Phase 2 Study of Cobicistat versus Ritonavir each with Atazanavir plus Fixed-Dose Emtricitabine/Tenofovir DF in the Initial Treatment of HIV Infection

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Objective: Assess efficacy and safety of cobicistat versus ritonavir as pharmacoenhancers for atazanavir when administered with emtricitabine/tenofovir df as initial treatment for HIV-1 infection.

Design: Randomized, partially placebo-controlled, double-blind, multicenter study

Subjects: Antiretroviral treatment-naïve adults, screening HIV-1 RNA $\geq$5000 copies/mL, and CD4 cell count $>$ 50 cells/μL.

Intervention: Randomized 2:1 (stratified by HIV RNA $\leq$ or $>$ 100,000 copies/mL) to receive placebo-blinded once-daily cobicistat 150 mg or ritonavir 100 mg with open-label atazanavir plus fixed-dose emtricitabine/tenofovir df Main outcome measures: Efficacy and safety at Weeks 24 and 48.

Results: Eighty-four percent of ATV/co subjects and 86% of ATV/r subjects suppressed HIV-1 RNA (<50 copies/mL) at Week 24, and 82% and 86% at Week 48, respectively, and mean CD4 count (cells/μL) increased 203 and 199 at Week 24, and 208 and 177 at Week 48.

Study treatment discontinuation due to adverse event occurred 4% ATV/co and 3% ATV/r subjects through 48-weeks. Treatment-related adverse events occurred in 36% ATV/co and 48% ATV/r subjects; hyperbilirubinemia occurred in 96% and 100%, and ocular icterus or jaundice occurred in 14% and 17%, respectively. Mean estimated glomerular filtration rate (Cockcroft-Gault, mL/min) decreased occurred in both treatment groups and was evident at Week 2 (ATV/co, -9 and ATV/r, -4), reached a nadir by Week 24 (-15 and -14), and did not progress further through Week 48 (-13 and -14).

Conclusion: Using cobicistat and ritonavir as pharmacoenhancers for atazanavir and administered with emtricitabine/tenofovir df achieved comparable rates of virologic suppression and CD4 count increase with satisfactory safety profiles.

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Introduction

Mechanism-based inhibition (MBI) of cytochrome P4503A (CYP3A) enzymes by low doses (100–400 mg/day) of the HIV-1 protease inhibitor (PI) ritonavir (RTV) to pharmacologically enhance ("boost") plasma levels of other PIs (PI/r) that are metabolized by CYP3A enzymes was a serendipitous therapeutic advancement early in the use of PIs as components of highly active antiretroviral therapy (HAART) [1–5]. Pharmacologic boosting of PIs has several desirable outcomes: (a) raises pharmacologic barrier to the development of virologic resistance; (b) the PI may be administered at lower dose and decreased pill burden; (c) often decreases dosing frequency; and (d) may decrease side effects, thereby improving a HAART regimen [6]. RTV is used primarily to boost the eight approved PIs [7–10].

Cobicistat (COBI, formerly GS-9350) is a more specific MBI of CYP3A without antiretroviral activity. In vitro studies demonstrate COBI, compared to ritonavir, is a weak inhibitor of CYP2D6 ($IC_{50} = 9.2\,\mu M$), does not inhibit other CYP isoforms, and displays low liability for induction; thus COBI exhibits a PK profile associated with fewer clinically significant drug-drug interactions. Other favorable characteristics of COBI include reduced perturbation of the normal adipocyte functions such as lipid accumulation and/or response to insulin that may offer the potential for fewer adverse biochemical effects relative to ritonavir [11–13].

