

# HIV-2 Infection and Chemokine Receptors Usage – Clues to Reduced Virulence of HIV-2

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**Abstract:** Human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) are the causative agents of Acquired Immunodeficiency Syndrome (AIDS). Without therapeutic intervention, HIV-1 or HIV-2 infections in humans are characterized by a gradual and irreversible immunologic failure that ultimately leads to the onset of a severe immunodeficiency that constitutes the hallmark of AIDS. In the last two decades AIDS has evolved into a global epidemic affecting millions of persons worldwide.

Although sharing several identical properties, HIV-1 and HIV-2 have shown some important differences *in vivo*. In fact, a significant amount of epidemiologic, clinical and virologic data suggest that HIV-2 is in general less virulent than HIV-1. This reduced virulence is revealed by the longer asymptomatic period and the smaller transmission rate that characteristically are observed in HIV-2 infection. In this context, studies using HIV-2 as a model of a naturally less pathogenic infection could bring important new insights to HIV pathogenesis opening to new strategies to vaccines or therapeutic design.

The reasons underlying the reduced pathogenicity of HIV-2 are still essentially unknown and surely are the outcome of a combination of distinct factors. In this review we will discuss the importance and the possible implications in HIV-2 pathogenesis, particularly during the asymptomatic period, of a less fitted interaction between viral envelope glycoproteins and cellular receptors that have been described in the way HIV-2 and HIV-1 use these receptors.

**Keywords:** HIV-2 infection, Coreceptor usage, Pathogenesis, HIV-2 – cell interactions, Viral fitness.

## INTRODUCTION

Human immunodeficiency virus (HIV) type 2 (HIV-2) was initially isolated in 1986 from a symptomatic patient from Guinea-Bissau [59]. Despite the fact that HIV-2 is only about 40% similar to HIV-1 in nucleotide sequence [101], both retroviruses share identical morphological and genomic organizations. Replication cycle within infected cells is also similar and either HIV-1 and HIV-2 infection of a human host lead to immunological failure and apparently to a similar array of clinical manifestations [60]. Despite that, HIV-2 infection has clinical course and pathogenic mechanisms distinct from HIV-1, showing in general a less virulent phenotype *in vivo*.

As a pathogen, HIV-2 is less efficient in developing disease. This notion is suggested by a significant amount of epidemiologic and virologic data. The molecular aspects that could account for this less efficiency are far from being fully characterized or even identified.

The initial events that lead to viral entry into target cell are one of the most deeply studied steps in HIV replication cycle and have been related to several important biologic characteristics of HIV. Modifications, either in cellular receptors or in viral receptor-interacting glycoproteins, lead inevitably to major viral phenotype changes that include adjustment of cell tropism, altered replicative fitness,

different abilities to escape neutralizing antibodies and, ultimately, to unique pathogenic characteristics.

Due to its inherently attenuated phenotype, the study of HIV-2 infection constitutes an exceptionally good model to understand virologic and immunologic mechanisms that enable the human host to cope with an HIV infection for such a long period of time and may help us to learn how to develop immunity against HIV-1. This review focuses on studies of HIV-2 early interactions with target cell, particularly those related to coreceptors usage. The implications of this usage in viral fitness and pathogenic outcome of HIV-2 infection will also be discussed.

## EPIDEMIOLOGIC DATA

While HIV-1 and HIV-2 share identical transmission routes, HIV-2 has maintained a restricted geographic distribution compared to the remarkable worldwide spread of HIV-1. At present, the majority of HIV-2 infections are found predominantly in West Africa. Outside this region, HIV-2 is found in countries where current or historical connections to West African nations exist; Portugal, France and their former colonies are elucidative examples of this. Portugal has the highest prevalence of HIV-2 infection in Europe with 3.8% of all AIDS cases<sup>1</sup>. HIV-2 infection was also noteworthy in the former Portuguese colonies Angola [221] and Mozambique [22], as well as in Brazil [65, 248]

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and India [17, 133, 193, 215]. In all other countries where no such ties exist, little or no evidence of HIV-2 infection is found; for instance, in the United States, between 1992 and 1995 only 62 HIV-2 infected individuals were detected [47].

Although the zoonotic episode that was responsible for the introduction of HIV-1 into human host had apparently occurred about two decades earlier than that of HIV-2 [127, 141, 217, 228], both viruses had begun to spread nearly at the same time, somewhere between 1950 and 1970 [141, 156, 202]. In other words, the distinct epidemiologic profile of HIV-1 and HIV-2 cannot be attributed to a significantly different timescale for epidemic history in human population. It is also highly unlikely the existence of a genetic resistance to HIV-2 or a particular susceptibility to HIV-1 infection in human population. Therefore, which factors are responsible for the discrepant epidemiologic profile of these two viruses?

