Correlates and prevalence of co-receptor switch in ART naive HIV patients

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Background

HIV-1 co-receptor tropism determination is a prerequisite before starting a CCR5 blocker. European guidelines provide recommendations for the application of co-receptor testing before prescribing CCR5 blockers, but some issues, such as the validity of a tropism prediction result in time, remain unresolved. This study aimed at determining prevalence and correlates of co-receptor switch in antiretroviral therapy (ART)-naive individuals at the AIDS Reference centre of Ghent, Belgium.

Material and methods

Co-receptor tropism determination

Co-receptor tropism prediction was performed after population V3 sequencing and using geno2pheno (http://coreceptor.bioinf.mpi-inf.mpg.de/index.php). Results were interpreted using a False Positive Rate (FPR) cut-off of 10%.

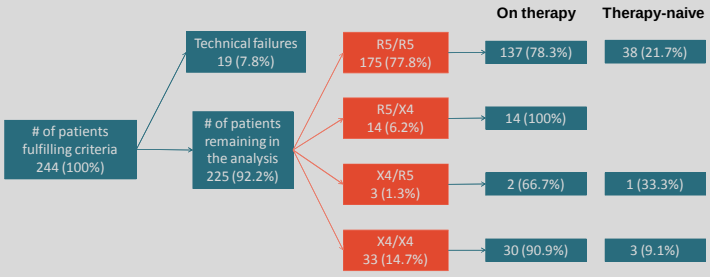
Patient selection

A total of 244 patients were retrospectively selected from individuals newly diagnosed between 2001 and 2009 and presenting for follow-up at the Aids Reference Centre (ARC) of Ghent University Hospital, Belgium. Inclusion criteria were first consultation after diagnosis in the ARC, the availability of a plasma sample collected within 1 year of diagnosis and a plasma sample collected at the start of treatment or by the end of the study period (August 2011) if ART was not initiated. Discordant tropism predictions were confirmed by additional testing of at least 2 intermediate samples. The mean interval between the first and last sample analyzed was 32 months (IQR: 17-44).

Statistical analyses

Groups were compared using a χ^2 test for categorical variables and the Mann-Whitney *U* nonparametric test for continuous variables. The level of significance was set at $p \leq 0.05$. Kaplan-Meier analysis was used to estimate the rate of switch over time in different groups. All data was analyzed using SPSS 18.0 (SPSS Inc., Chicago, IL).

Prevalence of co-receptor switch



Of the 225 patients from whom two consecutive plasma samples were analyzed, 175 (77.8%) were predicted as exclusively CCR5-using (R5/R5), both on the first and last sample analyzed, and 33 (14.7%) were predicted as CXCR4-using on both samples (X4/X4). There was no statistical difference in prevalence of R5/X4 switch in patients with an R5 in the original sample, compared to X4/R5 switch in patients with an original X4 sample (14/189 versus 3/36; $p > 0.05$).

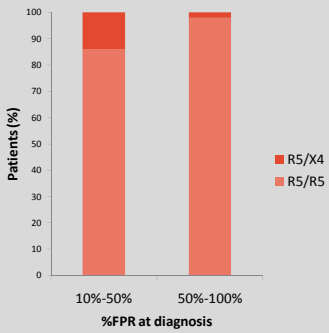
Conclusions

- Overall low rate of co-receptor switch pre-ART initiation
- The FPR of the first sample was predictive for R5/X4 switch
- The Kaplan-Meier analysis suggests that in ART naive patients the R5 predictions can remain valid for at least 2 years in patients with an FPR >50%
- The lower CD4 counts at ART initiation in R5/X4 switchers supports the correlation between the presence of X4 virus and faster disease progression

