Virologic and Immunologic Outcomes in Patients Switched from Amprenavir to Fosamprenavir in a Clinical Practice Setting

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Abstract

In a 24-week phase 4, non-randomized, open-label, single-arm study, 19 HIV-infected patients receiving amprenavir (APV)-based highly active antiretroviral therapy (HAART) for 1.3-4.2 years (mean, 3.1 years) were switched to equimolar fosamprenavir (FPV) doses with no other changes in their treatment regimens. Most patients (74%) received APV/ritonavir 600mg/100mg twice daily at screening. All but one were switched to FPV/ritonavir 700mg/100mg twice daily. Between baseline and week 24 after switching, clinical status generally remained stable or improved: median viral load 751 vs 71 copies/mL; CD4+ count 570 vs 622/mm³; proportion with viral load <400 copies/mL 47% vs 71%, and <50 copies/mL, 32% vs 35%. In 13 patients whose baseline HIV-1 RNA was >50 copies/mL, eight remained at this level and three were below it at week 24 (the other two were lost to follow-up). No study drug-related adverse events were reported and laboratory values did not notably change.

Introduction

Since the introduction of protease inhibitors (PI) in highly active antiretroviral therapy (HAART) for HIV infection in the mid-1990s, HIV-related morbidity/mortality has decreased to one-fifteenth the level observed prior to the HAART era [1,2]. Amprenavir, the fourth PI to become available, offered some advantages over earlier PIs, including the option for once- or twice-daily dosing, minimal effect of food on its pharmacokinetics and a favorable resistance profile [3,4]. However, APV's low aqueous solubility necessitated a large, cumbersome capsule formulation containing propylene glycol and vitamin E as solvents and APV administration involved a high pill burden (16 capsules daily for unboosted treatment in adults), both of which could negatively impact adherence.

Research efforts to reduce the pill burden of APV delivery while retaining APV's dosing flexibility led to the development of fosamprenavir (FPV), the more water-soluble calcium phosphate ester prodrug of APV. An oral dose of 700 mg of FPV is equimolar to APV 600 mg [5]. FPV is rapidly hydrolyzed to APV and inorganic phosphate as it is absorbed through the gut epithelium. A daily regimen of unboosted FPV requires that the patient take only four 700-mg tablets daily, which is less than one-quarter the pill burden associated with an equimolar unboosted APV daily regimen. Subsequent clinical trials with FPV combined with a nucleoside backbone confirmed its clinical value in both antiretroviral naïve- and -experienced patients [6-10].

As patients stabilized on APV are currently being switched to FPV in HAART regimens (as the capsule formulation of APV is being discontinued in most countries), it is important to evaluate if and how this switch affects treatment response and the patients' clinical status. The purpose of the present study was to assess over 24 weeks virologic and immunologic response and treatment tolerability in antiretroviral-experienced patients who switched from APV-containing HAART regimens to regimens containing equimolar doses of FPV with no other changes in their regimens.

Materials and Methods

COL101310 was a phase 4, non-randomized, open-label, single-center study for which the inclusion criteria were as follows: male or non-pregnant, non-breastfeeding female ≥18 years old,

HIV-1 infection documented by HIV-1 antibody enzyme-linked immunosorbent assay (ELISA) and Western blot test; any HIV-1 RNA level and CD4+ cell count; not currently receiving other PIs; and not enrolled in any other clinical trial of an investigational agent. The APV component of regimens was replaced by an equimolar dose of FPV, as shown in (Table 1) and patients were followed for 24 weeks. No change in the type or dose of any other antiretroviral regimen component was permitted.

