Safety and Effectiveness of Tenofovir/Emtricitabine or Lamivudine Plus Ritonavir Boosted Atazanavir in Treatment Experienced HIV Infected Adults at Two Urban Private Medical Practices


1University of California School of Pharmacy, San Francisco, CA
2Dupont Circle Physicians Group, Washington, DC
3Virginia Mason Medical Center, Seattle, Washington
4Gilead Sciences Inc., Foster City, CA
5Private Practice, San Francisco, CA

Abstract

Objectives: The efficacy and safety of once daily ritonavir-boosted atazanavir (ATV/r) plus tenofovir (TDF) and emtricitabine (FTC) or lamivudine (3TC) was evaluated in the management of treatment experienced HIV-infected patients in routine clinical practice.

Research design and methods: A retrospective analysis was performed in HIV infected patients residing at two active, urban clinical practices receiving at least one month of tenofovir, emtricitabine or lamivudine plus ritonavir boosted atazanavir following a change from another antiretroviral regimen to simplify or reduce toxicity. Parameters evaluated included the proportion of patients with HIV RNA <400 copies/mL; change in CD4 count from baseline (start of both TDF and ATV/r), adverse effects, and laboratory changes over time in estimated glomerular filtration rate (calculated creatinine clearance and MDRD) and lipids.

Main outcome measures: One hundred sixty five patients, the majority being Caucasian and male, were studied. Twenty nine (18%) discontinued therapy, including 4 for adverse events and 5 for virologic failure. At baseline, 71% of patients had HIV RNA values <400 copies/mL. At 12 months, 81/90 (90%) patients remaining on therapy had HIV RNA <400 copies/mL, including 17/25 (68%) of those with baseline HIV RNA ≥400 copies/mL. Median increase in CD4 count at 12 months was 26 cells/µL. Grade 4 hyperbilirubinemia occurred in 12% of patients. Estimated glomerular filtration rates did not change significantly by either the Cockcroft-Gault or MDRD method. At 12 months, median declines from baseline in total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides were -14, -18, -1, and -12 mg/dL, respectively.

Conclusions: In routine clinical practice, a once-daily regimen containing ATV/r plus TDF/FTC or 3TC controlled HIV in most patients without renal toxicity and improved the lipid profile.

Keywords: Antiretroviral therapy; Tenofovir; Ritonavir boosted atazanavir; Treatment-experienced HIV infected patients; Renal function; Lipids

Introduction

HIV infection can now be managed as a chronic disease due to the availability of effective and tolerable antiretroviral therapy (ART) that can be administered once daily to promote long term adherence and survival. However, drug toxicities, particularly metabolic complications such as dyslipidemia from protease inhibitors (PI), and renal toxicity from nucleoside reverse transcriptase inhibitors (NRTIs) such as tenofovir can be problematic [1-5]. The combination of ritonavir boosted atazanavir (ATV/r) plus tenofovir (TDF) and emtricitabine (FTC) is recommended as initial ART by US and European HIV treatment guidelines and as an alternative regimen in the WHO guidelines [6-8].

Tenofovir disoproxil fumarate (TDF), a once-daily nucleotide reverse transcriptase inhibitor, has proven immunologic and virologic efficacy when administered in combination with other antiretroviral agents in both treatment naive and treatment-experienced patients [9-12]. In clinical trials, TDF has displayed a more favorable effect on the lipid profile compared to thymidine analogs such as zidovudine and stavudine [13]. TDF is renally excreted and discontinuations due to renal-related adverse events have been reported with an estimated incidence of 0.5-2% [14-16].

Ritonavir boosted atazanavir (ATV) has been associated with less adverse lipid effects when compared to other PIs such as ritonavir boosted lopinavir [16-21]. Atazanavir typically is associated with indirect hyperbilirubinemia but infrequently causes scleral icterus and jaundice and rarely produces clinical hepatitis. This cosmetic effect is often rapidly reversible upon its discontinuation. Ritonavir boosting allows a lower daily dose (300 mg) of ATV to be effective; however, such an addition may produce additional adverse gastrointestinal effects and adverse consequences on serum lipids. Since TDF concentrations are increased by an unknown mechanism when co-administered with ATV, the potential for tenofovir-induced renal toxicity may be also be increased.

*Corresponding author: Betty J. Dong, University of California School of Pharmacy, San Francisco, CA, E-mail: dongb@pharmacy.ucsf.edu

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Although data from controlled trials demonstrate virologic efficacy and safety, experiences in routine clinical practice may not always be similar. Therefore, a retrospective study was undertaken to evaluate the virologic and immunologic efficacy as well as the safety and tolerability of once-daily regimens containing ATV/r and TDF in treatment-experienced patients at two large, urban HIV clinical practices.

