

Detection of Viral Co-receptor Tropism Changes with a High Sensitivity Phenotypic Assay among HIV-infected Patients with Drug-resistant Viremia

Poster #: 864

Correspondence:
Peter W. Hunt, MD
SFGH Bldg 80, Ward 84
995 Potrero Avenue
San Francisco, CA, 94110
(415) 476-4082 x345
phunt@ghp.ucsf.edu

PW Hunt¹, JN Martin¹, W Huang², E Coakley², D Hart², C Petropoulos², M Bates², R Hoh¹, SG Deeks¹, and J Reeves²
¹University of California and San Francisco General Hospital, San Francisco, USA; ²Monogram Biosciences, Inc., South San Francisco, CA, USA

Background

- ~10% of treated patients with drug-resistant viremia harboring apparently purely CCR5-tropic viruses (R5) will have detectable CXCR4-using viruses on subsequent follow up with currently available assays.
- Apparent "switches" from R5- to dual or mixed-tropic viruses (DM) between screening and enrollment have been associated with virologic failure of CCR5 inhibitor-based salvage regimens in clinical trials.
- A pre-existing clinically significant minority CXCR4-using virus population, present below assay detection limits at screen, might account for these changes.
- We hypothesized that improvements in assay sensitivity for CXCR4-using viruses might allow for earlier detection of DM-tropic viruses.

Methods

- Chronically HIV-infected patients with drug-resistant viremia sampled from SCOPE:
 - Clinic-based cohort study of >700 chronically-infected patients, half with drug resistance.
 - Patient interview and biologic specimen archiving performed every 4 months
- Patients meeting the following eligibility criteria were randomly sampled:
 - Stable antiretroviral therapy regimen for ≥ 120 days prior to baseline.
 - ≥ 2 plasma HIV RNA levels above 100 copies/ml in 80 days prior to baseline.
 - Plasma HIV RNA level > 1,000 copies/ml at baseline.
 - Evidence of ≥ 1 major or minor genotypic resistance mutation (excluding L69P).
 - 1st plasma HIV RNA level post-baseline within 1.5 log₁₀ copies/ml to ensure steady state.
 - ≥ 2 plasma HIV RNA levels > 1,000 copies/ml during observation.
- Patients receiving CCR5-inhibitors were excluded
- Observations censored at the time of treatment modification.

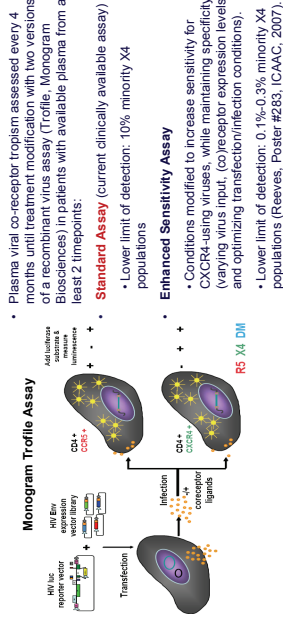
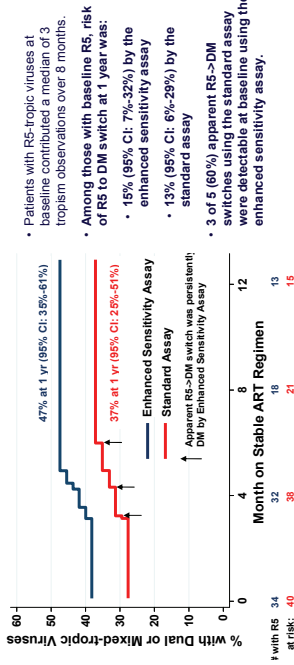


Fig. 1: Cumulative Probability of Detecting Dual/Mixed-tropic Viruses over 1 Year



- Patients with R5-tropic viruses at baseline contributed a median of 3 tropism observations over 8 months.
- Among those with baseline R5, risk of R5 to DM switch at 1 year was:
 - 15% (95% CI: 7%-32%) by the enhanced sensitivity assay
 - 13% (95% CI: 6%-28%) by the standard assay
- 3 of 5 (60%) apparent R5->DM switches using the standard assay were detectable at baseline using the enhanced sensitivity assay.

Results

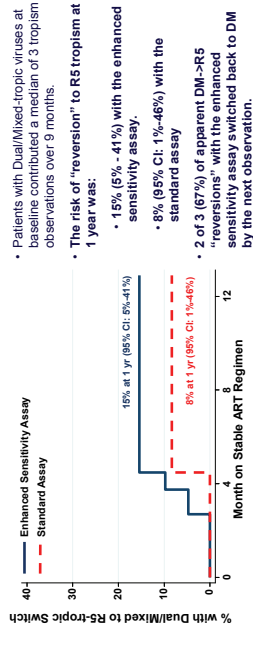
Table 1: Baseline Characteristics of Participants

Characteristic	Median (IQR)
CD4 Count, cells/mm ³	238 (162-374)
Nadir CD4 Count, cells/mm ³	50 (17-164)
Plasma HIV RNA Level, log ₁₀ copies/ml	3.9 (3.4-4.6)
Total Drug Resistance Mutations	10 (6-16)

Table 2: Baseline Tropism Using Enhanced Sensitivity vs. Standard Assay

Standard Assay	Enhanced Sensitivity Assay		Total (%)
	R5-tropic	Dual/Mixed-tropic	
R5-tropic (%)	34 (85)	6 (15)	40 (70)
Dual/Mixed-tropic (%)	0 (0)	15 (100)	15 (26)
X4-tropic (%)	0 (0)	0 (0)	2 (4)
Total (%)	34 (60)	21 (37)	57 (100)

Fig. 2: Time to DM->R5 "Reversion" with Enhanced Sensitivity and Standard Assays



- Patients with Dual/Mixed-tropic viruses at baseline contributed a median of 3 tropism observations over 9 months.
- The risk of "reversion" to R5 tropism at 1 year was:
 - 15% (5% - 41%) with the enhanced sensitivity assay.
 - 8% (95% CI: 1%-16%) with the standard assay
- 2 of 3 (67%) of apparent DM->R5 "reversions" with the enhanced sensitivity assay switched back to DM by the next observation.

Conclusions and Implications

- The majority of apparent R5 to DM transitions detected with the currently available Trofile assay among treated patients are due to pre-existing minority CXCR4-using populations.
- Use of a modified assay with enhanced sensitivity for CXCR4-using variants may improve the identification of patients who are unlikely to respond to CCR5 inhibitors.
- Transitions between R5 and DM may still occur over time with the enhanced assay, but remain relatively uncommon.
- The clinical significance of these presumably low-level shifts in CXCR4-using virus populations remains to be established in clinical trials.



This work was supported by the NIAID (K23 AI065244).