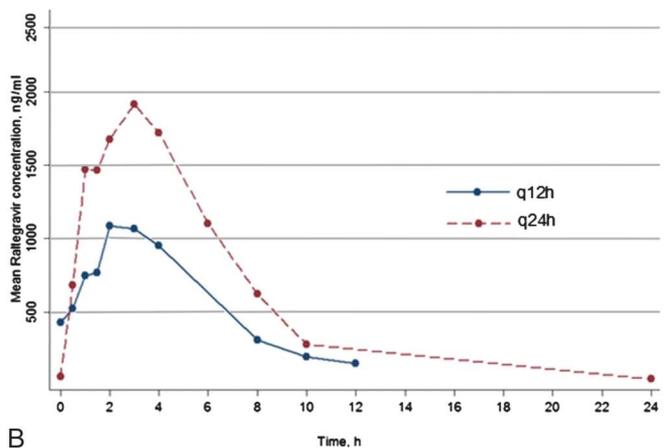
Plasma HIV RNA remained <50 copies per milliliter in all participants during 8 weeks, and CD4⁺ counts did not change. After the week 8 visit, 19 participants (76%) elected to remain on a study regimen (16 on q12h and 3 on q24h); all consented to long-term follow-up. Nineteen participants attended the week 24 visit and 18 (95%) at week 48. Plasma viral load was undetectable in all participants at weeks 24 and 48. There were no confirmed virologic failures, and CD4⁺ counts remained stable.

Optional Components

Nine participants consented to the CSF component. In 2 participants, the CSF volume was insufficient for the determination of HIV RNA and ATV concentration. Figure 2 shows total CSF and plasma RAL concentrations relative to sampling time post dose. RAL was detected in 9 CSF samples but was below the limit of quantification (10 ng/mL) in 2. CSF concentrations ranged from 5 to 117 ng/mL (median, 19 ng/mL) exceeding the RAL in vitro 95%



A



B

FIGURE 1. Mean plasma concentration–time curves for (A) ATV and (B) RAL.

inhibitory concentration of wild-type HIV-1 (15 ng/mL)¹³ in 5 participants. RAL concentration was quantifiable in all plasma samples [median, 310 (range, 83–1430) ng/mL]. CSF-to-plasma ratios for paired samples ranged from 0.024 to 0.17 (median, 0.060) ($n = 9$). Although all ($n = 7$) ATV plasma concentrations were quantifiable [median, 1217 (range, 449–3601) ng/mL], CSF concentrations were detectable in only 1 participant. HIV RNA was <50 copies per milliliter in plasma and CSF in 7 evaluable participants.

Ten participants consented to semen collection. Although urine PCR was positive for chlamydia in 1 participant, the seminal viral load was <400 copies per milliliter. Semen volume was insufficient for analysis in one participant and for ATV concentration measurement in another. In all participants, RAL semen concentrations were above the limit of quantification and above the protein-corrected 95% inhibitory concentration of wild-type HIV.¹³ RAL concentrations were highly variable with median 715 (range, 354–2688) ng/mL in seminal plasma ($n = 9$) and 346 (range, 57–2445) ng/mL in blood plasma ($n = 9$) (Fig. 3). Semen-to-blood concentration ratios for paired samples ranged from 0.55 to 10.93 (median 2.91). ATV was detectable in 8 semen samples but below the limit of quantification in 2 participants.

TABLE 2. ATV and RAL Plasma Pharmacokinetic Parameters in Regimens of ATV and RAL at 300 and 400 mg Twice Daily or 300 and 800 mg + RTV 100 mg Once Daily, Respectively

Pharmacokinetic Parameter	ATV (n = 25)					
	300 mg q12h		300 mg + RTV 100 mg q24h		GMR (90% CI)†	
	GM (90% CI)*	CV%	GM (90% CI)*	CV%		
C_{max} , ng/mL	3338 (2719 to 4098)	46	4184 (3330 to 5258)	47	1.25 (0.97 to 1.62)	
C_{min} , ng/mL	456 (347 to 600)	75	598 (442 to 808)	93	1.30 (1.08 to 1.58)	
AUC_{0-24h} , ng·mL ⁻¹ ·h ⁻¹	30,746 (25,142 to 37,598)‡	51	23,315 (18,565 to 29,280)	53	0.76 (0.59 to 0.98)	
T_{max} , h§	3.0 (1.5 to 5.0)	43	3.0 (2.0 to 8.0)	50	—	

Pharmacokinetic Parameter	RAL (n = 25)				RTV (n = 25)		
	400 mg q12h		800 mg q24h		100 mg q12h		
	GM (90% CI)*	CV%	GM (90% CI)*	CV%	GM (90% CI)*	CV%	
C_{max} , ng/mL	1262 (978 to 1630)	89	2512 (1914 to 3296)	91	1.99 (1.50 to 2.63)	923 (830 to 1027)	76
C_{min} , ng/mL	56 (37 to 84)	30	28 (20 to 37)	26	0.48 (0.31 to 0.75)	110 (91 to 134)	68
AUC_{0-24h} , ng·mL ⁻¹ ·h ⁻¹	10,825 (8552 to 13,703)‡	57	9260 (7396 to 11,595)	66	0.86 (0.65 to 1.12)	7407 (5677 to 9666)	40
T_{max} , h§	3.0 (1.0 to 6.0)	60	4.0 (1.5 to 8.0)	56	—	5.0 (2.0 to 6.0)	18

*Geometric mean computed from least-squares estimate from analysis of variance performed on natural log-transformed values.