Patients and Methods

Retrospective chart reviews were conducted from July 2003 to March 2005 on treatment experienced HIV-1 infected patients residing in two active, urban clinical practices (San Francisco, California and Washington, D.C.). Patients included were required to have received at least one month of concomitant once daily TDF and ritonavir boosted ATV (ATV/r) following the change from other ART regimens. The major reason for this ART change was to reduce toxicities and/or simplify therapy. At one site (Washington, D.C.), a small cohort of patients who received TDF with un-boosted-ATV (400 mg/day) were also included. This regimen was started before the pharmacokinetic drug interaction between TDF and ATV was identified.

The chart review included demographic information, HIV-1 RNA plasma concentrations, CD4 cell counts, clinical laboratory tests (including serum creatinine [SCR], total bilirubin, fasting lipids [total cholesterol, LDL cholesterol (LDL-c), HDL-cholesterol (HDL-c), triglycerides], prior and current ART, concurrent medications, and clinical adverse events as reported in the patient's medical record. This research was approved by the University of California Committee on Human Research and a private Institutional Review Board in Wash DC.

Data were collected for visits at baseline (defined as the first visit at which both TDF and ATV or ATV/r were being prescribed concurrently), and during clinic visit windows centered on 2-4, 5-7, 9-10, and 11-13 months after baseline. Data from both sites were pooled for analysis. The primary effectiveness endpoint was the proportion of patients with HIV RNA <400 c/mL (most sensitive assay available at that time at the WASH DC site). HIV RNA <75 c/mL at 12 months.

Of the 55 patients with HIV RNA <75 c/mL at baseline, using the last observation or through 12 months, 51 patients maintained HIV RNA <400 c/mL; 88% (35/40) had HIV RNA <75 c/mL. Sixty-three of the 64 patients (98%) with HIV RNA <400 c/mL at baseline maintained viral load suppression through 12 months, and 17 of 25 patients (68%) with baseline HIV RNA ≥400 c/mL achieved HIV RNA <400 c/mL at baseline.

The safety population included all subjects who received at least one dose of TDF with ATV, the efficacy population consisted of all patients remaining on therapy (as treated). Patients receiving lipid lowering agents at baseline and those initiated during the study were not censored during data analyses. The Wilcoxon signed-rank test was used to test the significance of changes from baseline. Descriptive statistics were used to summarize patient demographic data, baseline characteristics, and change from baseline for each of the endpoints.

Results

A total of 165 treatment-experienced patients were included in the final analysis; 88 patients from the Washington, D.C. site, and 77 from the San Francisco site. Nearly all study patients were male and Caucasian, with mean age of 46±9.1 (SD) years (Table 1). A cohort of 39 patients (21%) treated at the Washington, D.C. clinic site that received ATV 400 mg/day without ritonavir boosting were also included. Data were analyzed both for the overall population and separately for those patients who did and did not receive ritonavir boosting. Patients received antiretroviral therapy that included TDF and ATV/r (or ATV) for a median (interquartile range [IQR]) of 11 (9, 12) months. Sixty-eight percent of these patients also received either FTC (38%) or 3TC (30%) with TDF + ATV/r therapy. The majority of patients (>90%) were protease inhibitor (e.g. saquinavir, indinavir) and nucleoside reverse transcriptase experienced (e.g. abacavir, zidovudine, stavudine) while 29% were non-nucleoside reverse transcriptase inhibitor experienced.

There were 29 patients (18%) who had their TDF and/or ATV discontinued. This included one patient who expired while on therapy (determined not to be study drug-related), 4 patients that had TDF and/or ATV discontinued for an adverse event (1 patient each - scleral icterus, diarrhea, grade 3 serum creatinine elevation, and dizziness/fatigue), 5 patients who had their therapy changed for virologic failure (confirmed HIV RNA ≥ 400 copies/mL), 4 patients who were lost to follow-up, 4 patients who switched to other agents, and 11 patients who discontinued for personal or other reasons.

