Impact of HIV subtype on response and resistance in antiretroviral-naïve adults comparing treatment with once daily *versus* twice daily ritonavir boosted fosamprenavir in combination with Abacavir/Lamivudine

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Abstract

The impact of HIV-1 subtype on resistance mutation selection and on virologic response to fosamprenavir in combination with once-daily (QD) *versus* twice-daily (BID) dosing of ritonavir was examined in a prospective, open label, randomized study in antiretroviral-naïve, HIV-1 infected subjects. Study APV109141 compared QD fosamprenavir/ritonavir (1400 mg/100 mg) to BID fosamprenavir/ritonavir (700 mg/100 mg), administered in combination with a QD fixed-dose abacavir/lamivudine (600 mg/300 mg) combination tablet through 48 weeks in ART-naïve subjects. HIV genotypes were obtained from all subjects at screen. Subjects with virologic failure (VF) were also genotyped at baseline and VF. HIV subtypes observed in the ITT (n=214) population were A or AE or AG circulating recombinant forms (CRFs) 19%; B 62%; BF or BG CRFs 2%; C or CPX CRFs 7%; D 2%; F1 7%; G<1%. By TLOVR (ITT-exposed), 86/106 (81%) of subjects on QD study arm and 87/106 (82%) in the BID arm achieved plasma HIV-RNA<400 copies/mL at Week 48. Three subjects met VF criteria, 2 receiving QD fosamprenavir/ritonavir; 1 receiving BID fosamprenavir/ritonavir; (HIV subtype B, F1 A1, respectively). Baseline drug resistance was detected in 2/3 VFs: Subject 1-RT: K103K/N, T215C; major PI: V82A, L90M; and Subject 2-RT: M41L, L74V. Only virus from one subject with VF selected for any treatment-emergent mutation (Subject 1; M184V). Post-VF, Subject 3 (subtypeA1) suppressed HIV-RNA >400 copies/mL through 48 weeks. Subtype appeared to have no preferential impact on virologic response or selection for specific resistance mutations in subjects receiving fosamprenavir/ritonavir. Virologic failure rate was rare (3 subjects; each from different subtypes). At VF, virus from only one subject selected any HIV NRTI mutation (M184V); none selected major protease mutations.

Introduction

Naturally-occurring genetic polymorphisms in HIV protease (PR) and reverse transcriptase (RT) have been found among drug-naïve subjects infected with non-B subtypes.[1-6] The clinical relevance of these baseline polymorphisms in non-B viruses remains controversial, as most studies on drug susceptibility are conducted in countries where subtype B predominates, yet on a global scale, subtype B accounts for just 12% of HIV-1 infections worldwide.[7] Some investigators have concluded that there are subtype-specific differential effects of mutations, including selection of different pathways or more rapid emergence of resistance.[8-13] Other investigators have suggested that non-B subtypes may select for the same drug resistant mutations selected in subtype B but in different proportions in PR and RT,[14] while some have suggested that the response to antiretroviral therapy may be independent of subtype and baseline polymorphisms.[15-17] Specific drug resistance-associated protease mutations, including K20I, M36I and V82A are significantly more common among non-B viruses,[12] and for nelfinavir, one of the best-studied protease inhibitors (PI) in non-B subtypes, there are subtype specific pathways to resistance and the level of resulting drug susceptibility is different for subtypes B, C and G.[9-18]

For PIs, the use of lower doses of ritonavir (/r) to boost plasma drug levels, including fosamprenavir (FPV), is becoming more common,[19-20] however, any potential impact on response and resistance in non-B subtypes is less well documented. In the APV 109141 study antiviral-therapy (ART) naïve subjects were randomized to once-daily (QD) FPV/r (1400 mg/100 mg) or twice-daily (BID) FPV/r (700 mg/100 mg), both administered with QD abacavir/lamivudine (ABC/3TC) and virologic response and resistance was assessed over 48 weeks on therapy. The study was conducted in Europe, and included a sizeable number of subjects infected with HIV of non-B subtypes. This enabled examination of differences in response, and allowed for observation of drug resistance mutations prior to ART initiation and resistance mutations selected at virologic failure.