COBI has high aqueous solubility allowing formulation as a tablet and co-formulation with other drugs [11–15]. COBI is being developed specifically as a pharmacoenhancer for drugs metabolized by CYP3A to improve pharmacokinetic (PK) exposure to decrease total daily dose and/or less frequent dosing [13]. COBI and RTV boost plasma levels of ATV and DRV comparably when coadministered to HIV-1 uninfected adults [14,15]. These results formed the rationale for initiating a Phase 2 clinical trial in HIV-1 infected antiretroviral treatment-naïve adults to test efficacy and safety of HAART consisting of COBI compared to RTV as pharmacoenhancers for ATV coadministered with fixed-dose emtricitabine/tenofovir df (FTC/TDF).

Methods

Study Design

Inclusion: HIV-1 infected adults (≥18 years), screening plasma HIV-1 RNA ≥5,000 copies/mL, CD4 cell count > 50 cells/μL, no prior use approved or experimental anti-HIV drugs and no NRTI, NNRTI or primary PI genotypic resistance mutations (IAS-USA Guidelines), normal ECG, estimated glomerular filtration rate (eGFR, Cockcroft-Gault) ≥ 80 mL/min, AST/ALT ≤2.5 times upper limit of normal, total bilirubin ≤1.5 mg/dL), and for females a negative serum pregnancy test. Exclusion: hepatitis B or C co-infection, new AIDS-defining condition within 30 days of screening, or vaccination within 90 days of study treatment dosing. The study was conducted in the United States, approved by Institutional Review Boards, and subjects signed informed consent before screening.

Eligible subjects were randomized 2:1 (stratified by screening HIV-1 RNA ≤ or > 100,000 copies/mL) to treatment with open-label ATV 300 mg plus FTC/TDF 200/300 mg and either COBI 150 mg QD + RTV placebo QD (ATV/co subjects, group) or RTV 100 mg QD + COBI placebo QD (ATV/r subjects, group). Study assessments occurred at screening, baseline, Weeks 2, 4, 8, 12, 16, and then every 8 weeks through Week 48 including laboratory analyses (CD4, hematology, chemistry, and urinalysis; Covance Laboratories, Indianapolis, IN), HIV-1 RNA (AMPLICOR HIV-1 Monitor assays, Roche Molecular Systems; Pleasanton, CA), and physical examinations. HIV-1 reverse transcriptase and protease genotype (GeneSeq Assay, Monogram Biosciences; South San Francisco, CA) was analyzed at screening.

Virologic failure required confirmation and was defined as a suboptimal virologic response (HIV-1 RNA < 1 $\log_{10}$ reduction from baseline and ≥ 50 copies/mL at the Week 8 visit), or virologic rebound at any visit after achieving HIV-1 RNA < 50 copies/mL (an increase in HIV-1 RNA to ≥ 400 copies/mL, or a > 1 $\log_{10}$ increase in HIV-1 RNA from nadir). Adverse events and laboratory abnormalities were graded for severity using toxicity grading scale adapted from the Division of AIDS Table for Grading the Severity of Adult Adverse Events. Intensive PK assessments over 24 hours occurred in a subset of subjects at either Week 2, 4, or 8, and trough samples were drawn 20–24 hours post-dose at Weeks 8, 24, and 48).

Statistical Methods

Primary efficacy endpoint: proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 24 using point estimates and 95% confidence interval for difference in response rates by normal approximation methods, stratified by baseline HIV-1 RNA level. Secondary endpoints: proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48, and CD4+ cell count at Weeks 24 and 48. Safety and pharmacokinetic endpoints were summarized using descriptive statistics.

Table 1. Baseline Characteristics, Efficacy, and Safety Results.

