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Prevalence and clinical associations of CXCR4-using HIV-1 among treatment-naive subtype C-infected women in Botswana

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Abstract

Human immunodeficiency virus type 1 (HIV-1) coreceptor usage was determined using a phenotypic assay in plasma samples from treatment-naive women infected with subtype C virus who had CD4 cell counts below 200 cells/mm^3. Of 148 women 14.9% were infected with dual/mixed (DM) virus; the remainder had R5 virus. A greater proportion of women in the lowest CD4 cell count stratum had DM virus (p=0.026); change in coreceptor use after ART exposure was uncommon. CXCR4-using HIV-1 was less common in subtype C-infected women than reported in subtype B cohorts, but was most prevalent in women with the lowest CD4 cell counts.

Keywords

AIDS; HIV-1 tropism; CCR5; CXCR4; subtype C; antiretroviral therapy

INTRODUCTION

Coreceptor usage by HIV-1 is an important determinant of disease progression and response to CCR5 antagonist therapy. Much of the data relating coreceptor usage to clinical disease is based on studies of subtype B-infected patients. Most HIV-1 transmission involves CCR5-using (R5) viruses, which predominate in the early phases of infection[1–4]. Over time, CXCR4-using viruses emerge in approximately 50% of patients and are associated with an increased risk of disease progression and death[2, 5]. Less is known about patterns of coreceptor usage by HIV-1 subtype C (HIV-1C), which accounts for more than half of new infections worldwide. Studies to characterize coreceptor usage of HIV-1C are needed for a better understanding of pathogenesis, treatment and prevention of infection by this highly prevalent subtype.

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Data regarding the prevalence of CXCR4-using HIV-1C are conflicting, and come from relatively small, cross-sectional studies. Initial studies suggested that R5 virus predominates in HIV-1C infection throughout the course of disease[6–9]. Subsequent studies identified CXCR4-using virus in a small number of treatment-naive HIV-1C-infected patients with advanced HIV disease[10–13], with some studies showing that 30–50% of patients with AIDS harbor CXCR4-using virus[14–16]. One study suggested a possible association of ART with higher rates of CXCR4-using virus[14], but the relationship between ART and emergence of CXCR4-using virus was inferred by the comparison of prevalence rates between small cohorts of treatment-naïve and – experienced subjects. To obtain a better estimate of the prevalence of CXCR4-using virus in HIV-1C infection and its relationship to antiretroviral therapy we determined co-receptor usage of plasma virus from a large cohort of HIV-1C-infected women from Botswana with advanced HIV-1 disease.

METHODS

Patients

Subjects selected for testing were women participating in the Mashi study, a randomized clinical trial of prevention of MTCT conducted in southeastern Botswana from 2001–2003 (clinicaltrials.gov identifier: NCT00197587)[17, 18]. All participating women received zidovudine from 34 weeks gestation, and were randomized to single dose nevirapine or placebo intrapartum. Combination ART became available through the Botswana government to participating women with CD4<200 cells/mm^3 or AIDS-defining illness beginning in 2002, 19 months into the study. Participants who completed the Mashi study were offered enrollment into a follow-up study, in which clinical status, HIV-1 RNA and CD4 cell count were monitored at 3-month intervals[19]. For those who initiated ART, virologic failure was defined as confirmed HIV-1 RNA >400 copies/mL 6 or more months after starting ART or failure to achieve at least a 1-log$_{10}$ drop in HIV-1 RNA by 12 weeks[19]. Plasma HIV-1 RNA was assessed using the standard COBAS Amplicor HIV-1 Monitor assay (Roche Diagnostics); CD4 cell counts were measured by standard techniques. The use of Mashi samples for this study was approved by the ethics committees and institutional review boards at the Botswana Health Ministry, the Harvard School of Public Health and Partners HealthCare System. All participants had provided written informed consent for use of stored samples for approved HIV-related research.