At screening, weeks 6, 12 and 24 and withdrawal, assessments were made of plasma viral load (HIV-1 RNA) using Roche Amplicor MONITOR Ultrasensitive assay, Version 1.5 (lower limit of quantitation

	APV regimen	FPV regimen
Patients who received APV as first their PI	APV 1200 mg BID + SBG	FPV 1400 mg BID (or FPV 700 mg + RTV 100mg BID) + SBG
	APV 600 nmg + RTV 100 mg BID + SBG	FPV 700 mg + RTV 100mg BID + SBG
	APV 1200 mg + RTV 200 mg QD + SBG	FPV 1400 mg + RTV 200 mg QD) or FPV 1400 mg + RTV 200 mg QD (or FPV 700 mg + RTV 100 mg BID) + SBG
Patients who received APV as their second or third PI	APV 1200 mg BID + RTV 200mg QD + SBG	FPV 700 mg + RTV 100mg BID + SBG
	APV 600 mg + RTV 100 mg BID + SBG	FPV 700 mg + RTV 100mg BID + SBG

[a]*Abbreviations:* APV, amprenavir; BID, twice daily; FPV, fosamprenavir; QD, once daily; RTV, ritonavir.

Table 1: Initial APV Regimen and the FPV regimen to which Patients were Switched[a].

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Patient No.	Baseline		Week 6		Week 12		Week 24	
	VL	CD4+	VL	CD4+	VL	CD4+	VL	CD4+
1	180,000	325	399	299	4,670	288	6,150	367
2	ND	ND	49	524	49	738	59	990
3	1,040	440	1,510	359	49	423	152	316
4	492	788	1,630	624	49	518	695	868
5	3170	934	2,250	922	1.600	959	60,200^b	503
6	399	268	MV	MV	78	292	84	268
7	1,540	247	511	273	3,760	299	LTFU	LTFU
8	3,370	1699	1,160	1472	49	804	2,370	653
9	399	617	546	670	MV	MV	233	618
10	49	160	49	456	572	532	544	532
11	49	292	49	197	49	238	49	490
12	49	571	284	612	51	203	55	690
13	49	1056	49	1277	1,340	1193	49	1462
14	1,410	967	909	906	515	647	71	955
15	49	568	49	484	49	447	49	517
16	18,800	292	MV	MV	2,640	143	LTFU	LTFU
17	1,100	679	89	561	109	507	49	896
18	52	449	416	528	101	509	49	622
19	1,010	1049	673	1144	49	1102	49	1134
Median	751	570	416	561	90	508	71	622
Mean	13,264	633	625	665	877	547	4171	699

[a]*Abbreviations:* LTFU, lost to follow up; MV, missed visit to clinic; ND, laboratory values not done; VL, viral load.
[b]This patient stopped his antiretroviral regimen 2 weeks prior to his week 24 visit, and this lead to a marked viral rebound.

Table 2: Viral Load Change (copies/mL) and CD4+ Cell Count (Cells/mm³) in Each Patient following Switch from Amprenavir to Fosamprenavir[a].
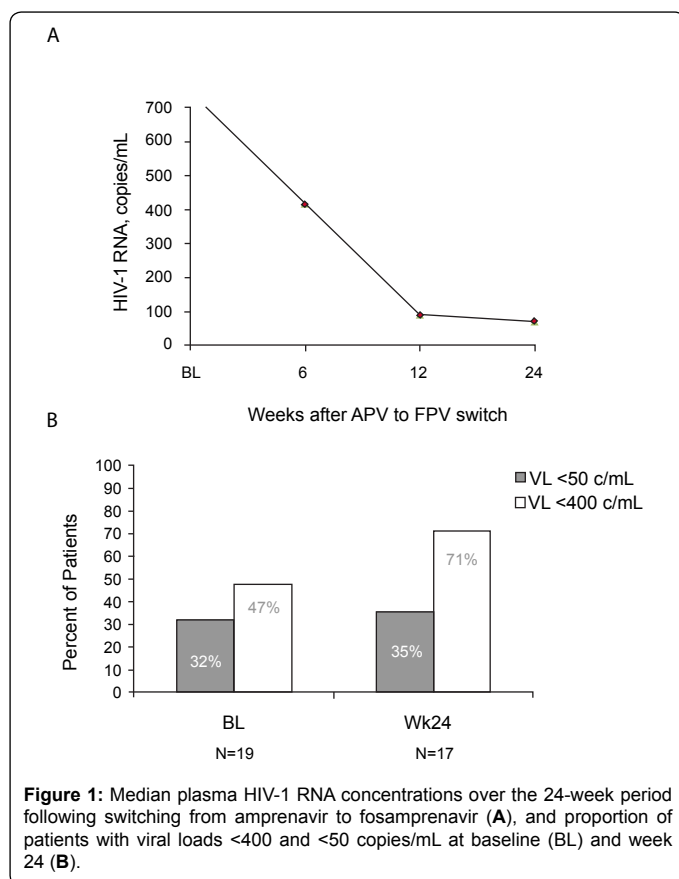

