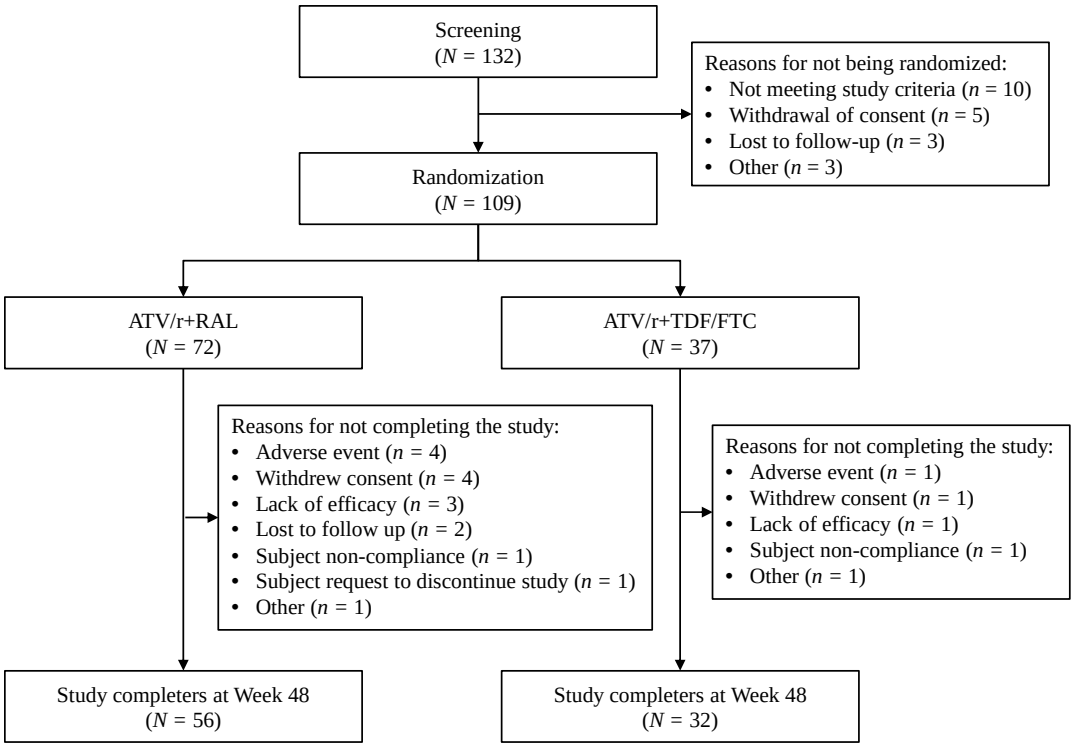
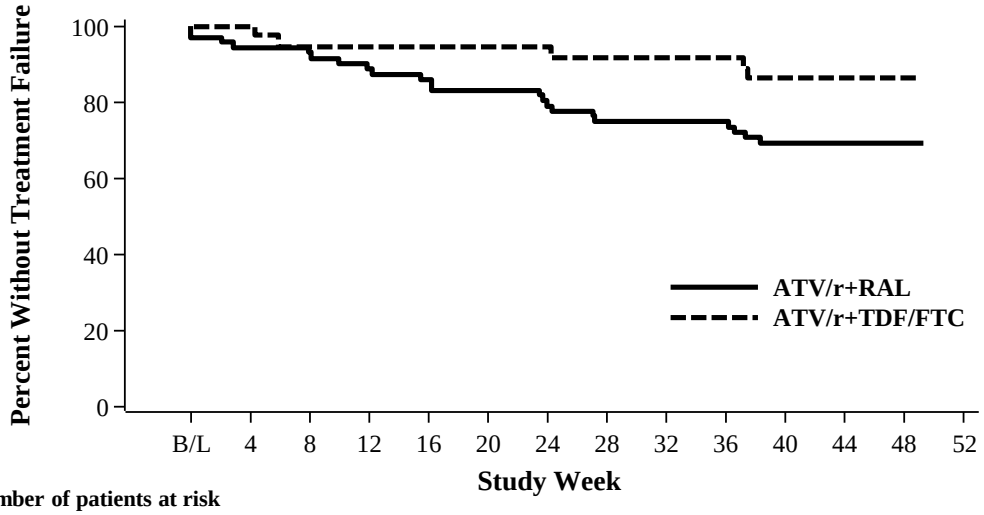
Supplemental Digital Content 1

Fig. S1. CONSORT flow diagram



Supplemental Digital Content 2

Fig. S2. Kaplan-Meier curve of time to treatment failure from baseline through Week 48 (defined as defined as discontinuation of study therapy before Week 48 or virological rebound at or before Week 48)



