

THE EPIDEMIOLOGY OF HIV CORECEPTOR TROPISM

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Abstract

According to their cellular coreceptor tropism, HIV variants are termed R5 if they use CCR5 as a coreceptor, whereas viruses with a preference for CXCR4 are termed X4. The prevalence of R5, X4 and dual/mixed (D/M) strains shows considerable variation in different patient populations. In treatment naive patients, R5 strains are found in 80-90 %, compared to only 50-55 % in patients with antiretroviral exposure. The most important predictor of R5 tropism seems to be a higher CD4 T-cell count in both naive and antiretrovirally pretreated patients. A low HIV plasma viremia seems to be associated with R5 tropism only in untreated patients. As the benefit of the new antiretroviral drug class of the CCR5 coreceptor antagonists will be probably limited to the HIV-infected patients harbouring R5 strains, determination of viral coreceptor tropism has become an important diagnostic prerequisite for the treatment of HIV infection. This review will focus on current knowledge of the epidemiology of HIV coreceptor tropism.

INTRODUCTION

In addition to CD4 receptors, entry of human immunodeficiency virus requires interaction between the viral envelope glycoprotein and a secondary cellular receptor [1]. The interaction between these coreceptors and the virus envelope triggers membrane fusion and virus entry into human lymphocytes and macrophages. Although a number of human chemokine receptors have been shown to mediate viral entry *in vitro*, only two coreceptors, named CCR5 and CXCR4, appear to play a major role *in vivo*. Both coreceptors were discovered in the middle of the 1990s [1, 15-17, 19]. The coreceptors were named after the natural chemokines that usually bind to them. The nomenclature is derived from the amino acid sequence. For CCR5 receptors these are the "CC-chemokines" MIP and RANTES, for CXCR4-receptors it is the "CXC-chemokine" SDF-1. After the discovery of the coreceptors, previous classification systems to describe biological HIV phenotypes which based on syncytium-inducing and on replicative capacities in different cell lines had been translated into a classification based on coreceptor tropism [4, 20]. In brief, HIV variants are now termed R5 if they use CCR5 as a coreceptor, whereas viruses with a preference for CXCR4 are termed X4. R5 strains predominantly infect monocyte-derived macrophages and activated CD4 cells while X4 strains

can also infect naive and resting T-lymphoid cells. Beside strains using exclusively R5 or X4, dual-tropic or mixed virus populations (D/M) which display a broad range of ability to use both CCR5 or CXCR4 coreceptors may also arise over the course of the disease [51]. While pure X4 virus populations are rarely seen *in vivo*, the vast majority of X4 strains present in D/M populations. As the benefit of the new antiretroviral drug class of the CCR5 coreceptor antagonists will be probably limited to the HIV-infected patients harbouring R5 strains, determination of viral coreceptor tropism has become an important diagnostic prerequisite for the treatment of HIV infection. To determine tropism, both phenotypic and bioinformatic approaches are currently in use. While the important caveats of these methods will be discussed elsewhere in this issue [6], this review will focus on current knowledge of the epidemiology of HIV coreceptor tropism.

CORECEPTOR TROPISM AND DISEASE PROGRESSION

Many years before the discovery of the coreceptors, elegant studies indicated evidence for a significant role of particular viral properties in the course of the disease. It was as early as 1988, when the presence of syncytium inducing variants (which today can be translated in X4 strains) has been shown to be associated with disease progression [21, 49]. Numerous studies had confirmed these early observations [29, 42] and it is now well established that the switch in the coreceptor tropism from R5 to D/M or X4 is frequently associated with accelerated decrease in CD4 T-cell counts and disease progression [5, 9, 10, 12, 45]. In contrast, long-term non-progressors maintain virus strains with exclusive tropism for R5 [57].

The reasons for the phenotypic switch which may arise from a few changes in the sequence of the HIV *env* gene are unclear. It also remains largely unexplained whether tropism shift is responsible for disease progression or whether it emerges as a consequence of progressive immune deficiency. Many authors postulated that the phenotypic switch is possibly a function of both viral and host factors and that low CD4 T-cell counts may be both a cause and an effect of X4 strain dominance [25, 30]. Moreover, it should be mentioned that the shift from R5 towards X4 strains is not a prerequisite for disease progression. Approximately half of the patients do never experience a shift during the natural course of the disease

and pure R5 strains may show considerable variation in their cytopathologic properties and replicative fitness [24, 28].