Figure 1: Median plasma HIV-1 RNA concentrations over the 24-week period following switching from amprenavir to fosamprenavir (**A**), and proportion of patients with viral loads <400 and <50 copies/mL at baseline (BL) and week 24 (**B**).

[LLOQ] 50 copies/mL; Roche Diagnostics, Branchburg, New Jersey) and HIV-1 MONITOR Version 1.0 polymerase chain reaction (PCR) assay (LLOQ, 400 copies/mL; Roche, Nutley, New Jersey). At these time points, the following were also assessed: CD4+ cell count by flow cytometry, adverse events by open-ended questions posed to the study patients and standard laboratory tests. Patients who never achieved a viral load <400 copies/mL or who achieved it during treatment but lost it by week 24 were considered virologic failures.

FPV was administered as 700-mg tablets of Lexiva® (GlaxoSmithKline, Research Triangle Park, NC) and ritonavir as 100-mg capsules of Norvir® (Abbott Laboratories, Chicago, Illlinois). Adherence was checked by pill counts made by study personnel. In virologic failures, drug-susceptibility phenotype was assessed by ViroLogic Inc. (South San Francisco, California, USA) using the GENESEQ and the PHENOSENSE assays. Statistical analysis of the study results was primarily descriptive. However, the Wilcoxon signed-rank test was used to test whether the median change from baseline of $\log_{10}$ HIV-1 RNA at week 24 was zero. The significance of change in CD4+ cell count between baseline and week 24 was analyzed by the non-parametric paired Wilcoxon test.

Results

Nineteen patients were enrolled in the study, including 18 males and 1 female. Twelve patients were African American, six white and one Hispanic. Mean duration of APV use was 3.1 years (range, 1.3-4.2 years). Most patients (14 [74%]) received APV/r 600mg/100mg BID. Baseline median viral load was 751 copies/mL (range 49-180,000 copies/mL). Forty-seven percent of patients (9) had HIV-1 RNA <400 copies/mL, of whom six (32%) were <50 copies/mL. Median CD4+ count was 570/mm³ (range, 160-1699/mm³). Seventeen patients completed the study and two were lost to follow-up.

Change in viral load over the study is shown in (Table 2) and (Figure 1A). The median change from baseline in $\log_{10}$ HIV-1 RNA at week 24 for the 16 patients with paired samples was a decrease of 0.09 $\log_{10}$ copies/mL, a difference that was not statistically significant (p=0.11). However, for the 10 patients who were detectable at baseline (>52 copies/mL), the median change from baseline was a statistically significant decrease of 0.76 $\log_{10}$ copies/mL (p=0.04).

With respect to proportions of patients achieving undetectable viral loads, a greater proportion had HIV-1 RNA <400 copies/mL (71% [12/17]) at week 24 compared with baseline (47% [9/19]) (Figure 1B). Of the nine patients whose HIV-1 RNA was <400 copies/mL at baseline, eight remained at this level and one was >400 copies/mL at week 24. Of the 10 patients whose HIV-1 RNA was >400 copies/mL at baseline, four remained at this level and four were <400 copies/mL by week 24, with two lost to follow-up.