	ATV/co + FTC/TDF (n = 50)	ATV/r + FTC/TDF (n = 29)	Intertreatment Group Comparison Statistic
Baseline Demographic and Disease Characteristics			
Mean age, yrs	37	34	p = 0.15[a]
Male sex, %	94	86	p = 0.41[b]
Race: Asian/Black/White/Other[c], %	0 / 36 / 62 / 2	7 / 28 / 55 / 10	p = 0.09[b]
Mean HIV-1 RNA, Log_{10} copies/mL	4.56	4.69	p = 0.28[a]
Mean CD4 cell count, cells/μL	365	343	p = 0.91[a]
Mean (SD) total bilirubin, mg/dL	0.6 (0.37)	0.5 (0.20)	p = 0.98[a]
Mean estimated glomerular filtration rate[d] (eGFR), mL/min	117	122	p = 0.92[a]
Primary and Secondary Efficacy Endpoints (ITT)			
Proportion with HIV-1 RNA < 50 copies/mL (M = F)			
Week 24	84%	86%	−4.6% (−21.7% to 12.5%)[e]
Week 48	82%	86%	−1.9% (−18.4% to 14.7%)
Proportion with HIV-1 RNA < 50 copies/mL (M = E)			
Week 24	91%	96%	−2.3% (−14.2% to 9.5%)[e]
Week 48	91%	96%	−5.2% (−17.3% to 6.9%)
Mean HIV-1 RNA change from baseline, log_{10} copies/mL			
Week 24	−2.80	−2.95	p = 0.90[f]
Week 48	−2.79	−2.94	p = 0.71
Mean CD4 count change from baseline, cells/μL			
Week 24	+203	+199	p = 0.92[f]
Week 48	+230	+206	p = 0.43
Safety Results Through Week 48			
Study treatment-related adverse events ≥ 5%, n	18 (36%)	14 (48%)	ND[g]
Ocular icterus	6 (12%)	4 (14%)	ND
Fatigue	1 (2%)	3 (10%)	ND
Diarrhea	3 (6%)	3 (10%)	ND
Nausea	5 (10%)	1 (3%)	ND
Flatulence	0	2 (7%)	ND
Incidence of hyperbilirubinemia[h], n *[> 2.6 mg/dL]*	47 (96%)	29 (100%)	ND
Incidence of Grade 3/4 hyperbilirubinemia, n	31 (63%)	13 (45%)	p = 0.16[b]
Mean (SD) indirect bilirubin, mg/dL			
Week 2	3.2 (2.41)	2.1 (1.42)	p = 0.05[a]
Week 24	2.7 (2.64)	2.2(1.43)	p = 0.76
Week 48	2.3 (1.96)	1.9 (1.72)	p = 0.40
Mean (mean change from baseline) fasting lipids, mg/dL			
Total cholesterol			
Week 24	177 (6)	163 (2)	p = 0.72[a]
Week 48	174 (4)	162 (4)	p = 0.85
Triglycerides			
Week 24	167 (37)	131 (8)	p = 1.00[a]
Week 48	136 (−1)	130 (7)	p = 0.67
Low density lipoprotein cholesterol			
Week 24	109 (7)	97 (4)	p = 0.82[a]
Week 48	108 (7)	93 (1)	p = 0.28
High density lipoprotein cholesterol			
Week 24	49 (1)	50 (5)	p = 0.12[a]
Week 48	48 (1)	50 (5)	p = 0.26
Mean (mean % change from baseline) eGFR, ml/min			
Week 2	108 (−8%)	117 (−3%)	0.02[a]
Week 24	102 (−13%)	111 (−11%)	0.5
Week 48	104 (−12%)	111 (−11%)	0.8

[a]Wilcoxon rank sum test.
[b]Fisher's Exact test.
[c]Other includes Hispanic, Hispanic/latino; and latino.
[d]ockcroft-Gault method.
[e]Difference in proportions (95% confidence interval), stratum weighted by baseline HIV-1 RNA category, normal approximation.
[f]ANOVA model, included HIV-1 RNA category.
[g]not done.
[h]total bilirubin; ITT, Intent-To-Treat; M = F, Missing data counted as Failure; M = E, Missing data Excluded from denominator.

Post-hoc intertreatment group statistical comparisons were performed for data presented in Table 1 that were not primary or secondary endpoints, excluding adverse events.

