



Rate of Viral Evolution and Risk of Losing Future Drug Options in Heavily Pre-Treated Patients Remaining on a Stable Partially Suppressive Regimen

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Background

Many treatment-experienced, HIV-infected patients with limited therapeutic options for complete viral suppression remain on a partially suppressive regimen pending the availability of at least 2 fully effective antiretroviral drugs. The major risk of this approach is ongoing viral evolution and the loss of future drug options. The rate at which drug options are lost in such patients has not been carefully defined.

Methods

Study Participants

All subjects were enrolled in an ongoing clinic-based cohort (SCOPE) focused on defining the natural history of drug-resistant HIV. As part of this cohort, subjects are evaluated every four months, at which time plasma is archived. All treatment decisions are made by the primary care providers. From this cohort, we identified all subjects with the following baseline characteristics:

1. Stable ARV regimen for ≥ 120 days
2. Plasma HIV RNA level > 1000 copies/ml
3. ≥ 1 genotypic resistance mutation
4. ≥ 1 follow-up visit

Study Measurements

Genotypic and phenotypic resistance testing was performed every four months until treatment modification. Resistance testing was performed at Monogram Biosciences (formerly ViroLogic) and ARI-UCSF Laboratory of Clinical Virology.

Primary Study Endpoints

1. Time to development of 1 new nucleoside analogue mutation (NAM)
2. Time to development of 1 new major protease inhibitor (PI) mutation
3. Time to development of any new mutation
4. Time to loss of phenotypic susceptibility (defined as loss of 1 fully effective drug or 2 partially suppressive drugs)

Baseline Characteristics (n = 106)

Age (years)	48 (42-54)
Duration of follow-up (months)	11.3 (7.4-21.0)
Number of observations per subject	3 (2-5)
CD4 (cells/mm ³)	292 (199-424)
Nadir CD4 (cells/mm ³)	60 (19-191)
HIV RNA viral load (log ₁₀ copies/ml)	3.74 (3.30-4.34)
Number of prior ARV	8 (5-10)
Maximum number of missed ARV doses in last month	0 (0-2)
Number of NAMS	4 (2-6)
Number of major PI mutations ^a	2 (2-3)
Number of total mutations	10 (6-15)
Tipranavir mutation score ^{a,b}	3 (1-5)
Number of available ARV	6.5 (4-9)
Abacavir fold-change	4.83 (3.1-7.41)
PI fold-change ^{a,c}	38 (13-98)
Phenotypic susceptibility score	1 (0.5-1.5)
Replicative capacity	35.5 (17-60)

Medians (IQR), unless otherwise indicated.

^aData are for PI-treated subjects (n=71).

^bNumber of mutations from the following: L10V, I13V, K20MRV, L33F, E35G, M36, K43T, M46L, I47V, I54AMV, Q58E, H69K, T74P, V82LT, N83D, I84V.

^cPhenotypic fold-change to PI that subject was taking.

Results

Using a Kaplan-Meier analysis, the estimated risks of developing the following at 1 year were:

- ▶ New NAM: 23% (95% CI 15-34) (Fig. 1)
 - Baseline predictors of new NAM (log rank test, above vs. below median):
 - Low number of total mutations ($p=0.001$)
- ▶ New major PI mutation for PI-treated subjects: 18% (95% CI 9-34) (Fig. 1)
- ▶ Any genotypic loss of susceptibility to tipranavir for PI-treated subjects: 4% (95% CI 1-13)
- ▶ Any new mutation: 44% (95% CI 33-56) (Fig. 1)
- ▶ Losing 1.0 fully effective drug equivalent: 30% (95% CI 21-43) (Fig. 2)

Loss of Mutations and Gain of Drug Options

A secondary analysis evaluating the converse endpoints of loss of genotypic mutations and gain of drug options was also conducted. At 1 year, the estimated probability of losing a NAM was 14% (95% CI 8-24); losing any mutation was 28% (95% CI 19-40) and losing a major PI mutation was 7% (95% CI 3-18) (Fig. 3). The estimated probability of gaining 1 fully effective drug equivalent was 22% (95% CI 14-34) (Fig. 4).