HIV-1 coreceptor usage assay

Coreceptor usage of plasma virus was determined using a sensitive single-cycle assay validated for subtype C viruses[20] at screening or enrollment into Mashi from women with screening CD4 counts below 200 cells/mm^3, and for women who initiated ART, at the time of virological failure. Viruses that used only CCR5 were considered R5; those that used only CXCR4 were considered X4; those that used both coreceptors were considered to have dual or mixed (DM) coreceptor usage. The study was powered to estimate the prevalence of CXCR4-using virus among treatment-naïve patients with a precision of ±6.1% (95% confidence interval [CI]), which required a sample size of at least 100 patients.

Statistical methods

Associations of viral tropism with clinical parameters were explored by univariable analyses, using Fisher's exact test for categorical parameters and the Wilcoxon rank-sum test for continuous parameters. The Cochran-Armitage exact test of trend was used to identify significant differences in prevalence across increasing categories of baseline (pre-ART) CD4 cell count and HIV-1 RNA. All reported P values are two-sided. Changes in HIV-1 RNA and CD4 cell count over time were explored using type 3 Tests of Fixed Effects, using SAS version 9.1.

RESULTS

In the Mashi study, 206 women had screening CD4 cell counts below 200 cells/mm^3. Of the 165 women with samples available for tropism testing, 12 were excluded because they had initiated ART prior to enrollment, leaving 153 samples for testing. Baseline characteristics of the 153 women with samples tested for co-receptor usage were similar to those of the 53 women who were not tested, except that baseline median viral load was higher (p=0.01) and the time to ART initiation was longer among women with a tested sample (p<0.001;Table 1). The exclusion of the 12 women who initiated ART prior to enrollment likely contributed to the difference in time to ART initiation between the two groups. Among those tested, the median baseline CD4 count was 130 cells/mm^3 (interquartile range [IQR], 95–171 cells/mm^3) and the plasma HIV-1 RNA level was 5.02 log_{10}copies/ml (IQR, 4.51–5.44 log_{10}copies/ml).

Prevalence of CXCR4-using viruses and the characteristics of the women by coreceptor usage

The coreceptor usage assay generated results for 148 of 153 (96.7%) women. Among those with an assay result, 22 (14.9%) had DM virus and 126 (85.1%) had R5 virus; no samples were X4 (Table 1). A maximum likelihood tree built from sequences of the C2–V4 region of a subset of env amplicons (N=61) confirmed that each sequence was unique and clustered with reference subtype C sequences (bootstrap value 98%).

Median baseline viral load, time to initiation of ART, death and MTCT did not differ significantly between women with DM versus R5 virus, but women with DM virus were significantly older than women with R5 virus (median age 33.1 years versus 28.1 years, respectively; p=0.025). Comparison of the median baseline CD4 cell count in women harboring DM virus to those with exclusively R5 virus showed differences that approached statistical significance (p=0.08) (Table 1). The distribution of women infected with DM virus varied significantly across the range of CD4 cell counts between 0 and 200 cells/mm^3, with the highest proportion having baseline CD4 cell counts below 50 cells/mm^3 (Cochran-Armitage exact test of trend, p=0.026) (Figure 1).

CXCR4-using virus as predictor of clinical progression

The association of baseline coreceptor usage with change in CD4 cell count and virus load from study entry to ART initiation was examined, but the number of women not on ART decreased substantially over time; the majority started ART shortly after enrollment when ART became available in 2002 through the Botswana government treatment program. By 12 months after enrollment 82% of women infected with R5 or DM virus had initiated ART; among those who remained treatment-naïve the mean CD4 cell count was 130 cells/mm^3 for DM virus (n=4) compared to 170 cells/mm^3 for R5 virus (n=23). The mean CD4 cell counts at sequential 3-month intervals were always lower among women with DM virus compared those with R5 virus, but these differences did not achieve statistical significance (p=0.149).