Results

Eighty-five subjects out of 137 screened were randomized 2:1 to the ATV/co or ATV/r groups. Six subjects

randomized to ATV/co never received study treatment. Thus 79 randomized subjects constituted the intent-to-treat analysis efficacy and safety populations: ATV/co (n = 50) and ATV/r (n = 29). Table 1 displays baseline characteristics (demographic and disease), efficacy (primary and secondary endpoints), and safety (adverse events and laboratory abnormalities through Week 48) for both treatment groups with post-hoc intertreatment group statistical comparisons. Baseline demographics and disease characteristics were similar between treatment groups. Seventy-six percent of ATV/co subjects had HIV-1 RNA $\leq$ 100,000 copies/mL and 24% > 100,000 copies/mL, and ATV/r subjects had 62% and 38%, respectively.

The stratum-weighted difference in the response rate (ATV/co − ATV/r) was -1.9% (-18.4% to 14.7%) at Week 24. The other efficacy endpoints were similar between the treatment arms. No subject experienced virologic failure.

Ten percent (8/79) of subjects discontinued study treatment prematurely. Five of the 8 subjects discontinued prior to Day 28; 5/50 (10%) ATV/co and 3/29 (10%) ATV/r subjects. Three of 79 (4%) subjects discontinued study treatment prematurely due to adverse event related to study treatment; 2/50 (4%) ATV/co (moderate vomiting, Day 3; and severe generalized maculopapular rash, Day 11), and 1/29 (3%) ATV/r subjects (mild ocular icterus, Day 21). Of the remaining 5 subjects, 1 on each treatment was lost to follow-up, 1 ATV/co subject withdrew consent and another was discontinued at the investigator's discretion due to nonadherence to protocol, and 1 ATV/r subject had a protocol violation.

Through 48 weeks, 39/50 (78%) ATV/co and 24/29 (83%) ATV/r subjects experienced $\geq$1 one treatment-emergent adverse event (TEAE) and the majority was assessed as mild or moderate severity. Three serious adverse events occurred in 3 subjects and were assessed as unrelated to study treatment: pneumonia (1 on each treatment) and cellulitis (ATV/co). Study treatment-related TEAEs in $\geq$ 5% of subjects were reported in 18/50 (36%) ATV/co and 14/29 (48%) ATV/r subjects; ocular icterus occurred most commonly 6/50 (12%) and 4/29 (14%) subjects, respectively, followed by fatigue, diarrhea, nausea, and flatulence.

Hyperbilirubinemia was reported in 96% ATV/co and 100% ATV/r subjects. Sixty-three percent of ATV/co and 45% of ATV/r subjects developed $\geq$Grade 3 hyperbilirubinemia. Mean indirect bilirubin (mg/dL) was numerically higher among the ATV/co versus ATV/r subjects, but was statistically significant only at Week 2 (3.2 and 2.1, respectively) (p = 0.05). Intertreatment group statistical comparison of mean change from baseline in fasting lipids revealed no statistically significant difference between treatment groups. Mean percent change from baseline in estimated glomerular filtration rate (eGFR) was significantly decreased only at Week 2, -8% (ATV/co group) versus -3% (ATV/r group) (p = 0.02), but not at Week 24 or 48.

Atazanavir exposure (Cmax and AUCtau; mean % [Coefficient of Variation, CV]) was estimated from the intensive pharmacokinetic samples: ATV/co subjects (n = 8): Cmax, 3880 ng/mL (36%) and AUCtau 41,300 ng.hr/mL (33%); and ATV/r subjects (n = 10): Cmax¬ 4390 ng/mL (47%) and AUCtau 49,900 ng.hr/mL (47%). Figure 1 illustrates the values for geometric mean ATV trough at week 8 for both treatment groups. Figure 1 Table Inset shows the ATV Ctrough (geometric mean) at Weeks 8, 24, and 48 for both treatments as well as their respective geometric mean ratio [90% confidence interval].