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Materials and Methods

Participants

Antiretroviral-naïve, HIV-infected therapy adult subjects (≥18 years) were recruited from 61 European centers in Europe. The full study design and safety and efficacy results have been published.[21] Briefly, all eligible subjects had HIV-1 RNA of ≥1000 copies/mL at the screening visit. Subjects were excluded if they had evidence of HIV genotypic as defined by the 2006 ANRS AC-11 algorithm,[22] resistance at screening or prior documented evidence of genotypic and/or phenotypic (above threshold for reduced susceptibility) resistance to FPV/r, ABC or 3TC or if they had protocol-specified abnormal laboratory values or if medical conditions that could compromise their safety or interfere with drug absorption. All sites were required to have ethics committee approval before patients could be enrolled in the study and all patients provided written informed consent. This study was conducted in accordance with good clinical practice. This study is registered with ClinicalTrials.gov, number NCT00450580.

Procedures

Study APV109141 was a multi-center, open-label, 1:1 randomized study that compared FPV 1400 mg (two tablets) QD plus /r 100 mg (one capsule) QD or FPV 700 mg (one tablet) BID plus /r 100 mg (one capsule) BID, each in combination with a QD fixed-dose combination tablet of 600 mg/300 mg ABC/3TC. Treatment allocation was stratified by screening HIV-1 RNA (<100,000 copies/mL and ≥100 000 copies/mL), BMI (< or ≥25 kg/m^2), and non-HDL cholesterol (< or ≥3.38 mmol/L [130 mg/dL]). Subjects experiencing a suspected ABC hypersensitivity reaction were allowed to substitute any approved nucleoside reverse transcriptase inhibitor (NRTI) and continue in the study. No other antiretroviral substitutions were allowed.

Viral genotypes were analyzed by VIRCO (Mechelen, Belgium) for all subjects at screening and supplied the subtype or CRF assignments associated with each genotype; virus from enrolled subjects who met virologic failure criteria were also genotyped at baseline and at virologic failure. Genotypic mutations were reported as any major or minor mutation that emerging on treatment (as defined by the International AIDS Society-USA Guidelines.[23] Enrolled subjects were evaluated at baseline, and at weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48, or withdrawal for HIV-1 RNA, CD4/CD8-positive lymphocyte subsets, clinical chemistries, and hematology (assessed centrally by Quest Diagnostics in Van Nuys, CA, USA and Heston, UK).

Virologic failure definition

Virological failure was defined as a failure to achieve a 1 $\log_{10}$ copies per mL decrease in plasma HIV-1 RNA by week 4 (relative to baseline value, confirmed by a second consecutive HIV-1 RNA determination), or two consecutive plasma HIV-1 RNA measures ≥400 copies/mL after being previously <400 copies/mL on or after Week 4, or two consecutive plasma HIV-1 RNA measures ≥400 copies/mL on or after Week 24.

Statistical analysis

The intent-to-treat exposed (ITT-E) population included all subjects randomized and exposed to at least one dose of randomized study medication. The primary efficacy analysis was based on the proportion of subjects who achieved HIV-1 RNA <400 copies/mL at 48 weeks ITT-E, using the time to loss of virologic response (TLOVR) algorithm. TLOVR responders were subjects with confirmed HIV-1 RNA <400 copies per mL on two consecutive occasions who had not yet met any non-responder criterion, while non-responders were subjects who never achieved confirmed HIV-1 RNA <400 copies per mL, who prematurely discontinued study or study drug for any reason, had confirmed rebound of 400 copies per mL or greater, or had an unconfirmed HIV-1 RNA of ≥400 copies/mL on their final study visit.