A similar proportion of patients had HIV-1 RNA <50 copies/mL at week 24 (35% [6/17]) compared to baseline (32% [6/19]) (Figure 1B). Of the six patients who had <50 copies/mL at baseline, three remained at this level over the study period and three had an HIV-1 RNA >50 copies/mL at week 24. Of the 13 patients whose HIV-1 RNA was >50 copies/mL at baseline, eight remained at this level and three were <50 copies/mL at week 24, with two patients lost to follow-up. Only one patient whose baseline viral load was <50 copies had a viral load >400 copies/mL at week 24 (544 copies/mL).

Median CD4+ counts increased by +52 cells/mm³ (from 570/mm³ at baseline to 622/mm³ at week 24); there was only slight fluctuation over time and no significant change between baseline and week 24 (p>0.05) (Figure 2). No study drug-related or significant adverse events were reported and no significant changes in laboratory values occurred. Figure 3 depicts the changes in median lipid values. No clinically important changes in total cholesterol, LDL-cholesterol, HDL-cholesterol, or triglycerides were observed over 24 weeks post-switch. The largest fluctuations in lipids were seen with triglycerides
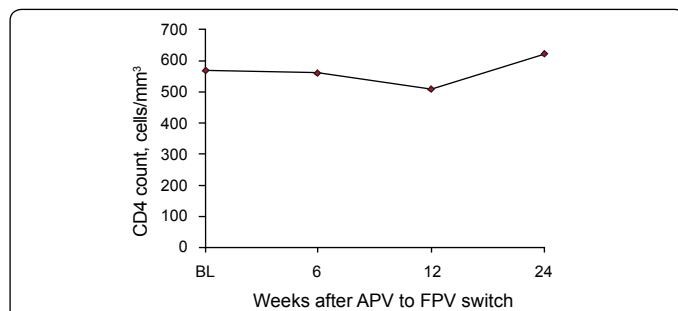
Figure 2: Changes in CD4+ cell count over the 24 weeks after switching from amprenavir (APV) to fosamprenavir (FPV).
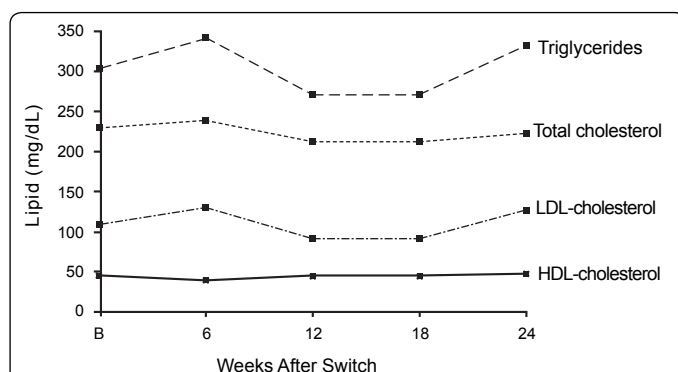

Figure 3: Changes in plasma lipid concentrations over the 24 weeks after switching from amprenavir to fosamprenavir.

and LDL-cholesterol, with variations of ±30-60 mg/dL and ±20-40 mg/dL, respectively, between each 6-weekly clinic visit through week 24.

Discussion

The results of this study show that in patients switched from equimolar doses of APV to FPV in HAART regimens with no other regimen changes, virologic suppression is maintained or improves and CD4+ counts increase over 24 weeks. Although we did not perform any pharmacokinetic assessment in this study, the FPV-containing regimens to which patients were switched were expected to provide an APV area under the plasma concentration-time curve (AUC) similar to that achieved by the patients' prior APV-containing regimens, based on the findings of a pharmacokinetics study, APV20001 [11]. In the latter randomized, crossover pharmacokinetic study in 78 HIV-infected patients, FPV 1395 mg BID and APV 1200 mg BID, each in combination with abacavir 300 mg BID and lamivudine 150 mg BID, delivered equivalent steady-state values for APV AUC at the end of a dosing interval (τ), although the minimum APV plasma concentration (C_{min}) was 28% higher and maximum APV plasma concentration (C_{max}) was 30% lower than what was seen with the APV regimen. In our study, it is possible that a higher APV C_{min} with the FPV regimen may have accounted for the greater proportion of patients achieving HIV-1 RNA <400 copies/mL following the switch. A higher APV C_{min} could have ensured APV plasma concentrations more consistently maintained above the 50% inhibitory concentrations of at least wild-type HIV isolates.