Discussion

The results of this phase 2 study demonstrated that HIV-1 infected treatment-naïve subjects using COBI or RTV as pharmacoenhancers for ATV coadministered with FTC/TDF achieved and maintained similar rates of virologic suppression (82% and 86%, respectively) and CD4 count increase (+230 and +206 CD4 cells/μL) through Week 48. These rates of virologic suppression are comparable to 48-week results from three randomized clinical trials wherein ATV/r plus FTC/TDF was compared to another HAART: fosamprenavir/r plus FTC/TDF once daily, 83% (ALERT) [16]; lopinavir/r twice daily plus FTC/TDF once daily, 78% (CASTLE) [17]; and efavirenz plus FTC/TDF or ATV/r plus abacavir/lamivudine, both once daily, 84% ACTG 5202 [18].

Statistical analysis of rates AEs occurring between treatment groups is generally not preplanned for studies with 2:1 randomization of a relatively small number of subjects. Both treatment groups appeared to have similar numbers of subjects with treatment-related adverse events except for nausea, which occurred in 5 subjects receiving ATV/co versus 1 ATV/r subject and did not cause study drug interruption or discontinuation. One ATV/co subject reported an episode of vomiting on Day 3 which was assessed as related to study treatment. The subject discontinued study treatment and did not attend any postbaseline study visits. The AE profile for COBI when given with ATV + FTC/TDF will be characterized more accurately with the accrual of additional safety data from the Phase 3 study with the same treatment groups.

Elevation of indirect bilirubin was the most common laboratory abnormality, a side-effect of atazanavir mediated through competitive inhibition of UGT1A1 enzyme and influenced by genetic factors. In one study, three MDR1 3435 genotypes were associated with:

Atazanavir Plasma C_{trough}	ATV/co + FTC/TDF GLS Mean	ATV/r + FTC/TDF GLS Mean	ATV/co : ATV/r GLS Mean Ratio [90% CI, %]
Week 8 (n=32)	598.40	642.29	93.17 [55.78, 155.61]
Week 24 (n=32)	690.94	731.93	94.40 [61.80, 144.19]
Week 48 (n=34)	654.72	784.99	83.40 [60.06, 115.82]

GLS Mean = Geometric Least Squares Mean; Only Weeks 8, 24 and 48 trough concentration data with trough sampling time within range (20-24 hours after observed dosing time) were summarized; Two subjects each had one PK sample (at Week 8 and 24) not evaluable and thus excluded. All subjects had evaluable samples at Week 48. Plasma concentrations below limit of quantitation (BLQ) were excluded from computing geometric means.