Results

Pre-antiviral treatment

Two hundred and forty-one subjects from 67 centers had HIV genotyped at the screening visit. The viral genotype obtained by VIRCO was analyzed for subtype distribution. The majority of these subjects were infected with subtype B virus (62%; 149/241). Subtype A1 and A circulating recombinant forms (CRFs) were the next most prevalent (19%; 46/241), however, numerous other subtypes or CRFs were detected (Table 1). Of the 241 subjects, 214 subjects met all enrollment criteria and were randomized. The subtype distribution between subjects who were randomized and those who were not were similar, although all subjects with some of the less abundant subtypes or CRFs (BG, CPX, D and F1) were represented in the randomized group and none failed to meet enrollment criteria. Two of 214 subjects received no study drug. The ITT-E population included 212 subjects (106 subjects per arm).

Baseline characteristics were similar between subjects randomized to the two treatment arms (Table 2). The ITT-E population had high median baseline HIV-1 RNA values (4.949 $\log_{10}$ copies/mL) and low median CD4 counts (247 cells/μL), with 45% having baseline HIV-1 RNA ≥100,000 copies/mL and 22% having CD4 count <150 cells/μL.

Relatively few major resistance associated mutations were detected in this ART naïve screening population (Table 3). The most commonly detected mutations were the RT non-nucleoside reverse transcriptase inhibitor (NNRTI) K103N (9/241) and V106I (7/241) and thymidine analogue mutations (TAMs) reversion mutations (11/241); while the RT TAMs T215F/Y mutations were not detected. There was no obvious bias with respect to randomization of the two arms based on screening resistance mutations, however one subject whose HIV had the RT L74V was randomized to the FPV/r QD, one subject with the major HIV PI mutation I46L was randomized to receive FPV/r BID, and several subjects on both study arms had virus containing one to two TAMs, as detection of these mutations were not exclusionary based upon the 2006 ANRS algorithm.

Response on therapy

At week 48, the response rates for the proportion of subjects who achieved HIV-1 RNA <400 copies/mL were 81% in the QD and 82% in the BID group by ITT-E, TLOVR analysis (95% CI for treatment difference -11.4 to 9.5). In the ITT-E observed analysis population, 179/212 had <400 copies/mL HIV-1 RNA response rates, including 98% of subjects (87/89) receiving QD FPV/r and 98% in subjects (88/90) receiving BID FPV/r. Similar results were seen between the two study arms for the ITT-E, TLOVR <50 copies/mL HIV-1 RNA endpoint at week 48, with response rates of 76% (81/106) in the QD arm and 77% (72/106) in the BID arm; ITT-E, while in the observed analysis, response rates were 94% (84/ 89) for the QD and 93% (84/90) for the BID arm.

Only three of the 212 subjects who received treatment met protocol-defined virologic failure criteria, one receiving fosamprenavir/ritonavir BID and two receiving fosamprenavir/ ritonavir QD (HIV subtypes A1, B and F1, respectively).

Subject 1, a 36 year old white male, was randomized to the FPV/r QD arm and met virologic failure criteria at Week 24 on therapy

Table 1. Summary of the prevalence of HIV-1 subtypes or circulating recombinant forms by frequency at screen.

Subtype or CRF	Not randomized (N=27)	FPV/r QD (N=107)	FPV/r BID (N=107)	Total (N=241)
A1	3 (11%)	6 (6%)	4 (4%)	13 (5%)
AE	1 (4%)	8 (7%)	2 (2%)	11 (5%)
AG	1 (4%)	11 (10%)	10 (9%)	22 (9%)
B	17 (63%)	59 (55%)	73 (68%)	149 (62%)
BF	1 (4%)	0	3 (3%)	4 (2%)
BG	0	1 (<1%)	0	1 (<1%)
C	3 (11%)	7 (7%)	4 (4%)	14 (6%)
CPX	0	2 (2%)	2 (2%)	4 (2%)
D	0	3 (3%)	2 (2%)	5 (2%)
F1	0	9 (6%)	6 (6%)	15 (6%)
G	1 (4%)	1 (<1%)	0	2 (<1%)
U	0	0	1 (<1%)	1 (<1%)

CRF, circulating recombinant forms; FPV, fosamprenavir; QD, once-daily; BID, twice-daily.