Some studies have helped shed light onto the causative reasons for the relatively slow spread of HIV-2. People infected with HIV-2 have a lower viral load than those infected with HIV-1 [200]. This difference is remarkably important throughout the asymptomatic stage and persists until late in the course of the disease. Interestingly, a similar proviral burden is detected in both HIV-1 and HIV-2-infected individuals [96, 199], suggesting that lower plasma viral load observed in HIV-2 infection may be due to different levels in virus production.

Undoubtedly, a lower viral burden implicates a lower transmission rate. Indeed, heterosexual spread in HIV-2 infection is remarkably slower than in HIV-1 [118]. Overall, it seems that HIV-2 is five to nine times less efficiently transmitted than HIV-1 by sexual route [117]; vertical transmission rate also suggests this lower spread efficiency with HIV-2 being transmitted in about 0-4% of all HIV-2-positive pregnancies, while in HIV-1 this transmission occurs in approximately one-third of untreated pregnancies [1, 9, 44, 45, 157, 167, 201]. So, in conclusion, the restricted geographic distribution of HIV-2 infection is mainly due to a lower transmission rate of HIV-2, and viral burden is an important clue to explain HIV-2 less efficient transmission.

## CLINICAL DATA

Soon after the isolation of HIV-2, the direct involvement in the onset of immunodeficiency and the development of clinical features similar to those of HIV-1 infection [39, 60] were reported. However, although human infection with HIV-2 eventually leads to immunologic failure and AIDS, rates of disease progression and mortality following HIV-2 infection are surprisingly lower than for HIV-1 [113, 155, 203, 252]. As a rule, HIV-2-infected individuals have a clinically latent period that can last for decades and in the majority of adults, HIV-2 infection apparently has no effect on survival [203]. In a prospective study conducted with untreated Senegalese prostitutes, two thirds (67%) of HIV-1-infected women enrolled remain AIDS-free after 5 years of infection in contrast with 100% for HIV-2-infected women [155]. The rate of developing abnormal CD4<sup>+</sup> lymphocyte counts (<400 cells/mm<sup>3</sup>) and the development of skin test anergy were also reduced in HIV-2 enrollees [155]. This

slower HIV-2-induced deterioration of the immune system seems to be a general hallmark of HIV-2 infection reported by several studies [144, 191]. Interestingly, the surface glycoprotein of HIV-2 (gp105) seems to be more immunosuppressive than HIV-1 gp120 [46], leading to minor immunocellular activation, which can be pathogenically important by limiting the level of viral replication *in vivo*. Another relevant finding was that in HIV-2 infected individuals the T-cell ability to produce Interleukin-2 (IL-2) is better preserved than in HIV-1-positive patients with similar CD4<sup>+</sup> cell counts [237], which can provide an additional explanation to the slower CD4 T lymphocyte depletion observed in HIV-2 infection. This slower depletion can also be explained by lower rates of T-cell apoptosis associated with HIV-2 infection when compared with HIV-1 infection [8, 114, 164]. Additionally, HIV-2 seems to evoke a broader neutralizing antibody response and a more efficient cell-mediated immunity than HIV-1 (for a more detailed discussion see [8]).

The clinical manifestations observed in AIDS patients infected with HIV-2 are similar to those of HIV-1, with only minor differences. Some of these differences are related to a higher frequency of encephalitis [150] and the lower incidence of Kaposi's sarcoma [11, 154]. Remarkably, even during the symptomatic stage, the survival time observed for HIV-2-infected patients seems to be greater than for HIV-1 AIDS patients [154, 155, 178, 179].

In summary, all these findings support the notion that in HIV-2 infected individuals several factors can account for a best fitted immune response that ultimately leads to a better control of HIV-2 infection compared to HIV-1 infection.

## HIV INTERACTION WITH TARGET CELL – EARLY EVENTS

The early events of HIV replication cycle involve interactions between viral envelope glycoproteins and cellular receptors, that enable the binding of the virion to target cell and, eventually, to the viral envelope and cell membrane fusion, with the consequent release of viral nucleocapsid into cell cytoplasm. Soon after isolation and identification of HIV-1 [21] the CD4 molecule was identified as its specific cellular receptor [66, 122]. However, the observation that human and non-human cells transfected with CD4 gene, were able to bind but unable to become infected by HIV, even when CD4 molecule was normally processed and expressed [35, 51, 56, 80], raised the possibility that additional cofactors were required for HIV entry, and that these cofactors were present in some cells but absent in others. During the next years the main quest for many HIV researchers was the identification of such cofactors/coreceptors. Several molecules were then proposed as potential candidates for such an important role. Remarkable attention and criticism was raised by the report of Hovanessian group, which claimed the role of CD26 (an enzyme also known as dipeptidyl peptidase IV) as a cofactor in HIV entry and infection [41]. However, contradictory results have readily put an end to this hypothesis [3, 37, 42, 187]. It was necessary two more years to finally identify these coreceptors as members of the chemokine receptors family.