CORECEPTOR TROPISM OF TRANSMITTED HIV AND DURING ACUTE INFECTION

In general, R5 strains seem to be more efficiently transmitted than X4 strains. The predominance of R5 strains during acute HIV infection is independent from the route of HIV transmission [54, 58]. Individuals who do not express functional CCR5 coreceptors because of a mutation in the CCR5-encoding gene are largely protected from HIV-1 infection despite the presence of functional CXCR4 coreceptors [12, 34, 44, 56]. Many mechanisms have been postulated to explain the preferential transmission of R5 strains. These include barriers at mucosal sites which may select against X4 strains but also specific humoral and cellular immune responses which may inhibit viral replication of X4 strains more effectively. Recently it has been postulated that the preferential transmission of R5 strains depends on the superimposition of multiple mechanisms rather than of one crucial 'gatekeeper' mechanism [35].

It should be noted that strains found in acute HIV infection are not exclusively R5. In a large cohort study on men who have sex with men from six major cities in the United States, X4 strains were found in 4 out of 195 samples collected within six months of HIV-1 seroconversion [18]. Among 296 Spanish HIV-1 seroconverters, X4 strains (either pure or D/M) were recognized even in 17.2 % of the patients. Of note, drug resistance mutations did not seem to influence coreceptor tropism [11].

CHRONICALLY HIV-INFECTED PATIENTS NAIVE TO ANTIRETROVIRAL THERAPY

Several cross-sectional studies have addressed coreceptor tropism in chronically HIV-infected patients naive to antiretroviral therapy [7, 14, 23, 37]. The results indicate that in this patient population, R5 strains are present in 80-90 % (Table 1). Virtually all the remaining strains are D/M; exclusive X4 strains are very rare in untreated HIV-infected patients.

In the largest study to date, pretherapy plasma samples from 1191 individuals initiating antiretroviral therapy in British Columbia, Canada, were analysed by

a phenotypic assay [7]. Of the 979 subjects in which tropism data were available, 81.8 % harboured R5 variants while 18.1 % harboured D/M variants. Only 1 patient (0.1 %) harboured exclusively X4. There was a strong association between the detection of D/M variants and the absolute CD4 cell count at baseline which is illustrated in Figure 1.

In multivariate analyses, predictors of D/M variants were low CD4 T-cell count (OR, 1.53 per 100-cell/ μ l decrement, $p < 0.0001$), a high baseline plasma viremia (OR, 1.46 per log₁₀ increment, $p = 0.04$) and the heterozygous CCR5 wt/ Δ 32 genotype (OR, 2.48; $p = 0.0005$). Sex, age, history of injection drug use or a previous AIDS diagnosis were not associated with coreceptor tropism. The results were largely confirmed by another large investigation from the Chelsea and Westminster Hospital in London [37]. Beside higher absolute CD4 cell counts and lower plasma viremia, in this study, a lower natural killer cell count was also associated with the presence of R5 strains.

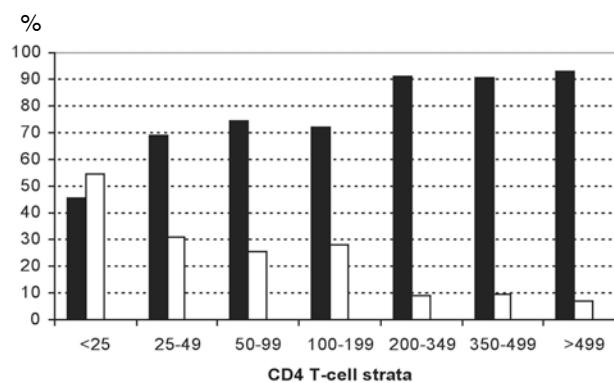


Fig. 1. Percentages of R5 strains (dark) and of D/M strains (white) within different CD4 T-cell strata (cells/ μ l). All patients were naive to antiretroviral therapy (adapted from [7]).