Table 2. Summary of demographic characteristics, intent-to-treat exposed population.

	FPV/r QD (N=106)	FPV/r BID (N=106)	Total (N=212)
Median age (range)	37	38	38
Male, n (%)	79 (75)	77 (73)	156 (74)
Median Height (cm)	172	173	173
Median Weight (kg)	70	70	70
Race, n (%)			
African American/African heritage	23 (22)	22 (21)	45 (21)
American Indian/Alaskan native	3 (3)	3 (3)	6 (3)
Asian – South East Asian	2 (2)	2 (2)	4 (2)
White – Arabic/North African	1 (<1)	1 (<1)	2 (<1)
White – White/Caucasian/European	75 (71)	78 (74)	153 (72)
Mixed race	2 (2)	0	2 (<1)
Ethnicity n (%)			
Hispanic or Latino	11 (10)	9 (8)	20 (9)
Not Hispanic or Latino	95 (90)	97 (92)	192 (91)

CRF, circulating recombinant forms; FPV, fosamprenavir; QD, once-daily; BID, twice-daily.

Table 3. Summary of the prevalence of IAS-USA defined HIV-1 major protease, nucleoside reverse transcriptase inhibitor or non-nucleoside reverse transcriptase inhibitor mutations or thymidine analogue mutations reversion mutations at screen.

Mutation	Not randomized (N=27)	FPV/r QD (N=107)	FPV/r BID (N=107)	Total (N=241)
Major protease				
L33F	0	2 (2%)	1 (<1%)	3 (1%)
M46L	0	0	1 (<1%)	1 (<1%)
Q58E	1 (4%)	1 (<1%)	1 (<1%)	3 (1%)
L90M	1 (4%)	1 (<1%)	1 (<1%)	3 (1%)
NRTI				
M41L	2 (7%)	3 (3%)	1 (<1%)	6 (2%)
D67N	1 (4%)	0	0	1 (<1%)
L74V	0	1 (<1%)	0	1 (<1%)
L210W	0	0	2(2%)	2 (<1%)
T215C/D/E/N/S	3 (11%)	3 (3%)	5 (5%)	11 (5%)
K219E/Q	1 (4%)	2 (2%)	2(2%)	5 (2%)
Major NNRTI				
K103N	2 (7%)	3 (3%)	4 (4%)	9 (4%)
V106I	0	5 (5%)	2 (2%)	7 (3%)
Y181C	0	2 (2%)	2 (2%)	4 (2%)
G190A	0	1 (<1%)	0	1 (<1%)

CRF, circulating recombinant forms; FPV, fosamprenavir; QD, once-daily; BID, twice-daily.

(Figure 1). The subject was Hepatitis B and C negative at screen, CDC classification A at time of treatment initiation, and listed homosexual contact as a risk factor. The subject was infected with subtype B HIV, and had both RT and PR drug resistance-associated mutation at baseline prior to initiation of therapy (Table 4). These mutations included the TAMs reversion mutation T215C, the NNRTI mutation K103K/N and multiple PR mutations, including L10I, I13I/V, K20I, M36I, F53L, L63P/T, A71V, V82A, L90M, and I93F. Interestingly, this subject was genotyped three weeks prior at the screening visit and all PR mutations detected at baseline were observed except for the V82A mutation. The subject experienced a >1 log decline in HIV-RNA by Week 4, but never suppressed HIV-RNA below 400 copies/mL. The site reported that this subject experienced a Lues reinfection after study enrollment; however no information was received from the site regarding whether the re-infection in any way altered study drug dosing compliance. By the time of virologic failure (Week 24), HIV from this subject had selected for the RT M184V mutation, associated with a reduced response to 3TC, a component of the therapy the subject was receiving.

