H-360

Fosamprenavir or Atazanavir Boosted with Ritonavir Given Once Daily with Tenofovir /Emtricitabine in Antiretroviral Naïve HIV-Infected Patients: ALERT Study Virology Analysis Through 48 Weeks

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Introduction

- The resistance profile of ART-naïve patients experiencing virologic failure (VF) on a once-daily regimen of 300 mg/200 mg tenofovir/emtricitabine (TDF/FTC) plus either 1400 mg fosamprenavir + 100 mg ritonavir (FPV/r) or 300 mg atazanavir+ 100 mg ritonavir (ATV/r) was examined in a 48 week open-label, randomized study.

Methods

- Plasma HIV samples were analyzed by population genotype and phenotype at sequential timepoints, including at baseline and at virologic failure (VF) through 48 weeks (Monogram BioSciences) from the patients experiencing virologic failure. Clade assignment was as given in the Monogram PhenoSense GT™ report.
- Virologic failure was defined as confirmed HIV-1 RNA ≥400 copies/mL at ≥24 weeks or rebounding >400 copies/mL after viral suppression.
- Resistance mutations shown are as per the current IAS-USA Drug Resistance Mutations group guidelines (http://www.iasusa.org), and mutations considered thymidine analogue mutation (TAM) reversions.

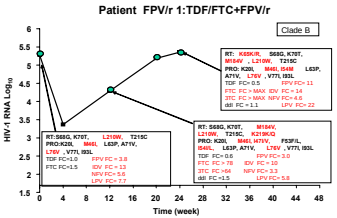
Results

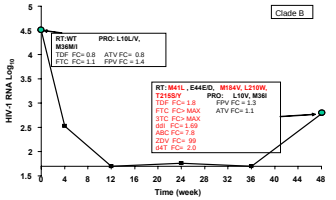
- 106 patients enrolled (53 per arm). The baseline characteristics of subjects enrolled in each study arm are shown in Table 1.
- At Wk 48, by ITT observed analysis, 93% (42/45) on the FPV/r arm vs 96% (46/48) on the ATV/r arm achieved VL<400c/mL and 89% (40/45) on the FPV/r arm vs 92% (44/48) on the ATV/r arm achieved VL<50c/mL.[1]
- A total of seven subjects met VF criteria through 48 weeks. Four patients met VF criteria on the FPV/r arm and three patients met VF criteria on ATV/r arm. Six of these seven subjects had Clade B HIV (one had Clade G virus).
- The genotypic and phenotypic profiles for subjects with VF on the FPV/r arm are shown in Figure 1, while the genotypic and phenotypic profiles for subjects with VF on the ATV/r arm are shown in Figure 2.

Table 1. Baseline Characteristics

	FPV/r (N=53)	ATV/r (N=53)
Median Age, years	40	40
Male	79%	89%
Race		
African American	34%	45%
Caucasian	62%	49%
Ethnicity		
Hispanic	23%	23%
Mean HIV-1 RNA, $\log_{10}$ c/mL	4.8	4.8
HIV-1 RNA ≥100,000 c/mL	24 (45%)	24 (45%)
Mean CD4 count, cells/mm^3	176	205
<50 cells/mm^3	14 (26%)	9 (17%)
50-<200 cells/mm^3	21 (40%)	9 (36%)

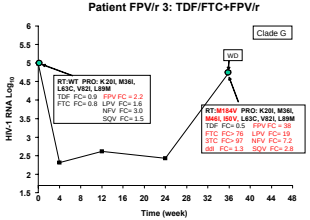
Figure 1. Longitudinal Population Genotypic and Phenotypic Changes for Subjects with Virologic Failure Treated with tenofovir/emtricitabine +fosamprenavir +100 mg ritonavir . Major mutations and fold change in IC_{50} above cut-off are shown in red.