Taken together, prevalence of R5 strains approximate 80-90 % in HIV-infected patients naive to antiretroviral therapy. Although high baseline CD4 T-cell counts and low plasma viremia may enhance the probability of the presence of R5 strains in an individual patient, in all studies, R5 and D/M strains were found at all CD4 T-cell strata. Thus, screening for coreceptor tropism will remain necessary before the treatment with CCR5 coreceptor antagonists in antiretroviral naive patients.

Table 1. Frequency of coreceptor tropism and factors associated with presence of D/M in chronically HIV-infected patients naive to antiretroviral therapy. In all studies, phenotypic assays were used to assess coreceptor tropism.

Reference	n	R5 (%)	D/M (%)	Factors associated with presence of D/M
14	299	88.0	12.0	Low CD4/CD8 ratio
7	979	81.8	18.2	Low CD4 T-cells, high HIV plasma viremia, heterozygous CCR5 wt/ Δ 32 genotype
37	402	81.1	18.9	Low CD4 T-cells, high HIV plasma viremia, higher natural killer cell counts
23	294	89.1	10.9	Low CD4 T-cells, Hispanic origin

PATIENTS WITH EXPOSURE TO ANTIRETROVIRAL THERAPY

Compared to treatment-naïve patients, in subjects with previous exposure to antiretroviral therapy, D/M or X4 strains are more common. Several large studies have addressed this issue, a selection is depicted in Table 2.

The lowest percentage of R5 strains was found in an analysis of the baseline samples of the two TORO trials [36]. Within these worldwide randomized phase III studies, patients with extensive exposure to antiretroviral therapy had been treated with enfuvirtide or not. Inclusion criteria were an HIV plasma viremia of > 5.000 copies/ml and at least 3-6 months of therapy with at least 1 NRTI, 1 NNRTI, and at least 2 PI or documented resistance to these drugs or both. Less than half of the 724 patients for which phenotyping of the baseline samples were available had R5 strains at baseline. The presence of D/M strains was associated with significantly lower CD4 T-cell counts but similar plasma viremia, compared with R5 strains.

Similar findings were made in ACTG 5211, a Phase IIb study on the CCR5 coreceptor antagonist vicriviroc in 391 pretreated patients [55]. In this trial, also only approximately 50 % of the patients harboured R5 strains. In 46 % D/M strains were present whereas 4 % of the patients harboured pure X4 strains. On multivariate analysis, only the baseline CD4 T cell count remained significantly associated with coreceptor tropism. Subjects in the D/M group had significantly lower CD4 T-cell counts than subjects in the R5 group. Interestingly, the 16 subjects with pure X4 strains had a median plasma HIV-1 RNA level that was significantly lower than that of subjects with R5 strains or D/M strains. The median screening CD4 T-cell count for subjects with X4 strains was not significantly different than that of subjects with R5 strains or D/M strains. No other characteristics were found to be independently associated with the presence of pure X4 strains.

The results of a recent published study illustrate the importance of tropism testing in treatment-experienced patients. Out of 451 patients screened in the VICTOR-E1 study which examined the use of vicriviroc in heavily pretreated patients, only 116 subjects

could be enrolled in this trial [48]. Of the 335 screening failures, 53 % were due to the presence of D/M or X4 strains. In this study, D/M or X4 strains at screening were significantly associated with lower mean CD4 counts than R5 virus, but not associated with viral load, number of resistance mutations, age, sex or non-B clade. In VICTOR-E1, in which about half of all screened subjects were from Brazil, the proportion of R5 strains was similar between patients from North America and rest of the world.

Taken together, R5 strains are found in around 50-55 % of patients with exposure to antiretroviral therapy, indicating that at best half of this patient population would have had a benefit from treatment with CCR5 coreceptor antagonists. As in treatment naïve patients, CD4 T-cell count seems to be the strongest predictor of coreceptor tropism. However, R5 and D/M strains are also found at all CD4 T-cell strata. The level of HIV plasma viremia does not appear to be associated with coreceptor tropism, by contrast with the findings in treatment naïve patients.