Subject 2, a 19 year old white female, was randomized to the FPV/r QD arm and met virologic failure criteria at Week 36 on therapy (Figure 1). The subject was CDC classification C (AIDS-defined) at time of treatment initiation, hepatitis B positive and hepatitis C negative. The subject listed transfusion as a risk factor. The subject was infected with subtype F1 HIV-1. Genotyping performed prior to ART initiation (Table 4) detected NRTI mutations that could impact the response to abacavir (L74V, M41L), as well as several minor PR mutations. The subject experienced a rapid decline in viral load to <400 copies/mL by Week 4 and remained virologically suppressed through Week 24, followed by a viral rebound detected at Week 36. At the time of initial (Week 36) and confirmation (at Week 38) of virologic failure, there was no selection for any treatment emergent mutation. The site reported at the time of the suspected and confirmed

Table 4. HIV resistance mutation genotypes observed in virus from patients with virologic failure.

	Timepoint	RT mutations	Protease mutations
Subject 1	Day 1	K103K/N, T215C	L10I, I13I/V, K20I, M36I, F53L, L63P/T, A71V, V82A, L90M, I93F
Subject 1	Week 24 (initial VF)	K103K/N, M184M/I, T215C	PR: L10I, I13V, K20I, M36I, F53L, L63P, A71V, V82A, L90M, I93F
Subject 1	Week 26	K103K/N, M184M/I, T215C	L10I, I13V, K20I, M36I, F53L, L63P, A71V, V82A, L90M, I93F
Subject 2	Day 1	M41L, L74V	I15V, G16E, K20R, M36I, I64L, I72I/V
Subject 2	Week 36 (initial VF)	M41L, L74V	I15V, G16E, K20R, M36I, I64L
Subject 2	Week 38	M41L, L74V	I15V, G16E, K20R, M36I, I64L, I72I/V
Subject 3	Day 1	None	I13V, M36I, H69K, V77I
Subject 3	Week 24 (VF)	None	I13V, M36I, H69K, V77I

Treatment-emergent mutations are shown in bold. The screening genotype, which was obtained 2-4 weeks earlier, is not shown; however both pre-therapy genotypes generally had the same resistance associated mutations. One exception is Subject 1, whose virus had multiple major and minor protease mutations in the screening and baseline genotypes, however, the V82A mutation was only detected in the baseline genotype.

virologic failure that the patient had become noncompliant and was not taking her medication consistently.

Subject 3, a 27 year old white male, was randomized to the FPV/r BID arm and met virologic failure criteria at Week 24 on therapy (Figure 1). The subject was CDC classification A at time of treatment initiation, was co-infected with hepatitis B and C, and listed drug use as a risk factor. This subject was infected with subtype A1 HIV-1. The subject experienced an initial drop in viral load of >1 log by Week 4, and viral load declined gradually but had not suppressed his HIV-RNA to <400 copies/mL by Week 24. The site reported that the patient experienced a 2 week therapy interruption during this period. At the time of virologic failure (Week 24), there was no selection for any treatment-emergent mutation (Table 4). The subject remained on therapy and subsequently suppressed his viral load to <400 copies/mL by Week 36 and remained virologically suppressed with HIV-1 RNA <400 copies/mL through Week 48.