Number of patients at risk													
ATV/r+RAL	72	68	67	64	62	60	57	54	54	54	50	50	39	0
ATV/r+TDF/FTC	37	37	35	35	35	35	35	34	34	34	32	32	25	0

Supplemental Digital Content 3

Table S1. Categorization of range of responses to the safety/tolerability reasons for switch questionnaire

Categorization	Response
Gastrointestinal	Diarrhea
	Nausea
	Gastrointestinal complaints
	Gastric distress, bloating, nausea
	Digestive discomfort
CNS symptoms	Sleep disorders
	Insomnia
	Unrefreshing sleep
	Vivid dreams
	Poor sleep
	CNS side effects
	Sleeping disorder
	Sleep pattern disruption
	Bizarre dreams
	Sleep problems
	Dizziness
	Situational mood swings
	Nightmares
	Dizziness, feeling of uneasiness = CNS toxicity
	Morning vertigo
	CNS toxicity
	Memory loss
	Psych affects from current regimen, ("wild dreams")
Dyslipidemia	Hypercholesterolemia
	Hypertriglyceridemia
	Hypetrigliceridemia
	Dyslipidemia
	Hyperlipidemia
Lipodystrophy	Lipodystrophy
	Lipoatrophy
	Lipodystrophia
	Lipodystrophie
	Abdominal fat increase
	Abdominal lipohypertrophia
Pill burden	Heavy pill burden
	Pill fatigue
	Too large number of pills - problems swallowing

	Too high number of pills, problems swallowing
	High number of pills - problems swallowing
Other	Fatigue
	Tiredness
	Elevated transaminases
	Increase in body weight
	Increased alt and ast values
	Peripheral neuropathy
	Metallic taste
	Intolerability to efavirenz

Supplemental Digital Content 4

Pharmacokinetic methods

ATV and RAL trough concentrations (Ctrough – 24-h post-dose for ATV and 12-h post-dose for RAL) were collected at Weeks 4, 8, 12, 16, and 24. An intensive pharmacokinetic substudy collected plasma samples over a 24-h period at steady state in a subset of patients enrolled in selected sites at Week 4; the maximum observed concentration (Cmax), area under the concentration-time curve in 1 dosing interval (AUCTAU), and minimum concentrations (Cmin – 24-h post-dose for ATV and 12-h post-dose for RAL) were derived by non-compartmental methods using WinNonlin (Version 5.2).

Pharmacokinetic results

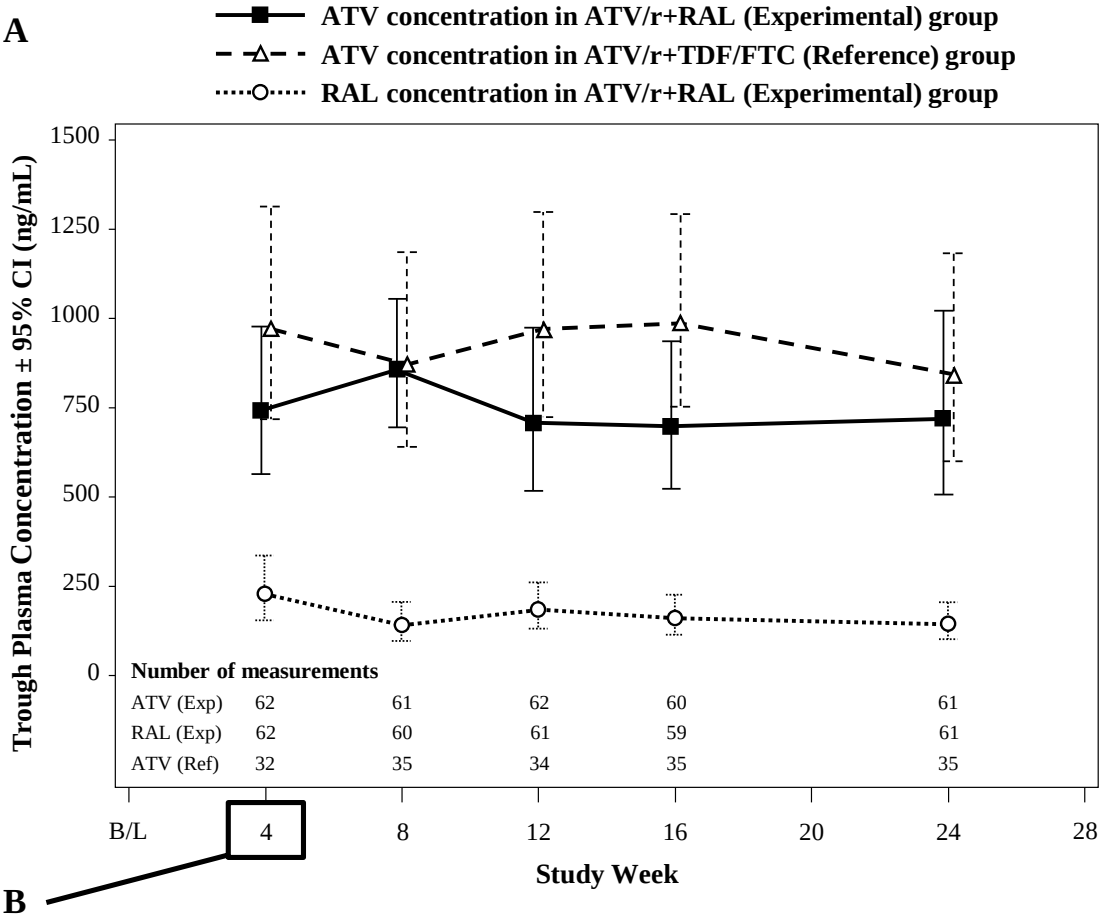
Geometric mean ATV Ctrough values across Weeks 4 to 24 reached steady state and were maintained in both groups. ATV Ctrough values were slightly lower with ATV/r+RAL than with ATV/r+TDF/FTC, although variation in ATV Ctrough values was high. Geometric mean RAL Ctrough values across Weeks 4 to 24 reached steady state and were maintained (Fig. S3A).