**Table 1. Described Coreceptors for HIV-1, HIV-2 and SIV**

Receptors <sup>a</sup>	Ligands <sup>a</sup>	Predominant expression/Tissue distribution	Virus <sup>b</sup>	Ref.
CCR1	MIP-1 $\alpha$ , MIP-1 $\beta$ , RANTES, MCP-3	Monocytes, NK cells, activated and naïve T lymphocytes, immature DC	HIV-2, SIV	[38, 99, 159]
CCR2b	MCP-1, MCP-2, MCP-3, MCP-4	Monocytes, activated T lymphocytes, B cells	R5X4, HIV-2, SIV, HIV-1	[38, 50, 79]
CCR3	Eotaxin, RANTES, MIP-1 $\alpha$ , MCP-3, MCP-4	Th2 polarized T cells, eosinophils, basophils, activated T lymphocytes, microglial cells, astrocytes	R5X4 HIV-1 NSI	[38, 54, 235]
CCR4	TARC, MDC	Peripheral blood lymphocytes, thymocytes, B cells, NK cells, monocytes and neutrophils	HIV-2	[38, 99, 159]
CCR5	MIP-1 $\alpha$ , MIP-1 $\beta$ , RANTES, MCP-2	IL-2 cultured activated T cells, monocytes, Th1 type T cells, memory T cells, immature DC, Langerhans cells, astrocytes, microglial cells	R5, R5X4, HIV-2, SIV	[4, 38, 75, 81, 235]
CCR8	I-309	Monocytes, thymocytes, Th2 type T cells, neutrophils, other tissues, e.g., brain, lung, spleen, skeletal muscles	R5X4, HIV-2, SIV	[216]
CCR9	TECK, RANTES, MIP-1 $\alpha$ , MIP-1 $\beta$	Thymocytes, lymphoid cell lines and PBMC	R5X4, HIV-1	[53]
CXCR2	GRO $\alpha$ , GRO $\beta$ , ENA-78, GCP-2, IL-8	Neutrophils, monocytes and on a small portion of lymphocytes, placenta	HIV-2	[38]
CXCR4	SDF-1 $\alpha$ , SDF-1 $\beta$	CD4+ and CD8+ T cells, monocytes, DC, B lymphocytes, astrocytes, microglial cells, lung and spleen tissue	X4, R5X4, HIV-2	[92, 223, 255]
CXCR5	BLC/BCA-1	B lymphocytes, T lymphocytes type CD4+, CD8+, CD25-, CD44+, CD62L-, CD45RO+	HIV-2	[116]
CXCR6	CXCL16	CD-4+ T lymphocytes, memory T cells, NK cells, placenta, monocytes	R5X4, HIV-2, SIV	[76, 143, 184]
CX3CR1	Fractalkine	CD-8+ T cells, NK cells, monocytes, neutrophils, brain, liver, skeletal muscle and peripheral blood	R5X4, HIV-2, SIV	[207, 216]
GPR-1	ND	Tissue macrophages, brain	HIV-2, SIV	[90, 229]
GPR-15	ND	T cells, colon	R5X4, SIV	[76, 90]
Apj	ND	CNS	R5X4, SIV	[53, 84]
ChemR23 $\ddagger$	ND	Macrophages, DC	SIV, HIV-1	[218]
RDC1	ND	CD4+ T lymphocytes, CNS	HIV-2, SIV	[230]
BLTR	ND	Leucocytes, B lymphocytes	HIV-1	[185]
US28	RANTES, MIP-1 $\alpha$ , MIP-1 $\beta$	Fibroblasts infected with HCMV	R5X4	[195]

<sup>a</sup> The nomenclature adopted for chemokines receptors and chemokine were based on references [174, 175]. <sup>b</sup> Described viruses using this chemokine receptor for infection. Abbreviations: BCA, B cell-activating chemokine; BLC, B lymphocyte chemoattractant; CNS, central nervous system; DC, dendritic cells; ENA78, epithelial-derived neutrophil-activating peptide-78; GCP, granulocyte chemoattractant protein; GPR, G protein coupled receptor; GRO, growth-related oncogene; HCMV, human cytomegalovirus; IL, interleukin; MCP, monocyte chemotactic protein; MDC, macrophage-derived chemokine; MIP, macrophage inflammatory protein; ND, not determined; RANTES, regulated on activation, normal T cell expressed and secreted; SDF, stromal cell-derived factor; NK, natural killer; TARC, thymus- and activation-related chemokine; TECK, thymus-expressed chemokine.