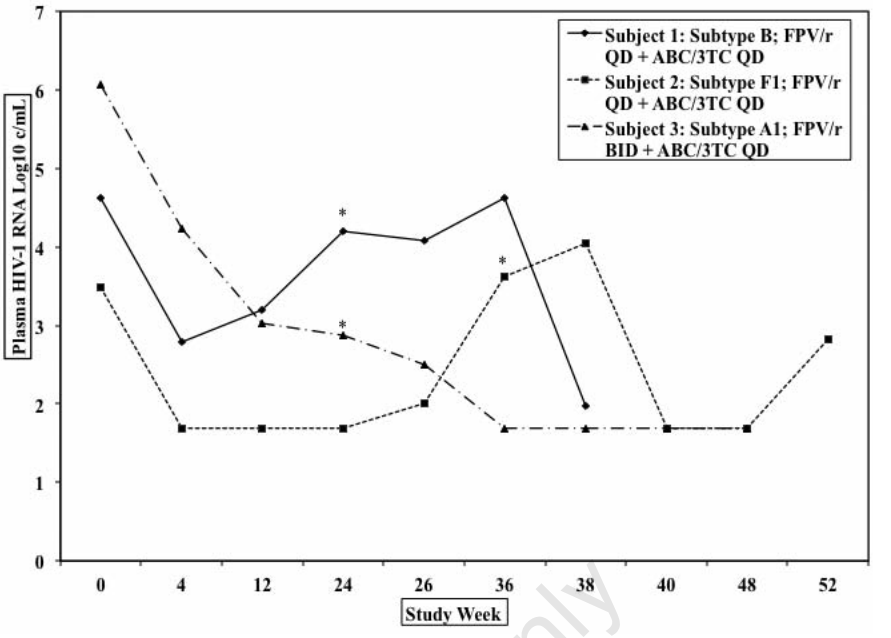

Figure 1. Viral response profiles at baseline and at initial virologic failure for those subjects who experienced virologic failure while on therapy (n=3/212) on FPV /r QD or FPV/r BID, in combination with QD fixed-dose ABC/3TC. The initial virologic failure timepoint is shown with an asterisk. FPV, fosamprenavir; QD, once-daily; BID, twice-daily.

Discussion

In the APV109141 study, there was a diverse representation of non-B, type M subtypes in ART-naïve subjects randomized to receive either FPV/r QD or BID in combination with ABC/3TC through 48 weeks on therapy. The efficacy results of the APV 109141study demonstrated non-inferiority of the response rate for QD FPV/r arm to the BID arm at <400 copies/mL plasma HIV-1 RNA at week 48, with 81% (86/106) subjects in the FPV/r QD and 82% (87/106) in the FPV/r BID arm virologically suppressed to <400 copies/mL.

Although drugs resistance mutations were detected in several subtype B and non-B HIV-infected subjects who met enrollment criteria, there was no obvious over-representation of subjects with resistant mutations in one of the two study arms, nor was detection of other major NRTI or NNRTI mutations at screen always predictive of a lack of later successful suppression.

There was a high prevalence of subjects (38%; 82/214) who had non-B subtype isolates who were randomized to the two study arms, representing 10 additional HIV-1 subtypes or CRFs. There was a low rate of virologic failure (3/214 subjects), which was notable given the broad distribution of subtypes within this study. With respect to those subjects who met virologic failure endpoints, there was no obvious bias with respect to response by subtype, as only three subjects met protocol-defined virologic failure endpoints (one from each of subtypes B, A1 and F1, the three most prevalent subtypes observed in the study). Two of these subjects had virus with evidence of drug resistance at baseline. Only in virus from one virologic failure subject was a treatment-emergent mutation detected at virologic failure (NRTI mutation M184V), with no selection for any treatment emergent major PR mutation. Meeting protocol-defined virologic failure criteria was also not necessarily indicative of later response, as one of the three subjects with virologic failure continued in the study after meeting virologic failure criteria and subsequently experienced HIV RNA suppression to <400 copies/mL and remained suppressed through Week 48.

While the in vivo and in vitro results from studies utilizing other PIs such as NFV have suggested that for specific antivirals, subtype might influence response or the resistance mutation selection pathway, the results from this study are in agreement with the findings from another recently published study. This study utilized viral isolates from subjects treated with the PIs darunavir or lopinavir and similar rates of efficacy were observed for HIV subtypes C and CRF01AE, compared to those from subjects with subtype B infection and comparable in vitro susceptibility was observed across a broad panel of group M subtypes.[24] The results of this analysis suggest that HIV subtype was not a predictor for lack of response in this study using either dosage of RTV with FPV , and that the presence of drug resistance mutations prior to ART initiation and the impact of therapy interruption remain sources of concern for lack of sustained virologic response.

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