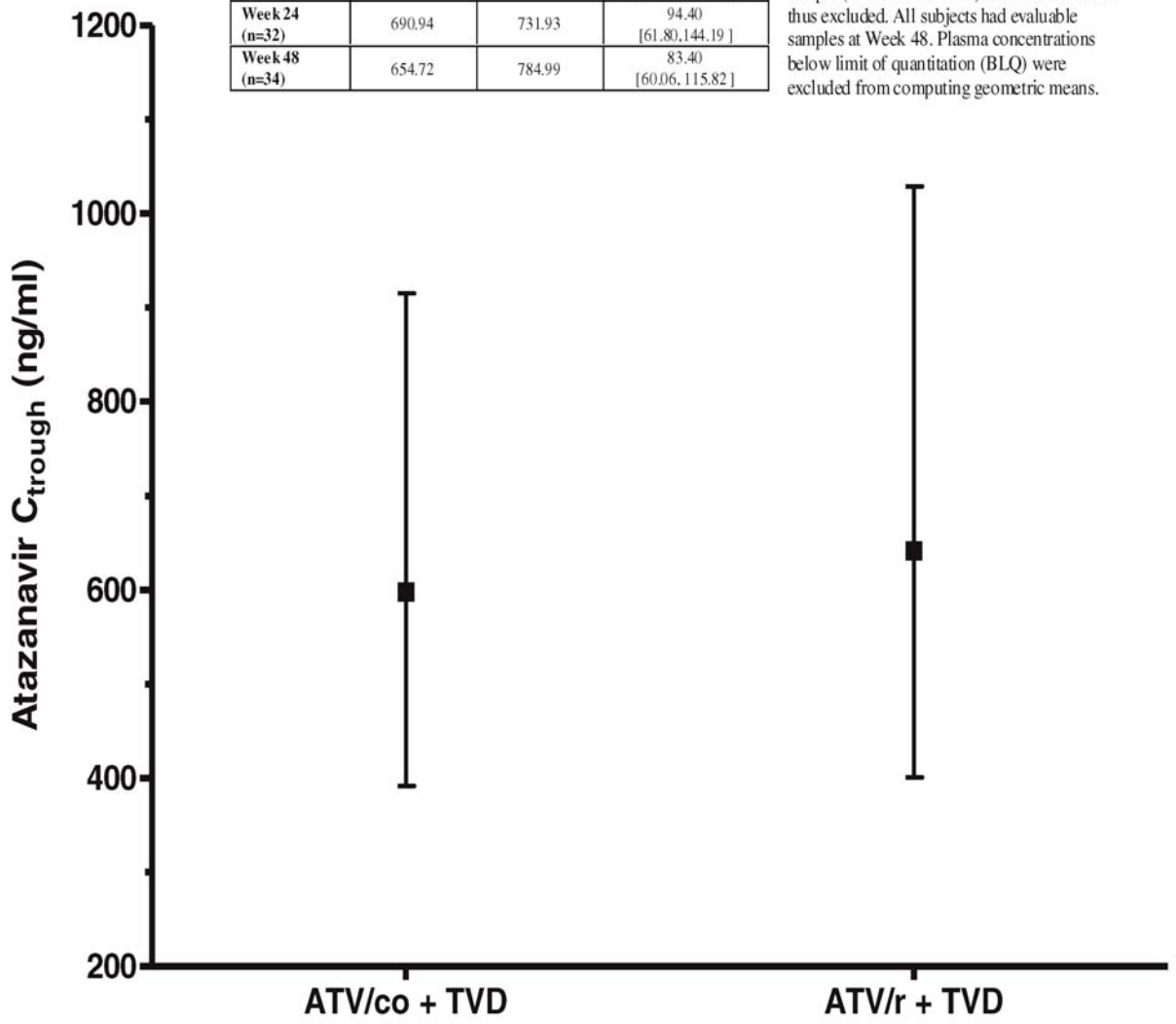

Fig. 1. Atazanavir trough plasma concentrations ng/ml) at Week 8 following administration of ATV/co + TVD and ATV/r + TVD. Data presented as geometric mean (± 95% CI).

significantly higher plasma atazanavir plasma levels in subjects with CC, compared to CT and TT genotypes, and bilirubin levels correlated with atazanavir concentrations [19]. In our study, the incidence of ≥Grade 3 hyperbilirubinemia was similar between treatment groups. Mean indirect bilirubin levels at most postbaseline time points were slightly higher in subjects receiving ATV/co compared to ATV/r however, there did not appear to be a disproportionate number of subjects manifesting clinical sequelae of elevated indirect bilirubin, namely ocular icterus and jaundice. A theoretical possibility might lie in the differences between cobicistat and ritonavir in affinity for off-target metabolic enzymes. For example, ritonavir is a better PXR activator than COBI and so might increase UGT1A1 levels and thus decrease indirect bilirubin by increased metabolism independent of ATV plasma level.

Mean eGFR decrease occurred in both treatment groups, was statistically significantly larger only at Week 2, reached a nadir by Week 24 and did not progress further through Week 48. Three ATV/co subjects had confirmed Grade 1 elevation of serum creatinine. No subject receiving either treatment developed persistent serum

electrolyte or urinalysis abnormalities, or discontinued or interrupted study treatment due to change in serum creatinine or eGFR [20,21]. A pharmacokinetic/pharmacodynamic study in healthy HIV-uninfected adults using iohexol [22], which exclusively undergoes glomerular filtration and is not secreted or reabsorbed, has shown that cobicistat can cause a mild increase in serum creatinine (mild decrease in eGFR) but does not affect iohexol-measured (actual) GFR, suggesting that the observed increase in serum creatinine may be due to an effect of COBI on the tubular secretion and not glomerular filtration of serum creatinine [20]. Additional *in vitro* and clinical studies of COBI in both HIV-infected and -uninfected subjects are in progress and may provide additional insight into the biological mechanism responsible for the mild increase in serum creatinine seen with COBI.