Change in coreceptor usage over time

Paired samples from 24 women collected prior to ART and at virological failure were tested for HIV coreceptor usage to determine the association of ART exposure with emergence of CXCR4-using virus. The mean interval between entry and virologic failure was 28 months (range, 8 to 64 months). The majority of women (n=17, 71%) had R5 virus at both time points. In four women (17%) with R5 virus at entry, DM virus emerged after ART exposure. Seven women without a sample at study entry had R5 virus at virological failure.

DISCUSSION

This study determined the prevalence and clinical correlates of CXCR4-using virus in a cohort of ART-naïve HIV-1 C-infected women in Botswana. Because previous studies suggested a much lower frequency of CXCR4-using virus in HIV-1C infection, we selected women with low CD4 cell counts for testing in order to increase the likelihood of identifying DM or X4 virus. Because some studies suggest that ART may select for DM or X4 virus, the prevalence of CXCR4-using virus was examined in ART-naïve women.

Nearly 15% of women with CD4 cell counts below 200 cells/mm^3 harbored DM virus. By contrast, studies in subtype B-infected patients with similarly advanced HIV-1 disease show a prevalence of CXCR4-using virus of 50% or more[2, 3, 5, 21, 22]. Previous studies among treatment-naïve patients infected with HIV-1C virus show a prevalence of DM virus of 0 to 30%. These studies were generally based on small numbers of patients in Africa, with the largest having 40 patients[6–9, 11, 14, 15, 23–25]. One study of 174 HIV-1C-infected patients in India showed a prevalence of 3.5% for CXCR4-using virus in treatment-naïve patients who had a wide range of CD4 cell counts[26]. Because our study focused on patients with lower CD4 cell counts, the prevalence of DM and X4 virus among HIV-infected patients in Botswana overall most likely is considerably lower than 15%. The relatively low frequency of CXCR4-using virus even among persons with advanced disease suggests that CCR5 antagonists such as maraviroc may be particularly useful in the treatment of HIV-1C infection. These data also support evaluating the role of CCR5 antagonists as agents for the prevention of HIV-1 transmission in areas of the world where HIV-1 C predominates.

The association of HIV-1 coreceptor usage and disease is well-established in HIV-1 subtype B infection but less so for other subtypes[4, 27–29]. Because our study only examined HIV-1 coreceptor usage among patients within a narrow range of CD4 cell counts, it was not possible to assess fully the association between CD4 cell count and presence of CXCR4-using virus. Nevertheless, even among patients with CD4 counts below 200 cells/mm^3 there was a significant trend towards higher prevalence of CXCR4-using HIV-1 among patients with the lowest CD4 counts (p=0.02).

In cross-sectional studies of subtype B-infected patients, CXCR4-using virus is detected in approximately 20% of treatment-naive patients but in up to 50% of treatment-experienced patients[27, 29–32]. This difference suggests to some that ART selects for CXCR4-using viruses, independent of CD4 cell count. However, after adjusting for nadir CD4 cell count the association of ART and CXCR4 is no longer statistically significant[33, 34]. In a cross-sectional study of 28 HIV-1C-infected patients, CXCR4-using virus was not detected in any ART-naïve patients but was found in 50% of ART-experienced patients. This finding led the authors to propose that ART exerts a greater effect on coreceptor usage in HIV-1C infection as compared to subtype B[14]. In the current study, the majority of women with R5 virus at the start of ART remained R5 at the time of virologic failure; DM virus emerged in only 4 (19%) women. This rate is consistent with observations from natural history studies, in which DM or X4 virus emerged in 23% of patients over time[22].