†GMR for q24h vs. q12h.

‡ AUC_{0-24h} estimated as $2 \times AUC_{0-12h}$.

§Values are median (range).

CV, coefficient of variation; GM, geometric mean; q12h, twice daily; q24h, once daily.

ATV concentrations varied widely with median concentration 26 (range, 5–247) ng/mL in seminal plasma (n = 8) and 1511 (range, 1132–4171) ng/mL in blood plasma (n = 9). Semen-to-blood concentration ratios for paired samples (n = 8) ranged from 0.003 to 0.059 (median, 0.011). The ATV concentration exceeded the suggested plasma C_{trough} for efficacy against wild-type HIV-1 (150 ng/mL)³⁰ in 1 semen sample. In all participants, the viral load was <50 copies per milliliter in blood and <400 copies per milliliter in semen.

DISCUSSIONS

In virologically suppressed HIV-infected adults randomized to q12h RAL 400 mg plus ATV 300 mg for 4 weeks followed by q24h RAL 800 mg plus ATV/RTV 300/100 mg for 4 weeks or vice versa, regimens were efficacious, safe, and well tolerated. Both ATV and RAL demonstrated considerable pharmacokinetic variability. We found that ATV trough concentrations were lower with q12h dosing compared with q24h ATV/RTV, and troughs were lower when RAL was dosed q24h compared with q12h. RAL central nervous system (CNS) and semen penetration varied between compartments, whereas ATV penetrated both sites poorly.

Although the ATV q12h C_{min} was lower and nonequivalent to the q24h C_{min} , it exceeded the recommended plasma C_{trough} for successful viral suppression,³⁰ indicating that the q12h strategy is likely to confer durable efficacy as supported by undetectable HIV RNA during the study. Our q12h ATV C_{min} and AUC_{0-24} values are lower than those reported in ART-naive individuals receiving a similar regimen (687 ng/mL and 39,807 ng·h/mL, respectively),³¹ whereas ATV/RTV exposures assessed by AUC_{0-24} and C_{min} are comparable

with historical values in HIV-infected individuals (28,605 ng·mL⁻¹·h⁻¹ and 526 ng/mL, respectively).³²

Similar to ATV, RAL exhibited considerable pharmacokinetic variability. Although early studies indicated no relationship between RAL C_{min} and antiviral response,^{33,34} recent randomized data suggest reduced efficacy with the lowest C_{min} in recipients of 800 mg q24h but not 400 mg q12h.³⁵ Interestingly, the C_{min} GMR [0.22 (90% CI: 0.19 to 0.25)] in that study³⁵ was less than half the C_{min} GMR of the present study [0.48 (90% CI: 0.31 to 0.75)]. Our finding of no difference between the adjusted q12h RAL geometric mean AUC_{0-24} and q24h geometric mean AUC_{0-24} is of interest as in vitro data suggest that RAL AUC is the most important pharmacokinetic

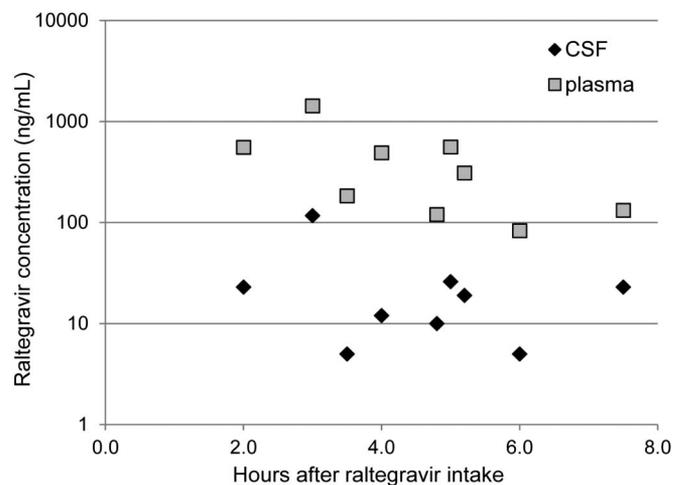


FIGURE 2. RAL concentrations in CSF and matched plasma (n = 9).