Pharmacokinetic analyses demonstrated that ATV exposures appear to be comparable including adequate ATV trough concentrations relative to its protein-binding adjusted EC_{90} (14 ng/ml) when boosted with COBI or RTV. Greater than 90% of quantifiable values for ATV C_{trough} at these visits were above the DHHS-recommended target of 150 ng/ml for both treatments. These ATV exposures are consistent with historical PK data from Phase 1 studies when ATV was boosted with COBI-boosted and RTV [13–15] and lend additional support for COBI as an appropriate pharmacoenhancer for the once-daily HAART regimen of ATV + FTC/TDF.

The results of this Phase 2 study helped design and initiate a 96-Week Phase 3 randomized, partially double-blind study to evaluate the efficacy and safety of ATV/co versus ATV/r each administered with FTC/TDF in HIV-1 infected antiretroviral treatment-naïve adults.

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Description of Role of each author

Role in the Study

Richard Elion: Site investigator; contributed to writing and editing manuscript.

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Conflicts of interest

None declared.

References

1. Kempf DJ, Marsh KC, Kumar G, Rodrigues AD, Denissen JF, McDonald E, *et al*. **Pharmacokinetic enhancement of inhibitors of the human immunodeficiency virus protease by coadministration with ritonavir.** *Antimicrobial Agents & Chemotherapy* 1997; **41 (3)**:654–660.
2. Merry C, Barry MG, Mulcahy F, Ryan M, Heavey J, Tjia JF, *et al*. **Saquinavir pharmacokinetics alone and in combination with ritonavir in HIV-infected patients.** *AIDS* 1997; **11 (4)**:F29–33.
3. van Heeswijk RPG, Veldkamp AI, Hoetelmans RMW, Mulder JW, Schreij G, Hsu A, *et al*. **The steady-state plasma pharmacokinetics of indinavir alone and in combination with a low dose of ritonavir in twice daily dosing regimens in HIV-1-infected individuals.** *AIDS* 1999; **13**:F95–F99.
4. Lal R, Hsu A, Chen P, *et al*. Single dose pharmacokinetics of ABT-378 in combination with ritonavir [Abstract]. 37th *Interscience Conference on Antimicrobial Agents and Chemotherapy*; 1997 Se 28-Oct 1; Toronto. I-194.
5. Lal R, Hsu A, Granneman R, El-Shourbagy T, Johnson M, Lam W, *et al*. Multiple dose safety, tolerability and pharmacokinetics of ABT-378 in combination with ritonavir [Abstract]. *5th Conference on Retroviruses and Opportunistic Infections*; 1998 Feb 1-5; Chicago. 647.
6. Hsu A, Granneman GR, Bertz RJ. **Ritonavir: Clinical Pharmacokinetics and Interactions with Other Anti-HIV Agents.** *Clin Pharmacokinetics* 1998; **35 (4)**:275–291.
7. Invirase package insert. Roche Laboratories, Inc., 2010.
8. Lexiva package insert. *GlaxoSmithKline*, 2010. Reyataz package insert. *Bristol-Myers Squibb Company*, 2008.
9. Aptivus package insert. *Boehringer Ingelheim Pharmaceuticals, Inc.*, 2010.
10. Prezista package insert. *Tibotec, Inc*., 2010.
11. Xu L, Liu H, Murray BP, Callebaut C, Lee MS, Hong A, *et al*. **Cobicistat (GS-9350): A Potent and Selective Inhibitor of Human CYP3A as a Novel Pharmacoenhancer.** *ACS Medicinal Chemistry Letters* 2010; **1 (5)**:209–213.
12. Callebaut C, Tsai L, Stray K, Liu H, Xu L, Desai M, *et al*. **Biological Profiling of GS-9350, a Novel Pharmacoenhancer that Lacks Anti-HIV Activity and Exhibits Low Potential for Metabolic Adverse Effects In Vitro [Abstract].** *Antiviral Research* 2010; **86 (1)**:A31.

