Longitudinal evolution of tropism in perinatal HIV-1 infection
The HICCUP Study

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Background

Data on changes over time in HIV tropism and association with disease progression in perinatally-acquired HIV-1 infection (PaHIV) is limited[1,2]. Optimal sequencing of antiretroviral therapy (ART) including CCR5 antagonists is a priority for a young population currently requiring life-long ART and requires a clear understanding of the natural history of co-receptor usage in PaHIV.

Methods

Eligible patients with PaHIV had never received a CCR5 antagonist and were defined as:

- Group (1) slow progressors - Initiated ART from 10+ years of age
- Group (2) rapid progressors – Initiated ART pre 5 years of age
- Group (3) long term non-progressors (LTNP) – no ART

Tropism was determined by the extraction of RNA from stored plasma samples at the following time points: baseline, then annually and /or at virological failure up until the most recent sample. The V3 region of gp120 was sequenced in triplicate and analysed using the Geno2pheno algorithm (FPR cut off = 5.75%) [3].

Logistic regression with generalised estimating equations was used to assess factors associated with the presence of CCR5-using virus. Time to tropism change was assessed using standard survival methods.

Results (1) – baseline samples

Demographics: (n=48) median age was 12 years, 52% were female, 79% black African with clinical categorisation (see Methods) as Group 1 (n=20), Group 2 (n=17) and Group 3 (n=11). 96% were non-B subtypes.

Figure 1 - Tropism at baseline

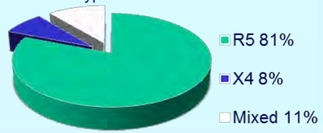


Table 1- Characteristics of children at time of study entry

		Group 1 – Late ART	Group 2 – Early ART	Group 3 - LTNP
Total		20	16	11
CD4 (cells/mm³)	*Median (IQR)*	460 (330, 760)	810 (520, 1000)	670 (510, 810)
CD4 Group	*≤200*	1 (5%)	0 (0%)	0 (0%)
	201-350	5 (25%)	2/15 (13.3%)	2 (18.2%)
	351-500	5 (25%)	1/15 (6.7%)	0 (0%)
	501+	9 (45%)	12/15 (80.0%)	9 (81.8%)
VL (copies/ml)	*Median (IQR)*	11435 (1691, 44431)	1223 (157, 10359)	3991 (2067, 7514)
VL group	*<500*	4 (20%)	5/15 (33.3%)	1 (9.1%)
	500-10,000	5 (25%)	6/15 (40.0%)	8 (72.7%)
	10,001-50,000	6 (30%)	3/15 (20.0%)	2 (18.2%)
	50,001+	5 (25%)	1/15 (6.7%)	0 (0%)
Clade	*C*	7/17 (41.2%)	3/13 (23.1%)	3/8 (37.5%)
	Non-C	10/17 (58.8%)	10/13 (76.9%)	5/8 (62.5%)
Ethnicity	*Black African*	17 (85%)	11 (68.8%)	10 (90.9%)
	Other	3 (15%)	5 (31.3%)	1 (9.1%)
Sex	*Female*	9 (45%)	9 (56.3%)	7 (63.7%)
	Male	11 (55%)	7 (43.8%)	4 (36.4%)
Age	*Median (IQR)*	12 (9, 15)	11 (8, 13)	15 (13, 17)
Tropism	*R5*	15 (75%)	12 (75.0%)	11 (100%)
	X4	2 (10%)	2 (12.5%)	0 (0%)
	Mixed	3 (15%)	2 (12.5%)	0 (0%)

Results (2) – Factors associated with CCR5-using virus

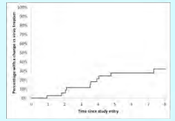
Analysing all samples, the presence of CCR5-using virus was associated with:

- higher current CD4 count (median 520 cells/μL for R5 virus vs 202 cells/uL for X4; p=0.0005)
- LTNP (35% vs 11% p=0.05)
- non Black African ethnicity (74% vs. 89%; p=0.05)
- female (55% vs 28%; p=0.005)

Follow up: Median of 7.7 years (308.6 person-years) with a median of 5 (range 1-14) samples per subject (252 samples total) analysed.

Results (3a) – tropism switch over time (figure 2)

Of 38 patients with CCR5-using virus at baseline and ≥1 follow-up sample, a switch to CXCR4/mixed using virus occurred in 12 (30.8%).