Figure 1. Time to Development of New Mutation

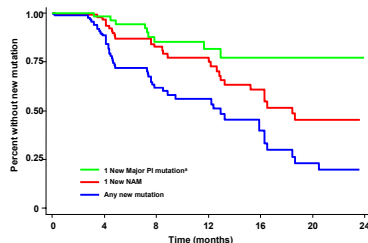


Figure 3. Time to Loss of Mutation

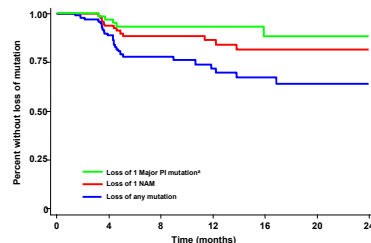


Figure 2. Time to Loss of 1.0 Drug Equivalent

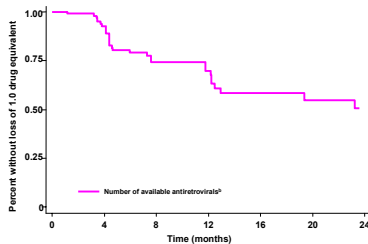
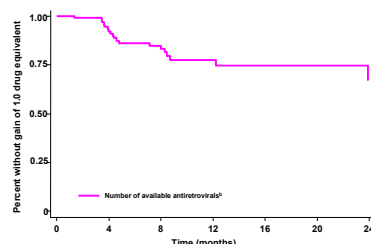


Figure 4. Time to Gain of 1.0 Drug Equivalent



^aData are for PI-treated subjects (n=71)

^bNumber of available antiretrovirals from the following: zidovudine, lamivudine, didanosine, abacavir, tenofovir, efavirenz, indinavir, nelfinavir, saquinavir, zalcitabine, amprenavir, lopinavir.

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Figure 5. Change in ABC* Fold-change

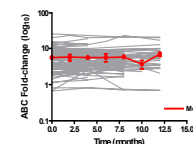
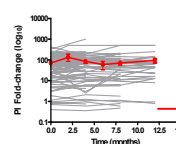


Figure 6. Change in PI^b Fold-change



Inhibitory concentration (IC₅₀) values relative to wild-type virus were determined for abacavir (ABC) (Fig. 5) and subject PI (Fig. 6). ^aABC IC₅₀ was used as a surrogate for IC₅₀ of all other NRTIs. ^bData are for PI-treated subjects (n=71).

Conclusions

In a cohort of heavily pre-treated patients with incomplete viral suppression on stable antiretroviral therapy, an estimated 44% developed at least one new drug resistance mutation over one year, while 30% lost the phenotypic equivalent of one susceptible drug at one year. This risk of losing future drug options is likely to be the major risk associated with maintaining patients on a partially suppressive regimen.

There was no consistent predictor of developing genotypic or phenotypic resistance. However, subjects with lower number of baseline mutations were more likely to develop at least one new nucleoside analogue mutation (NAM), suggesting that those with less resistance at baseline were at highest risk for losing future drug options. This also suggests that the risk of maintaining patients on a stable regimen is low if multiple NAMS are already present.

Although we observed a significant risk of viral evolution, the risk of accumulating genotypic resistance to tipranavir was low in this study. Carefully defining the risk of losing specific drugs which are commonly used for "salvage" therapy may be a more precise manner in which to balance the risks and benefits of not switching therapy in patients with limited therapeutic options.

We also observed a significant rate of "losing" drug resistance mutations (or of "gaining" a phenotypically effective drug). This apparent "gain" and "loss" of future drug options may reflect oscillations of minority variants that exist at or near the level of detection. These observations suggest that any single measure of drug resistance may not be an accurate assessment of resistance.