Efficacy

At baseline, 117 patients (71%) had HIV RNA values <400 copies/ml; of which 55 had HIV RNA <75 copies/mL; 44 patients (27%) had HIV RNA ≥400 copies/mL, and 4 patients (2%) had missing values at baseline. At the 12 month assessment, 90% of patients with available HIV RNA values (81/90 patients, including 9/25 on unboosted ATV) had <400 copies/mL; 88% (35/40) had HIV RNA <75 c/mL. Sixty-three of the 64 patients (98%) with HIV RNA <400 c/mL at baseline maintained viral load suppression through 12 months, and 17 of 25 patients (68.0%) with baseline HIV RNA ≥400 c/mL achieved HIV RNA <400 c/mL following treatment with TDF+ ATV/r (Figure 1). Of the 55 patients with HIV RNA <75 c/mL at baseline, using the last observation or through 12 months, 51 patients maintained HIV RNA <75 c/mL; 13 patients with detectable viral load at baseline achieved HIV-RNA <75 c/mL at 12 months.

A slightly higher proportion of patients receiving ATV/r (75%) than receiving unboosted ATV (65%) had HIV RNA <400 c/mL at baseline.

### Table 1: Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Boosted&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Unboosted&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Overall&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean SD)</td>
<td>47 ± 9.6</td>
<td>44 ± 6.4</td>
<td>46 ± 9.1</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>129 (80.5%)</td>
<td>34 (100%)</td>
<td>163 (98.8%)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>2 (1.5%)</td>
<td>0 (0%)</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian, n (%)</td>
<td>n/a</td>
<td>n/a</td>
<td>5 (3.0%)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>n/a</td>
<td>n/a</td>
<td>12 (7.3%)</td>
</tr>
<tr>
<td>Hispanic, n (%)</td>
<td>n/a</td>
<td>n/a</td>
<td>3 (1.8%)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>n/a</td>
<td>n/a</td>
<td>145 (87.9%)</td>
</tr>
<tr>
<td>Treatment duration in months, median (range)</td>
<td>11 (1–17)</td>
<td>19 (6–33)</td>
<td>11 (133)</td>
</tr>
</tbody>
</table>

Footnote: *all values in mg/dL

<sup>a</sup>300 mg atazanavir boosted with 100 mg ritonavir
<sup>b</sup>400 mg atazanavir given without ritonavir
<sup>c</sup>Data available for 99 patients

SD, standard deviation
n/a, not available
Patients in both groups had a positive response to treatment with TDF/FTC or 3TC + ATV/r: at 12 months, 94% and 75% of patients receiving ATV/r and unboosted ATV, respectively, had HIV RNA <400 c/mL at 12 months.

CD4 counts remained essentially unchanged from baseline. At baseline, the median (interquartile range [IQR]) CD4 count was 475 (317, 660), which was similar in patients receiving boosted compared to unboosted ATV. Overall, the median (IQR) change from baseline at 6 months (n = 128) and 12 months (n = 89) were 26 (-54, 103) and 26 (-46, 107) cells/mm³, respectively. Similar changes were observed for boosted versus unboosted ATV containing regimens.

Adverse events

During the study period, 20 patients (12%) experienced Grade 4 hyperbilirubinemia, 69 (42%) Grade 3, and 40 (30%) Grade 2. A higher proportion of patients receiving boosted ATV (46%, n = 60) than unboosted (27%, n = 9) had Grade 3 hyperbilirubinemia; 3 patients on unboosted ATV had Grade 4. One patient with scleral icterus, who also had Grade 3 hyperbilirubinemia, discontinued the study.

Renal assessment: Median (IQR) estimated glomerular filtration rate (eGFR) as determined by the C-G and MDRD methods through 12 months are presented in Figure 2. At baseline, the median (IQR) eGFR was 96 (82, 114) mL/min by C-G and 77 (68, 97) mL/min/1.73m² by MDRD. The median change in eGFR from baseline at 12 months (n = 88) was 0 (-11 to 11) mL/min by C-G and 0 (-11 to 11) mL/min/1.73 m² by MDRD. Neither measure changed significantly over the 12 months of the study. Confirmed creatinine increases from baseline were observed in 6 patients (3 with Grade 1, 2 with Grade 2, and 1 with Grade 3 events). Treatment (TDF + didanosine + 3TC + ATV/r) was discontinued in one patient, with history of right renal atrophy and nephrolithiasis, who experienced a Grade 3 Scr increase from 1.5 mg/dL to 1.7 mg/dL at baseline to 3.2 mg/dL. The last available Scr for this patient after TDF discontinuation was 1.7 mg/dL. Another patient with a history of nephrolithiasis continued TDF + ATV/r without any negative renal consequences; his last serum creatinine was 0.93 mg/dL.