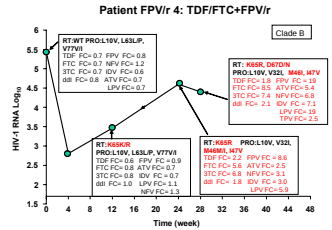




FPV/r arm:

- Subject FPV/r-1:
  - Baseline TAM, TAM reversion mutations, plus major protease mutations with reduced susceptibility (RS) to FPV and other PI's.
  - VF at Week 12- additional RT and protease mutations selected at Week 12 and at Week 28. Week 28- virus acquired RS to FTC and to FPV.
- Subject FPV/r-2:
  - Baseline- no detectable major resistance-associated mutations.
  - VF- M184V, TAMs and TAM reversion mutations, and RS to all NRTIs. Since TDF is not known to select for M41L, L210W, and T215Y, it is possible these mutations were reselected from archived drug-resistant HIV
- Subject FPV/r-3 (Clade G):
  - Baseline- no detectable major resistance-associated mutations, but RS to FPV
  - VF- M184V and RS to FTC was detected, plus major PI mutations and RS to FPV, lopinavir (LPV), nelfinavir (NFV) and saquinavir (SQV).
- Subject FPV/r-4:
  - Baseline- no detectable major resistance-associated mutations or RS.
  - Week 12-a mixture of K65K/R detected.
  - Week 24- the K65R detected, plus the M46M/I and I47V PI mutations, and RS to all study drugs.
  - Week 32- additional selection of RT D67N mutation also detected.

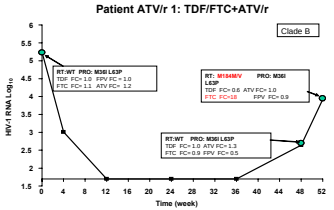


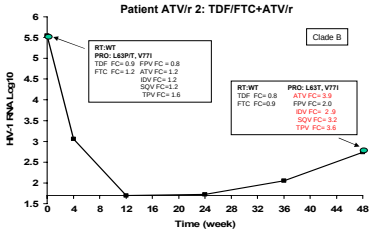


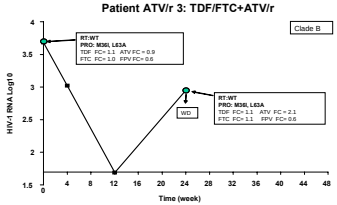
ATV/r arm

- Subject ATV/r-1:
  - Baseline- no detectable major resistance-associated mutations
  - VF- a M184M/V mutase detected along with RS to FTC and 3TC
- Subject ATV/r-2:
  - Baseline and VF- no detectable major resistance-associated mutations.
  - VF confirmation- no resistance mutations detected, but RS to ATV plus indinavir (IDV), SQV and tipranavir (TPV) observed
- Subject ATV/r-3:
  - Baseline and VF - no detectable major resistance-associated mutations. RS to study drug was not observed. However, the FC for ATV increased from 0.9 at baseline to 2.1 at VF (FC cutoff for ATV RS is 2.2).

Figure 2. Longitudinal Population Genotypic and Phenotypic Changes for Subjects with Virologic Failure Treated with tenofovir/ emtricitabine +atazanavir +100 mg ritonavir. Major mutations and fold change in IC_{50} above cut-off are shown in red.







Discussion

- Transmission of drug resistant HIV has been increasing in United States. Recently the DHHS guidelines were updated to recommended genotyping antiviral-naïve subjects prior to antiviral treatment initiation.[2]
- The resistance profiles at baseline and at failure, in conjunction with the baseline drug susceptibility data from three of the four subjects with VF in the FPV arm suggests that HIV isolated from these subjects contained drug resistance mutations prior to the start of their antiviral therapy. However, only one subject (Subject FPV/r 1) had major RT and PI drug resistance associated mutations detectable by conventional population sequencing.
- VF's in the ATV arm had reduced susceptibility to ATV or a >2X rise in ATV FC detected in the absence of detection of major PI mutations. This suggests that minority variants containing resistance mutations may be impacting virologic response.
- Clonal analysis is ongoing for samples from all seven subjects with VF to better understand the impact of these low abundance variants and these results will be reported at a future meeting.

Conclusions

- Comparable virologic suppression was observed in both once daily regimens through 48 weeks.
- Despite pre-existing resistance (detected by genotype or phenotype or both) to FPV or TDF/FTC in three patients randomized to the FPV/r arm, similar numbers of patients experienced VF on both arms.
- While the presence of pre-existing drug resistance was detected in patients with VF on the FPV/r arm using population genotype and phenotype, it cannot be ruled out that low abundance variants may have impacted virologic response in both treatment arms. Clonal analysis to address this question is ongoing.

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References

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2. DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. May 4, 2006 http://AIDSinfo.nih.gov