Estimated 5 year risk of tropism switch from CCR5 to CXCR4/mixed using virus was 24.4% (95% CI 9.7-39.2%).

3 children only had one evaluable sample and were excluded from analysis. 19/45 (42.2%) children had at least one change in their tropism over follow-up.

Table 2 – According to tropism at first sample

		Tropism at time of first sample		
		R5	X4	Mixed
Tropism changed at least once over follow-up	N	38	2	5
	Yes	12 (30.8%)	2 (100.0%)	5 (100.0%)
	No	26 (69.2%)	0 (0%)	0 (0.0%)

Table 3 – According to group

		Group		
		1 – Late ART	2 – Early ART	3 – LTNP
Tropism changed at least once over follow-up	N	19	14	11
	Yes	10 (52.6%)	7 (50.0%)	2 (18.2%)
	No	9 (47.4%)	7 (50.0%)	9 (81.8%)

Table 4 – According to tropism at first sample and group

	Tropism at time of first sample					
	Gp 1 – Late ART			Gp 2 – Early ART		Gp 3
Tropism changed at least once over follow up	R5	X4	Mixed	R5	X4	R5
N	14	2	3	12	2	11
Yes	5 (35.7%)	2 (100%)	3 (100%)	5 (41.7%)	2 (100%)	2 (18.2%)
No	9 (64.3%)	0	0	7 (58.3%)	0	9 (81.8%)

Table 5 – Factors associated with switch in virus tropism

		Hazard Ratio	95% CI	p-value
Current CD4 count	Per 50 cells higher	0.62	0.47, 0.81	0.0006
Group	1 – Late ART	2.45	0.46, 12.99	0.56
	2 – Early ART	1.54	0.28, 8.48	
	3 LTNP	1.00 (reference)		
Current Viral load	Per 1 $\log_{10}$ cps/ml higher	0.92	0.46, 1.84	0.81
Age	Per year older	1.02	0.85, 1.21	0.85

Results from Cox Proportional Hazards Regression Model (univariate due to limited numbers)

Results (3b) – tropism reversion over time

Of the 19 patients who had CXCR4/mixed using virus identified and at least one further sample subsequent to this, 11/19 (58%) were predicted to harbour CCR5-using virus solely at one or more subsequent time points. 5/11 had three or more switches between CCR5 and CXCR4/mixed using virus over time, 3 of whom were CCR5 at last follow up.

Table 7: Pt 19. Tropism switches/time

Sample date	CD4	VL	Tropism	FPRs
04/08/2004	780	1769	R5	68.3, 88.4, 89.1
27/11/2006	550	8853	R5	89.1, 84.9, 84.9
03/07/2008	170	107294	X4	1.7, 1.7, 1.7
06/10/2009	105	46753	R5	37.7, 37.7, 37.7
07/10/2010	90	2415	X4	1.7, 1.7, 1.7
20/06/2012	20	43923	R5	25.6, 25.6, 25.6
09/12/2012	40	18741	R5	80.7, 47.8, 77.2

Conclusions

- In PaHIV, CCR5 antagonists were a treatment option for 81% at 12 years of age, falling to 56% over 7.7 years of follow up.
- Estimated 5 year risk of tropism switch from CCR5 to CXCR4/mixed using virus was 24%.
- As seen in adult studies, lower CD4 count was predictive of co-receptor switching in PaHIV[4].

Clinical outcome data for the use of Maraviroc in paediatric patients following tropism determination by genotypic testing methods is limited. The relatively frequent 'switching' between CCR5-and CXCR4-using virus, and vice versa, demonstrated in this cohort, highlights a need for vigilant clinical monitoring of virological response in children receiving Maraviroc. Determination of CXCR4-using virus at any time should be considered long-lasting.

Globally 30% of children with PaHIV are triple class experienced. Paediatric studies of CCR5 antagonists should be expedited to ensure they are a treatment option before tropism switching occurs in children[5].

References: [1]Green et al. AIDS Res Hum Retroviruses 2012;28(4):324-335.
[2] Di Biagio et al. HIV Clin Trials 2014;15(1):45-50. [3] www.geno2pheno.org. [4]Verhofstede et al. Curr Opin HIV AIDS 2012;7(5):432-9. [5]Giaquinto et al. IAS Kuala Lumpur 2013. Abs MOAB0103.

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