13. Mathias AA, German P, Murray BP, Wei L, Jain A, West S, *et al*. **Pharmacokinetics and pharmacodynamics of GS-9350: a novel pharmacokinetic enhancer without anti-HIV activity.** *Clinical Pharmacology & Therapeutics* 2010; **87 (3)**:322–329.
14. Ramanathan S, Warren D, Wei L, Kearney BP. Pharmacokinetic Boosting of Atazanavir with the Pharmacoenhancer GS-9350 versus Ritonavir [Abstract]. *Interscience Conference on Antimicrobial Agents and Chemotherapy*, 2009, San Francisco, CA. 614.
15. Mathias A, Liu HC, Warren D, Sekar V, Kearney BP. Relative Bioavailability and Pharmacokinetics of Darunavir when boosted with the Pharmacoenhancer GS-9350 versus Ritonavir [Abstract]. *International Workshop on Clinical Pharmacology of HIV Therapy*. 2010, Sorrento, Italy. 28.
16. Smith KY, Weinberg WG, Dejesus E, Fischl MA, Liao Q, Ross LL, *et al*. **Fosamprenavir or atazanavir once daily boosted with ritonavir 100 mg, plus tenofovir/emtricitabine, for the initial treatment of HIV infection: 48-week results of ALERT.** *AIDS Res Ther* 2008; **5**:5.
17. Molina JM, Andrade-Villanueva J, Echevarria J, Chetchotisakd P, Corral J, David N. ***et al* for the CASTLE Study Team. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study.** *Lancet* 2008; **372 (9639)**:646–655.
18. Daar ES. ACTG 5202: ATV/r or EFV in Combination with ABC/3TC or TDF/FTC in Antiretroviral Naïve Patients [Abstract]. *17th Conference on Retroviruses and Opportunistic Infections (CROI)*. San Francisco, CA, February 16-19 2010. 59LB.
19. Rodr½?guez-Novoa R, Barreiro P, Rendon A, Barrios A, Corral A, Jimenez-Nacher I, Gonzalez-Lahoz J, Soriano V. **Plasma Levels of Atazanavir and the Risk of Hyperbilirubinemia Are Predicted by the 3435CrT Polymorphism at the Multidrug Resistance Gene 1.** *Clinical Infectious Diseases* 2006; **42**:291–295.
20. Cohen C, Shamblaw D, Ruane P, Elion R, DeJesus E, Liu HC, *et al*. The single-tablet, fixed-dose regimen of elvitegravir/GS-9350/emtricitabine/tenofovir DF (Quad) achieves a high rate of virologic suppression and GS-9350 is an effective booster. *17th Conference on Retroviruses and Opportunistic Infections (CROI)*. San Francisco, CA, 2010. 58LB.
21. Elion R, Gathe J, Rashbaum B, Shalit P, Hawkins T, Liu C, *et al*. *The Single-Tablet Regimen Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/COBI/FTC/TDF; ''QUAD'') Maintains a High Rate of Virologic Suppression, and Cobicistat (COBI) is an Effective Pharmacoenhancer Through 48 Weeks 50th ICAAC*. Boston, Massachusetts, 2010. H-938B.
22. Krutzén E, Bäck S-E, Nilsson-Ehle I, Nilsson-Ehle P. **Plasma clearance of a new contrast agent, iohexol: a method for the assessment of glomerular filtration rate.** *J Lab Clin Med* 1984; **104**:955–961.