IMPACT OF ANTIRETROVIRAL THERAPY ON THE EPIDEMIOLOGY OF CORECEPTOR TROPISM

Maraviroc and vicriviroc are currently the most promising compounds of the new class of CCR5 coreceptor antagonists. One hypothetical but potentially important consequence of the administration of these compounds is the selection of X4 strains. The clinical experiences and the implications of a tropism shift seen with CCR5 coreceptor antagonists will be described elsewhere in this issue [3, 43].

Data on coreceptor tropism changes during “classical” antiretroviral therapy (without the use of CCR5 coreceptor antagonists) is inconclusive. As described above, frequency of D/M strains is higher in patients with exposure to antiretroviral therapy. However, based on the design of these cross-sectional studies it is not possible to draw definitive conclusions about the effect of antiretroviral therapy on the evolution of coreceptor tropism. Moreover, data of longitudinal studies have shown inconsistent results. While some authors reported that antiretroviral therapy preferentially suppresses X4 and induces a shift towards R5 strains [22, 40, 46], others found that coreceptor tro-

Table 2. A selection of large studies evaluating coreceptor tropism in chronically HIV-infected patients with exposure to antiretroviral therapy.

Reference	n	Study acronym (drug tested)	R5 %	D/M %	X4 %
36	724	TORO 1 and TORO 2 (enfuvirtide)	49.9	47.9	2.2
55	391	ACTG 5211 (vicriviroc)	50.4	45.5	4.1
48	451	VICTOR E1 (vicriviroc)*	54.0	42.0	5.0
32, 38	2.560	MOTIVATE 1 and 2 (maraviroc)*	56.0	44.0	NA
27	182	Cohort study	58.8	40.6	0.6

*Incomplete data provided in these preliminary publications, NA = not available

pism remained stable during antiretroviral therapy [33, 53]. Contrasting these findings, one longitudinal genotypic analysis of HIV in cellular reservoirs in 32 patients with undetectable viral loads on antiretroviral therapy for five years revealed that there was a switch from R5 to X4 strains in 11 of the 23 patients with R5 strains at baseline [13]. X4 strains remained predominant in patients who harbored mainly X4 strains at baseline. These results of this study suggest that potent antiretroviral therapy produces the conditions necessary for the gradual emergence of X4 strains in cellular reservoirs.

CORECEPTOR TROPISM OF DIFFERENT HIV CLADES

While the majority of the above-cited studies focussed on HIV-1 clade B, data on coreceptor tropism of Non-B clades of HIV-1 and of HIV-2 is are limited. However, except for some studies reporting on a high frequency of D/M strains in antiretroviral drug naïve Ugandan women infected with HIV-1 clade D [26] and a lower frequency of X4 strains in clade C [52], most studies published to date did not find significant epidemiological differences of coreceptor tropism of Non-B clades or HIV-2 when compared to HIV-1 B clades [8, 31, 37, 41, 50]. However, numbers of analysed subjects are too low to draw definite conclusions.

CORECEPTOR TROPISM IN DIFFERENT COMPARTMENTS

There are several studies reporting on discordant coreceptor tropism in different compartments such as brain and the genital tract. There is at least one study reporting on discordant coreceptor tropism in the cerebrospinal fluid and plasma which may have implications for therapy with CCR5 coreceptor antagonists [47]. Other studies revealed discordant coreceptor tropism and genetic compartmentalization of HIV between plasma and gut, vaginal secretions or semen [2, 23, 39]. However, the clinical relevance of these observations remains to be elucidated.

In conclusion, the prevalence of R5, X4 and D/M strains shows considerable variation in different patient populations. In treatment naïve patients, R5 strains are found in 80-90 %, compared to only 50-55 % in patients with antiretroviral exposure. Although high baseline CD4 T-cell counts and low plasma viremia may enhance the probability of the presence of R5 strains in an individual patient, R5 and D/M strains are found at all CD4 T-cell strata. As the benefit of the CCR5 coreceptor antagonists will be probably limited to the HIV-infected patients harbouring R5 strains, in every patient for whom this new antiretroviral drug class is considered, determination of viral coreceptor tropism is an important diagnostic prerequisite.

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