H-1027

Prediction of disease progression by HIV co-receptor tropism (CRT) in persons (P) with untreated chronic HIV infection

Matthew B. Goetz[1], Robert Leduc[2], Jay R. Kostman[3], Ann Labriola[4], Yolanda Lie[5], Jodi Weidler[5], Eoin Coakley[5], Roberta Luskin-Hawk[6], for the Long Term Monitoring (LTM) Study, Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA 060)

[1]VA Greater Los Angeles Healthcare System, [2]University of Minnesota, Minneapolis, MN, USA, [3]UPHS/Presbyterian Medical Center, Philadelphia, PA, USA, [4] VA Medical Center, Washington, DC, USA, [5]Monogram Biosciences, South San Francisco, CA, USA, [6]Saint Joseph Hospital, Chicago, IL, USA

Background

The relative ease of new methods for assaying HIV-1 co-receptor tropism coupled with the development of specific inhibitors of HIV-1 utilization of the CCR5 co-receptor, has led to increased interest in assessing the relationship between HIV-1 co-receptor utilization and the rate of HIV disease progression. However, few studies have assessed the prognostic significance of infection by CCR5 or CXCR4 tropic HIV-1 isolates in a diverse population of chronically infected, treatment naïve patients with relatively preserved CD4+ cells counts. Herein we describe the relationship between viral tropism and HIV disease progression in such a cohort, namely the treatment-naïve participants who have been enrolled in the Long-Term Monitoring Protocol (LTM) sponsored by the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA).

Objectives & Methods

- To determine the distribution of co-receptor tropism at study entry
- To determine the relationship of baseline co-receptor tropism with
  - Baseline viral load and CD4+ count
  - The time to < 350 CD4+ cells/µL, initiation of therapy or death (first event), i.e., the primary endpoint

Study Population

Inclusion criteria for enrollment in the master CPCRA LTM treatment naïve cohort required that patients be HIV infected, be greater than 12 years old, be anti-retroviral naïve, and provide written informed consent. There were no exclusion criteria. The association between baseline viral tropism and HIV disease progression was determined in the subset of LTM treatment naïve patients who met the following additional eligibility criteria: a minimum of 4 months of follow-up during which antiretroviral therapy was not initiated, a baseline viral load ≥ 1,000 HIV RNA copies/mL and CD4 count ≥ 450 cells/µL, and the availability of sufficient plasma for laboratory analyses. Co-receptor tropism assays were done using the Trofile Assay (Monogram Biosciences, South San Francisco, CA).

Results

Of the 1050 treatment naïve patients enrolled in LTM, 359 met the entry criteria for analysis of viral tropism. Viral tropism assays were available for 313 patients; 18 participants did not have available baseline plasma specimens and viral tropism assays were unsuccessful in 27 other persons due to low viral loads and plasma volume.

Dual/mixed R5/X4-tropic virus (DM) was detected in 32 samples (10%) and R5-tropic virus was detected in 282 (90%) samples; no sample had pure X4-tropic virus. 185 patients reached the primary endpoint. The distribution of first events was as follows: reaching a CD4+ count < 350 cells/µL (n=112); initiation of antiretroviral therapy (n=65); and death (n=8).

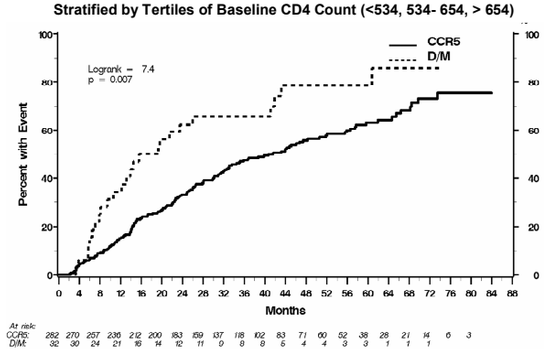
Results (Continued)

Patient Characteristics vs Tropism Status

Characteristic	R5		Dual/Mixed	
N	282	89.8%	32	10.2%
Female (%)	61	21.6%	10	31.3%
Race (%)				
Latino/a	22	7.8%	8	25.0%*
Black	122	43.3%	15	46.9%
White	125	44.3%	9	28.1%
IDU (%)	51	18.1%	4	12.5%
Same Sex Contact**	173	78.3%	15	68.2%
Prior OI/OM (%)	11	3.9%	1	3.1%
Age (years)	38.3		37.2	
CD4 (Median, 25 - 75%)	635	(526, 810)	571	(520, 670)
VL (Median, 25 - 75%)	4.1	(3.7, 4.5)	4.4	(3.8, 4.7)
Months known HIV+	47		53	
Months of follow-up	50		49	
+ HB Surface Antigen	14	5.0%	2	6.3%
+ Hepatitis C Antibody	49	17.4%	5	15.6%