Adherence was monitored by pill count in this study. As we had no pre-study adherence information, we could not determine whether adherence was different during FPV treatment compared to prior APV treatment. However, another clinical trial, CLASS (ESS40001) [12,13], did monitor adherence by a self-administered adherence questionnaire, PMAQ-7 [14], in patients switching from APV to equimolar doses of FPV with an abacavir/lamivudine nucleoside backbone. Sixty-six patients were followed for a median of 175 days on APV and 570 days on FPV. PMAQ-7 results showed no overall difference in adherence between the APV and FPV study phases, although patients reported greater satisfaction with FPV treatment than APV treatment. Seventy-nine percent of the study patients who had a viral load <400 copies/mL prior to the APV-to-FPV switch maintained this level of viral suppression while on FPV.

Patients in our study reported no change in treatment tolerability following the APV to FPV switch, an observation also noted among the treatment-experienced patients in CLASS [13]. In general, treatment-experienced patients may not detect important changes in regimen tolerability because they frequently gain tolerance to certain adverse events over time, especially those affecting the gastrointestinal tract [14]. In contrast, studies in antiretroviral-naïve subjects that have directly compared equimolar FPV and APV have reported a considerably better gastrointestinal safety profile with the FPV regimens. Thus, in the healthy subjects in APV10022, FPV 700 mg BID plus RTV 100 mg BID was associated with one-fifth the rate of nausea (6% vs 33%) and half the rate of vomiting and abdominal pain (6% vs 13%) over a 14-day dosing period [16]. Similarly, in APV20001, which directly compared FPV 1395 mg BID plus abacavir/lamivudine with APV 1200 mg BID plus the same nucleoside backbone, the FPV regimen was associated with a lower frequency of nausea (4% vs 22%) and abdominal pain (4% vs 17%) [11]. Better GI tolerability with FPV, where observed, could in part be explained by the lower bulk/pill count associated with FPV dosing compared to APV dosing and possibly to the lower APV C_{max}'s that result following FPV doses.

No important lipid changes were noted following the APV to FPV switch. This is consistent with a similar finding noted in CLASS following an equimolar switch from APV to FPV [12]. It is also expected by the lack of clinically important differences in lipid changes observed over 4 weeks when equimolar doses of APV and FPV were directly compared [11]. The considerable fluctuations in triglycerides and LDL-cholesterol we observed after the APV-to-FPV switch were likely related to temporary alterations in diet and/or physical activity by the patients during the study (not monitored), rather than to treatment-related reasons because changes in components of antiretroviral regimens or in antihyperlipidemics were not made.

The design of our study was limited by the absence of inclusion of MEMS adherence measures, plasma APV assessments, resistance measurements and a quality-of-life evaluation before and after the switch to the FPV regimens. However, improvement has been reported previously in one quality-of-life measurement in CLASS following an APV to FPV switch [12]. A large number of studies have shown that the degree of T cell activation predicts disease progression better than either viral load or peripheral blood CD4+ T cell counts (using classical markers such as HLA-DR, CD38 and Ki-67) [17-20]. It would be interesting to see how an APV-to-FPV switch impacts levels of CD4+ and CD8+ T cell activation and/or proliferation using such classical markers. This type of study needs to be explored in future clinical trials of patients converting from APV-based to FPV-based regimens.

In conclusion, in treatment-experienced patients switched from APV- to FPV-containing HAART, virologic suppression was maintained or improved and CD4+ counts increased over the ensuing 24 weeks, without drug-related adverse events or worsening laboratory values.

Acknowledgments

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