This study has several limitations. As noted above, the inclusion only of women with low CD4 cell counts may have limited the ability to detect significant associations between coreceptor usage and other clinical factors. In addition, data were obtained from pregnant women only; gender and pregnancy, however, are not known to affect the emergence of CXCR4-using virus. The phenotypic assay used in the current study can detect minority CXCR4-using variants present at 1% to 5% of the population, depending on the plasma virus load. It is possible that a somewhat higher frequency of CXCR4-using virus would have been detected using the enhanced-sensitivity Trofile assay (Monogram BioSciences,

South San Francisco, CA), which has a threshold of detection of 0.3% for CXCR4-using variants[35]

In summary, DM virus was readily detected in HIV-1C-infected women with advanced disease, but its prevalence was considerably lower than that reported in subtype B- or D-infected patients with similarly advanced disease[36, 37]. Exposure to ART did not appear to be a major factor in emergence of CXCR4-using virus in the cohort studied here. Such knowledge is essential for an improved understanding of the biological and clinical differences between HIV-1 subtypes, and for the design of therapeutic agents and preventive vaccines targeted against the most prevalent HIV-1 subtype.

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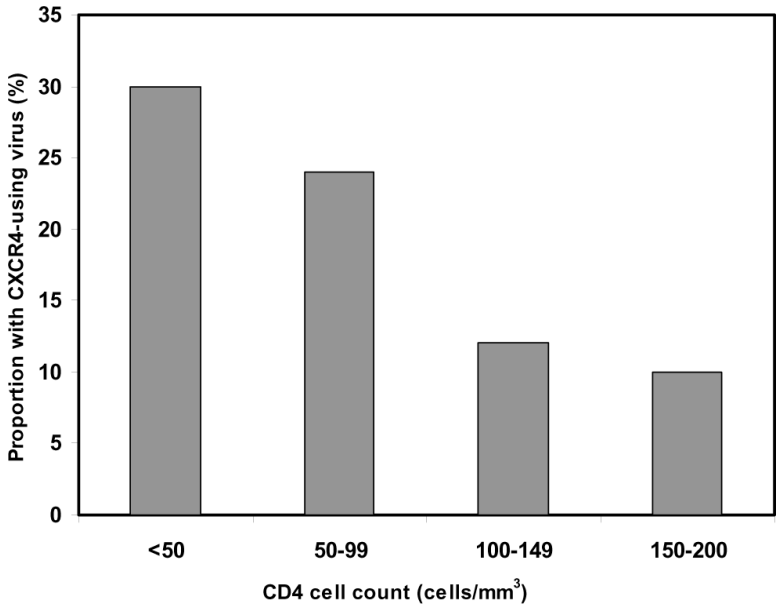

Figure 1.
Proportion of patients with CXCR4-using virus by CD4 cell count category (p=0.026, Cochran-Armitage exact test of trend).

Table 1

Clinical characteristics and coreceptor usage of women infected with HIV-1C

	Availability for testing of coreceptor usage				Stratified by coreceptor usage			
Baseline characteristics	**total**	**available**	**not available**	**P**	**total**	**R5**	**DM**	**P**
Maternal age (n)	206	153	53	0.49	148	126	22	0.03
median age		28.3	29.4			28.1	33.1	
Baseline CD4 cell count (n)	206	153	53	0.8	148	126	22	0.08
median cells/mm^3 (IQR)		130 (95–171)	139 (94–167)			141 (103–172)	121 (56–157)	
Baseline HIV-1 RNA (n)	203	151	52	0.01	147	125	22	0.94
median $\log_{10}$copies/ml (IQR)		5.0 (4.5–5.4)	4.6 (3.9–5.2)			5.0 (4.5–5.4)	5.2 (4.4–5.4)	
Time to start of ART (n)	166	119	47	<0.001	116	99	17	0.25
months (IQR)		7.0 (2.1–13.7)	2.2 (−0.3–5.8)			7.2 (2.5–14.3)	3.9 (1.1–10.7)	
ART initiation (n)	206	153	53	0.11	148	126	22	1
yes (%)		119 (78)	47 (89)			99 (79)	17 (77)	
Maternal death (n)	206	153	53	0.77	148	126	22	1
yes (%)		12 (8)	5 (9)			10 (8)	1 (5)	
HIV transmission to infant (n)	206	153	53	0.65	148	126	22	1
yes (%)		22 (14)	6 (11)			19 (15)	3 (14)	

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