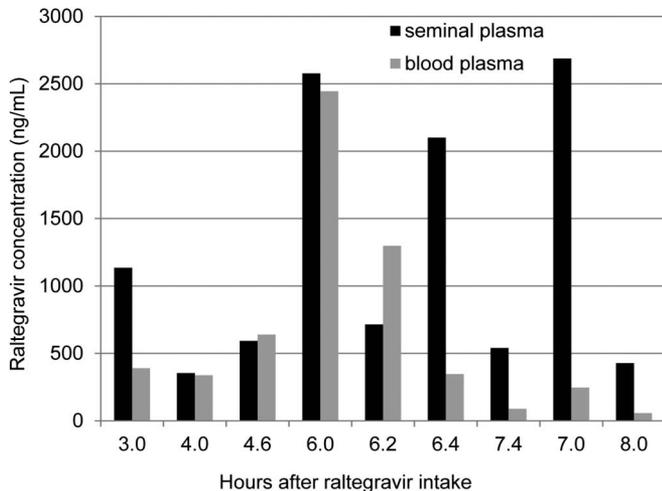


FIGURE 3. RAL concentrations in seminal plasma and matched blood plasma (n = 9).

parameter for antiviral response.³⁶ To date, relationships between antiviral efficacy and RAL pharmacokinetic parameters seem inconsistent; hence, further studies to define pharmacokinetic–pharmacodynamic relationships are needed.

Strategies were safe and well tolerated. In contrast to an earlier study,³¹ rates of grade 4 hyperbilirubinemia were low and not different between strategies. Triglyceride increases between weeks 0 and 4 in the q24h strategy are consistent with dyslipidemic effects of RTV,^{19,20} most likely reflecting changes in participants receiving unboosted ATV at baseline. The absence of discontinuations and low incidence of AEs contrasts with findings in treatment-naïve individuals³¹ and probably reflects our inclusion criteria with receipt of an unchanged ATV-containing regimen for at least 24 weeks, a surrogate for proven safety and tolerability.

This study demonstrated that virologically suppressed adults switched to regimens of ATV plus RAL maintained HIV RNA below 50 copies/mL and stable CD4⁺ counts with no virologic failures over the short or medium term. Our findings contrast with ATV plus RAL (300/400 mg q12h) as initial ART where RAL genotypic and/or phenotypic resistance was observed in 5 participants at 24 weeks.³¹ More recent randomized data indicate that q24h RAL is virologically inferior to q12h in adults commencing initial ART particularly when baseline HIV RNA exceeds 100,000 copies per milliliter.³⁵ Hence, the present study suggests that ART-experienced individuals with demonstrated high-level adherence are able to maintain virologic suppression and avoid the rapid development of resistance.

Exploratory analyses demonstrated variable RAL CSF concentrations that averaged 6% of plasma concentrations. The median CSF concentration (19 ng/mL) was lower than expected based on unrestricted distribution of unbound RAL from plasma to CSF (17% of 310 ng/mL; 53 ng/mL), suggesting barriers to CSF entry. ATV CSF concentrations were extremely low (<5 ng/mL), perhaps reflecting collection during the unboosted strategy.³⁷ RTV is a potent P-gp inhibitor³⁸; hence, P-gp inhibition should facilitate ATV CNS entry increasing

CSF concentrations. Alternately, RAL may have acted by unknown mechanisms to limit ATV CNS entry. Assuming CSF drug concentrations reflect antiviral activity in the brain, these data suggest that RAL and ATV may not provide adequate antiviral benefit in all participants. Undetectable plasma and CSF viral loads in all participants may reflect undetectable baseline viral loads and short-term strategy exposure at the time of sampling.

RAL penetration into semen was high and variable with concentrations about 3-fold higher than plasma although inter-individual variation was considerable. The semen-to-plasma concentration ratio (2.9) is comparable with the 2.3 cervicovaginal fluid-to-plasma ratio reported in HIV-positive women.³⁹ Unlike RAL, ATV had extremely limited semen penetration with concentrations about 1% of those in plasma. Our finding contrasts with penetration values of 10% and 14% reported in participants predominantly receiving ATV/RTV.^{28,40} Although HIV RNA in semen was undetectable in all participants, this may reflect baseline levels and short-term strategy therapy exposure; hence, the long-term significance of poor ATV penetration on transmission of resistant virus is unknown.

This study has limitations. Participants were white men, reflecting the HIV Australian epidemic. Data after week 8 are not randomized, so we were unable to ascertain any difference in strategy efficacy over this period, nevertheless, with no failures or treatment discontinuations, both seem to be efficacious and safe. Participants had demonstrated long-term ATV tolerability; accordingly, AEs were few and clinically insignificant. Therefore, safety findings should be extrapolated carefully to ATV-naïve individuals.

In conclusion, this study demonstrated that in virologically suppressed adults, a switch to RAL plus ATV is safe and well tolerated and can maintain undetectable viral loads and stable CD4⁺ counts over the short and long term. Our findings suggest that RAL plus ATV regimens may have the potential for use in induction–maintenance therapy and in individuals with ART-related toxicities especially dyslipidemia or where nucleoside-sparing regimens are required. However, further investigation in large randomized studies with longer follow-up and careful virologic and resistance monitoring are crucial to ensure efficacy and minimize unnecessary patient risk.

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