Intensive pharmacokinetic substudy results (n=14) are presented in Fig. S3B. Systemic exposures to ATV were comparable when ATV/r was administered with RAL or with TDF/FTC (90% CIs for geometric mean ratios included unity).

Fig. S3. A). ATV and RAL geometric mean trough concentrations (with 95% confidence intervals) from Week 4 to Week 24 in treated patients with pharmacokinetic data; and B) summary of pharmacokinetic parameters from the 24-hour intensive pharmacokinetic substudy conducted at Week 4. ATV/r, ritonavir-boosted atazanavir; RAL, raltegravir; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine. Experimental group:

ATV/r 300/100 mg once daily plus RAL 400 mg twice daily. Reference group: ATV/r 300/100 mg once daily plus TDF/FTC 300/200 mg once daily.

A



B

INTENSIVE PK SUBSTUDY AT WEEK 4	**ATV/r+RAL (*n* = 9)** [Experimental] Geometric Mean (%CV)	**ATV/r+TDF/FTC (*n* = 5)** [Reference] Geometric Mean (%CV)	**Treatment comparison** [Experimental vs. Reference] GMR (90% CI)
Atazanavir			
C_{max}, ng/mL	5071 (19)	4620 (23)	1.10 (0.87, 1.39)
AUC_{TAU}, ng•h/mL	50824 (18)	44816 (35)	1.13 (0.82, 1.56)
C_{min}, ng/mL	988 (45)[a]	832 (51)	1.19 (0.71, 1.98)
Raltegravir			
C_{max}, ng/mL	2292 (60)	NR	NR
AUC_{TAU}, ng•h/mL	9524 (57)	NR	NR
C_{min}, ng/mL	239 (160)	NR	NR

[a] *n* = 8. AUC_{TAU}, area under the plasma concentration-time curve in one dosing interval; CI, confidence interval; C_{max}, maximum plasma concentration, C_{min}, minimum plasma concentration (24 hours post-dose for ATV and 12 hours post-dose for RAL); CV, coefficient of variation; GMR, geometric mean ratio; NR, not relevant; PK, pharmacokinetic.

Discussion

The intensive pharmacokinetic substudy did not identify reduced ATV exposures in the ATV/r+RAL group and, consistent with the inhibition of the UDP-glucuronosyltransferase 1A1 enzyme by ATV,[1,2] RAL Cmin values were higher than those observed in the RAL twice-daily treatment arm of the QDMRK study[3] in which RAL was administered without ATV. Moreover, ATV and RAL geometric mean Ctrough values, available for most patients, were within therapeutic ranges over the study course. Taken together, it is unlikely that pharmacokinetic reasons contributed to the between-group difference in maintenance of virological suppression.

References

1. Merck and Co. Inc. IsentressRM (raltegravir) prescribing information. Available at: http://www.merck.com/product/usa/pi_circulars/i/isentress/isentress_pi.pdf (Updated February 2015. Accessed 05 June 2014)

2. Bristol-Myers Squibb Company. US prescribing information for atazanavir. Available at: http://packageinserts.bms.com/pi/pi_reyataz.pdf (Updated March 2015. Accessed 05 June 2015)

3. Rizk ML, Hang Y, Luo WL, et al. Pharmacokinetics and pharmacodynamics of once-daily versus twice-daily raltegravir in treatment-naive HIV-infected patients. Antimicrob Agents Chemother. 2012;56:3101–3106.