



Epidemiology of HIV-1 Co-Receptor Usage: Association of CXCR4 Use with CD4 Count, CCR5 Δ32 Genotype and HIV V3 Sequence in Antiretroviral-naïve Individuals

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Abstract

Background: CXCR4-using HIV variants may emerge over the natural history of HIV-1 infection and are associated with accelerated disease progression and differential susceptibility to co-receptor inhibitors. We wished to characterize the Epidemiology and clinical correlates of CXCR4-using HIV in a cross-sectional analysis of a cohort of HIV-infected, antiretroviral naïve individuals.

Methods: HIV co-receptor usage (Virologic Phenotense Assay) was determined in the last pretherapy plasma sample from 1191 antiretroviral naïve individuals initiating triple therapy in British Columbia, Canada. Baseline variables investigated for association with HIV co-receptor usage included sociodemographic characteristics, plasma viral load (pVL), CD4 count, AIDS diagnosis, HIV envelope V3 loop sequence, and the human CCR5 Δ32 genotype.

Results: Individuals harboring CXCR4-using HIV (X4 variants) (N = 178 of 979 successfully phenotyped samples: 18.2%) displayed a poorer baseline clinical profile (median pVL 175,000 vs 120,000 [p = 0.0006], median CD4 count 110 vs 260 [p < 0.0001]) than individuals harboring exclusively CCR5-using HIV. Individuals heterozygous for the CCR5 Δ32 deletion (N = 128 of 967, 13.2%) were at 2.5 times increased risk of harboring X4 variants when compared to CCR5 wt/wt individuals (multivariate p = 0.0005). The presence of basic amino acids at codons 11 and 25 of the HIV V3 loop (N = 109 of 955, 11.4%) was associated with 9.1 times increased risk of harboring X4 variants (multivariate p < 0.0001), regardless of CCR5 Δ32 genotype. In multivariate analyses adjusting for baseline parameters including CCR5 Δ32 genotype, HIV co-receptor usage was not a significant predictor of survival or treatment response after initiating triple therapy.

Conclusion: Baseline CD4 count, pVL, HIV V3 sequence, and CCR5 Δ32 genotype were the strongest determinants of CXCR4-using HIV in this population. The association between CCR5 Δ32 and CXCR4 use suggests that decreased target cell availability of CCR5 may select for X4 variants. These observations may be of relevance to the use of CCR5 antagonists as antiretroviral agents.

Introduction

Human Immunodeficiency Virus type 1 (HIV-1) uses chemokine receptors CCR5 and/or CXCR4 in combination with CD4 in order to gain entry into host cells. CXCR4-using strains of HIV have been associated with poorer prognosis and inferior response to antiretroviral therapy, although the implications of co-receptor usage on the efficacy of HAART remain to be determined. In addition, HIV co-receptor usage is also of particular relevance due to the development of co-receptor antagonists, a class of antiretrovirals designed to specifically inhibit HIV binding to CCR5 and/or CXCR4. Although co-receptor inhibitors currently show promise in clinical trials, it is not known on a population basis what proportion of HIV-infected individuals may potentially benefit most from these agents. It is of importance, therefore, that the Epidemiology and prognostic implications of HIV co-receptor usage be re-evaluated at the present time.

Study Population and Objectives

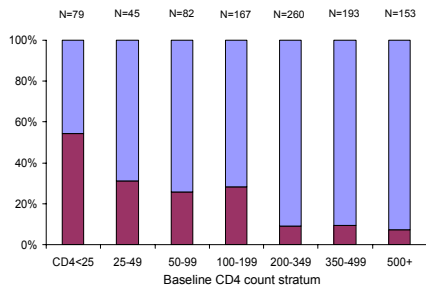
The Epidemiology and clinical implications of HIV co-receptor usage were investigated in 1191 antiretroviral-naïve individuals initiating their first triple combination therapy between Aug/96 and Sept/99 in Vancouver, Canada (HOMER cohort).

Objectives:

1. To characterize the prevalence of CXCR4-using HIV strains at therapy initiation and to identify sociodemographic, clinical and genetic predictors of X4 HIV in this population of antiretroviral-naïve individuals.