* p < 0.01; ** Men only. IDU = injection drug use; OI/OM = opportunistic infection/malignancy; VL = viral load (log HIV RNA/mL); HB = Hepatitis B

Time to CD4 < 350 cells/µL, Treatment Initiation or Death
Stratified by Tertiles of Baseline CD4 Count (<534, 534- 654, > 654)



Time to CD4 < 350 cells/µL, Therapy Initiation or Death

Covariate	HR* DM/R5 [95% CI]	p
Tropism [Dual Vs. R5]	2.14 [1.29,3.54]	0.003
BL CD4+ [per 50 cells/µL]	0.87 [0.83,0.91]	0.000
Baseline Log RNA/mL [per 1.0 log]	2.02 [1.53,2.66]	0.000
Male vs Female	1.00 [0.60,1.68]	0.987
Latino vs White	0.58 [0.30,1.12]	0.106
Black vs White	0.77 [0.50,1.17]	0.220
Other race vs White	0.97 [0.45,2.10]	0.937
+ Hepatitis C antibody	0.83 [0.53,1.30]	0.292
Same sex exposure	0.65 [0.41,1.03]	0.067

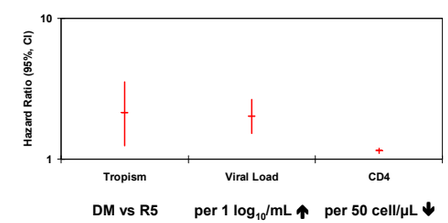
* Hazard ratio adjusted for baseline CD4 and viral load, gender, race, same sex exposure, HCV status; stratified by study unit
Similar results were observed if patients who began therapy within 8 or 12 months of study entry were excluded from analysis

Time to Component Outcomes

Event	R5*	DM*	HR+	95% CI	p
CD4+ <350**	11.1	25.9	2.40	[1.28,4.51]	0.006
CD4+ <200**	1.94	4.95	3.50	[0.93,13.1]	0.063
Initiation of ART	11.4	24.0	2.03	[1.19,3.45]	0.009
Death**	1.1	1.2	1.01	[0.12,8.69]	0.990
Combined endpoint#	20.2	38.9	2.15	[1.32,3.50]	0.002

* Rate per 100 patient-years
\+ Hazard ratio adjusted for baseline CD4 and viral load; stratified by study unit
** Censored for initiation of ART (antiretroviral therapy)
\# CD4+ <350 cells/µL or initiation of therapy or death

Tropism, VL and CD4 vs. Progression to Composite Outcome



Discussion

In this prospectively studied cohort of 314 patients with chronic untreated HIV-1 infection, individuals with Dual/Mixed tropic virus had a faster rate of HIV disease progression whether assessed by a composite outcome of CD4+ count <350 cells/µL, treatment initiation or death, or by separate analyses of time to CD4+ count <350 cells/µL or treatment initiation.

These data confirm and extend earlier reports regarding X4 tropism and disease progression to truly treatment naïve adults with relatively early stage HIV-1 infection (median of 630 CD4+ cells/µL at baseline). Previous studies have shown a similar relationship between tropism and:

- CD4+ decline in patients with approximately 300 cells/µL CD4+ cells (3)
- Progression to AIDS in patients from the Multicenter AIDS Cohort Study (2)
- Viral load increases during the first year after HIV seroconversion (4)

Strengths of this study include the demographic diversity, prospective data collection and long follow-up. A potential weakness is that persons categorized as having R5 virus may harbor subpopulations of X4 virus below the limits of detection of the Trofile assay (1). Thus individuals categorized as having only R5 tropic virus may have had small subpopulations of Dual/Mixed tropic virus. However, such misallocations would tend to weaken rather than strengthen the association between baseline dual/mixed tropic virus with more rapid disease progression. In other studies of this cohort, we have found that baseline Dual/Mixed tropic and viral replicative capacity independently predict the rate of HIV disease progression (5).

Summary

In this population of treatment naïve patients with early stage HIV infection

- Patients with detectable X4 virus had evidence of more rapid of HIV disease progression than did persons with pure R5 virus
- The impact of Dual/Mixed tropic virus was:
  - similar to that of a one log/mL increase in plasma HIV RNA
  - greater than that of a 50 cell/µL decrease in the CD4+ cell count
- These effects was observed in analyses that controlled for the baseline CD4+ count, viral load, HIV risk factors, demographic factors and other laboratory variables

References

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C•P•C•R•A insight