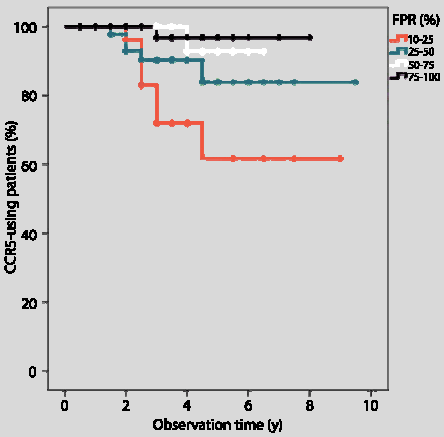
Correlates of R5-to-X4 co-receptor switch

	R5/R5	R5/X4	p-value
n = 189	**175**	**14**	
Age (yr) (n = 189)	175	14	
Median (IQR)	40 (34-46)	41 (31-51)	0,788
Gender (n = 189)	175	14	
Male	144 (82%)	11 (79%)	0,720
Female	31 (18%)	3 (21%)	
Race or ethnicity (n = 189)	175	14	
Caucasian	145 (84%)	14 (100%)	0,228
Other	27 (16%)	0 (0%)	
Transmission route (n = 170)	158	12	
Homosexual contact	109 (69%)	10 (84%)	0,514
Heterosexual contact	43 (27%)	1 (8%)	0,190
Other	6 (4%)	1 (8%)	0,407
CCR5 genotype (n = 184)	170	14	
wt/wt	144 (85%)	13 (93%)	0,697
wt/Δ32	26 (15%)	1 (7%)	
Therapy initiation (n = 189)	175	14	
Yes	137 (78%)	14 (100%)	0,077
No	38 (22%)	0 (0%)	
Baseline CD4⁺ T cell count (cells/mm⁺) (n = 178)	164	14	
Median (IQR)	498 (365-653)	491 (339-590)	0,457
CD4 <350	36 (22%)	4 (29%)	0,496
CD4 between 350 and 500	47 (29%)	3 (21%)	0,520
CD4 >500	81 (49%)	7 (50%)	0,781
Treatment initiation CD4⁺ T cell count (cells/mm⁺) (n = 178)	164	14	
Median (IQR)	360 (274-482)	227 (159-409)	0,015
Baseline viral load (log cp/ml) (n = 186)	172	14	
Median (IQR)	4,46 (3,95-4,96)	4,43 (3,96-4,77)	0,867
Treatment initiation viral load (log cp/ml) (n = 183)	170	13	
Median (IQR)	4,55 (3,84-4,98)	4,81 (4,24-5,07)	0,297
FPR at diagnosis (%) (n = 189)	175	14	
Median (IQR)	59 (31-81)	27 (15-48)	0,001
FPR < 50	73 (42%)	12 (86%)	0,001
FPR > 50	102 (58%)	2 (14%)	
Transmitted drug resistance (n = 189)	175	14	
Yes	9 (5%)	0 (0%)	1,000
No	166 (95%)	14 (100%)	
Virus subtype (n = 189)	175	14	
B	128 (75%)	11 (79%)	0,411
non B	43 (25%)	3 (21%)	
Drug free period, Mean (IQR), months (n = 152)	32 (15-44)	31 (21-38)	0,947
Follow-up period, Mean (IQR), months (n = 189)	35 (19-46)	31 (21-38)	0,703

The CD4 count at ART initiation - but not at baseline - was lower in the R5/X4 switchers than the CD4 count at ART initiation in the R5/R5 patients ($p = 0.015$). The %FPR at diagnosis was significantly associated with the chance of co-receptor switch. Of the 85 patients with an FPR <50%, 12 (14%) switched co-receptor use, compared to 2 (2%) of 104 patients with an FPR >50% ($p = 0.001$).



Predictive value of %FPR at diagnosis



The Kaplan-Meier analysis illustrates the rate of tropism switch over time in different groups.
The lower the FPR value, the higher the chance to switch in co-receptor use at an early stage during the infection.
No R5/X4 switch was observed in patients with an FPR of >50% two years after collection of the first sample.