2. To establish the impact of baseline CXCR4-using HIV on clinical outcomes, as well as survival in the five-year period following initiation of HAART.

Distribution of R5/X4 HIV by baseline (pre-therapy) CD4 count strata

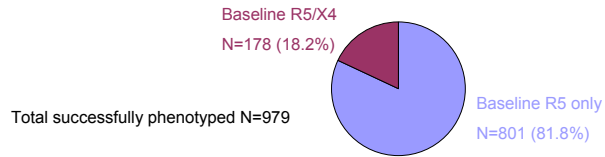


Sociodemographic and clinical predictors of R5/X4 HIV in this antiretroviral-naïve population

Baseline Risk Factor	Univariate			Multivariate (N=943)		
	Odds Ratio	95% CI	p	Odds Ratio	95% CI	p
Male gender	1.36	0.83-2.22	0.227	-	-	-
Age (per 10 year increment)	1.04	0.87-1.24	0.705	-	-	-
Baseline HIV RNA (per log increment)	1.62	1.19-2.20	0.002	1.46	1.02-2.08	0.040
Baseline CD4 cell count (per 100 cell decreas)	1.52	1.03-1.95	<0.0001	1.53	1.04-1.73	<0.0001
Baseline AIDS diagnosis	2.26	1.50-3.42	0.0001	1.17	0.72-1.91	0.531
History of injection drug use	0.70	0.48-1.03	0.072	-	-	-
CCR5 w/Δ32 genotype	1.78	1.15-2.73	0.009	2.48	1.48-4.15	0.0005
HIV V3 '1125' genotype	6.61	4.32-10.1	<0.0001	9.11	5.54-14.98	<0.0001

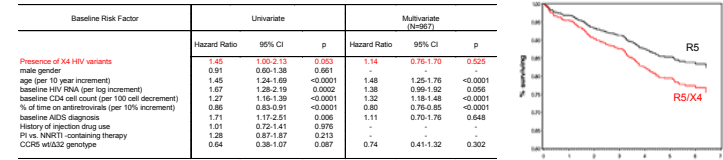
Objective 1: Prevalence and clinical correlates of CXCR4-using HIV in an antiretroviral naïve population

Prevalence of CXCR4-using HIV in this population = 18.2%

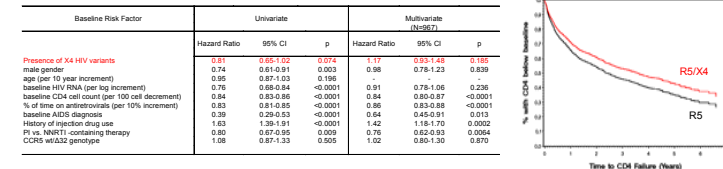


Objective 2: Influence of CXCR4-using HIV on survival and clinical response to HAART

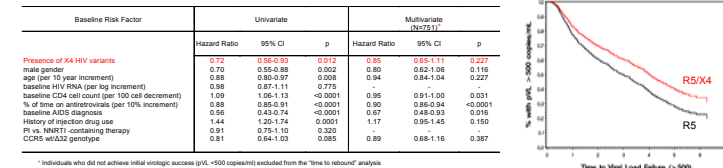
Influence of baseline factors on time to non-accidental death after initiation of HAART



Influence of baseline factors on time to CD4 decline below baseline after initiation of HAART



Influence of baseline factors on time to pVL rebound >500 copies/ml after initiation of HAART



*Individuals who did not achieve initial virologic success (>500 copies/ml) excluded from the 'time to rebound' analysis

Conclusions

- Baseline CD4 count, plasma viral load, HIV envelope V3 sequence and CCR5 Δ32 genotype were the strongest determinants of the presence of CXCR4-using HIV in this antiretroviral-naïve population
- In multivariate analyses adjusting for baseline parameters, HIV co-receptor usage was not an independent predictor of survival or clinical treatment response following initiation of HAART
- The association between the CCR5 Δ32 and the presence of CXCR4-using HIV suggests that decreased target cell availability of CCR5 may select for X4 variants. These observations may be of relevance to the use of CCR5 antagonists as antiretroviral agents.