Lipid assessments: Fasting lipid profiles are presented in Table 2. At the 12 month treatment window, reductions in median total cholesterol (p=0.02), HDL-c, LDL-c, and triglycerides were observed. Median LDL-c and total cholesterol were at the optimal (LDL-c <100 mg/dL) and desirable range (total cholesterol <200mg/dL) as defined by the National Cholesterol Education Program, Adult Treatment Panel III at baseline and remained there 12 months after study initiation [22]. Lipid lowering agents were used by 45 of 77 patients at the San Francisco site; these agents were used prior to study initiation in all patients and continued at the same dose level throughout the period of evaluation. This data was not available for the Washington DC site.

Discussion

In this retrospective study of treatment-experienced patients in the real world community setting, >90% of patients achieved or maintained
HIV RNA <400 c/mL after changing to at least 12 months of once daily treatment that included mostly ritonavir boosted ATV and TDF. Two-thirds of patients were also receiving either FTC or 3TC as their NRTI backbone. For the primary endpoint, a threshold of HIV-1 RNA <400 copies/mL was chosen since at the time of study, an ultrasensitive HIV-1 RNA assay was not available for all patients. However, the ultrasensitive assay was available in 47% (n=55) of subjects, mostly located at the SF site. Our results generated from a clinical practice community setting are very consistent with those reported in a prospective, open-label, randomized trial, in which 84% of treatment-experienced patients had HIV RNA <400 c/mL after 96 weeks of treatment with ATV/r and TDF in an as-treated analysis [23]. In contrast, a prospective study of TDF + ATV/r found little improvement in viral load in patients with extensive prior ART therapy due to presence of mutations at baseline showing genotypic and phenotypic resistance to ATV/r [24].

Administration of TDF with ATV results in a bi-directional pharmacokinetic drug interaction that results in an approximately 25% increase in tenofovir serum concentrations while reducing ATV trough concentrations by as much as 40% [25]. This reduction in ATV serum concentrations by TDF is overcome by boosting ATV with low dose (100 mg once daily) ritonavir [26]. Although the combination of unboosted ATV and TDF is not recommended, 9/25 of our patients achieved viral load suppression consistent with previous reports [27,28].

Adverse events observed in our subjects are similar to other reports. As expected, ATV induced hyperbilirubinemia was common, but was not usually bothersome enough to warrant treatment discontinuation [19,23,29]. Grade 3 hyperbilirubinemia was more common in patients receiving boosted than unboosted ATV but Grade 4 elevations were uncommon. Grade 3 to 4 laboratory abnormalities were reported in 59% of those receiving ritonavir boosted ATV compared to 20% on unboosted ATV [30]. A single-arm 48-week study assessing safety and efficacy of TDF/FTC with ATV/r in antiretroviral naïve patients observed Grade 3 elevations in 44% of patients and Grade 4 elevations occurred in 5% of patients [31].

Routine serum creatinine was regularly monitored in this cohort. One patient discontinued ART with a Grade 1 elevation in Scr which continued to increase after discontinuation of TDF. However, no significant deterioration of renal function was observed during the 12 months using eGFR calculated by C-G and MDRD, a more accurate assessment of renal function. These findings are similar to several other prospective, controlled studies showing minimal reductions in GFR and less than a 2% incidence of serum creatinine elevations [10,13-16,21,31]. Our findings suggest that TDF given with ATV is well tolerated from a renal perspective with few patients experiencing moderate to severe renal events.

Both ATV and TDF have been reported to have favorable lipid profiles when compared other antiretroviral classes, especially TDF plus LPV/r [16,17,23,29,32]. In this study even with the inclusion of ritonavir, median fasting total cholesterol, LDL-c, and triglycerides improved with the therapy change to TDF + ATV/r. A slight reduction in HDL-c was seen which is not likely to be of clinical relevance.

The primary limitation of this study is the non-comparative, retrospective design. In addition, the somewhat heterogeneous population consisted of mostly young men with minimal co-morbidities.

In addition, the design precluded an assessment of adherence to once daily therapy. Nonetheless, our results are noteworthy as they represent first-hand community experience on the efficacy, tolerability, and toxicity of these agents and, despite the limited design, are consistent with those reported in other prospective, controlled studies [30,31].

In conclusion, the combined use of ATV plus TDF in combination with FTC or 3TC in two large urban clinical practices was safe, well tolerated, and maintained virologic control of HIV in treatment-experienced patients. Changing to an ATV/r plus TDF/FTC or 3TC containing regimen also resulted in a favorable effect on lipid parameters while eGFR remained stable.

Acknowledgement

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References

8. European guidelines for HIV infection.