## CHEMOKINE RECEPTOR AS HIV CORECEPTORS

The first report suggesting a possible role of chemokines and their receptors in HIV pathogenesis was published in the late 1980s, when Walker and co-workers showed that HIV infection was inhibited by soluble factors, produced by CD8+ lymphocytes [249]. The  $\beta$ -chemokines RANTES, MIP-1 $\alpha$  and MIP-1 $\beta$  were identified as being part of these soluble factors [61] and responsible, when in high plasma concentration, for the non-progression to symptomatic stage in some HIV-infected individuals. The presence of increased concentrations of these  $\beta$ -chemokines was also associated

with a relative protection to infection in frequently exposed uninfected individuals [188].

The identification of CXCR4 (initially known as Fusin [92]) as a coreceptor for HIV strains adapted to infect transformed T-cell lines (T-tropic strains), its relation with chemokine receptors family and the observation that  $\beta$ -chemokines inhibited the infection by HIV strains able to infect primary macrophages (M-tropic), lead to the identification of the  $\beta$ -chemokine receptor CCR5 as a second coreceptor, mediating M-tropic strains entry [4, 75].

Nowadays, nineteen of these seven-transmembrane domain G-protein-coupled receptors (GPCRs) have been thus considered, *in vitro*, as coreceptors for HIV-1, HIV-2 and Simian Immunodeficiency Virus (SIV): CCR1, CCR2b, CCR3, CCR4, CCR5, CCR8, CCR9, CXCR2, CXCR4, CXCR5, CXCR6, CX3CR1, GPR1, GPR15, APJ, ChemR23, RDC1, BLTR and US28 [36, 232] (Table 1 summarizes current data of HIV coreceptor repertoire *in vitro*).

Interestingly, despite the extensive range of molecules that potentially could act as viral coreceptors, CCR5 and CXCR4 are the major coreceptors for HIV-1 and they seem to be of major importance in HIV-1 pathogenesis [232, 266]. CCR5-dependent (R5) strains are predominant during early stages of HIV infection and only in approximately 40% of infected humans, a viral population arises that can use CXCR4 in addition to (R5/X4 strains), or sometimes instead of CCR5 (X4 strains) [23, 24, 233]. The appearance of such strains is usually associated with accelerated CD4+ T-lymphocytes loss and disease progression [31, 62, 64, 210]. Moreover, CCR5 usage is also critical in HIV transmission, as suggested by the finding that humans homozygous for an inactive mutant CCR5 allele ( $\Delta 32_{ccr5}$ ), that lack functional cell surface CCR5 molecules, had greatly diminished risk of infection with HIV-1 [73, 147, 172, 219]. Those rare cases where an HIV-1 infection could be demonstrated [20, 27, 132, 162, 163, 180, 242], suggest that either M-tropic viruses use coreceptors other than CCR5, or infect independently from the presence of a functional CCR5 coreceptor. Therefore, a primary infection mediated and sustained by X4 strains, although exceptional, may occur [163].

The identification of chemokine receptors as HIV coreceptors has clarified crucial structural and functional aspects of HIV entry into host cells. In the most favored model, HIV-1 entry begins with a specific interaction between the virion heterodimeric Env complex, formed by surface (SU) and transmembrane (TM) glycoproteins, and two cellular proteins: CD4 and the coreceptor. Binding of viral SU glycoprotein to CD4 is the first event and appears to cause structural changes in this glycoprotein that exposes, creates and/or stabilizes the coreceptor-binding regions. After binding of SU glycoprotein to the coreceptor molecule, further conformational changes induce the disclosure of the fusion peptide in TM glycoprotein, that ultimately leads to viral envelope fusion with cellular membrane and the release of viral nucleocapsid into the cell cytoplasm (reviewed in [57, 205]).

According to this model, HIV cell tropism is largely determined by the expression patterns of the appropriate coreceptor (namely, CCR5 and/or CXCR4) at the target-cell membrane. Therefore, M-tropic viruses, that require CCR5 coreceptor for viral entry, do not infect transformed T-cell lines because these cells do not express this coreceptor. This well-defined pattern reported for HIV-1 coreceptor usage is not observed in HIV-2. In fact, one of the most remarkable features of HIV-2 strains is the enormous variability in the way they interact with chemokine receptors [38, 99, 159]. The fact that the majority of reported HIV-2 isolates are able to interact efficiently with several chemokine receptors will be discussed further later on, as this feature has direct implications in the pathogenesis of HIV-2 infection.

Additional factors, besides distribution/regulation of coreceptor availability on the cell surface are involved in the selection for usage of different coreceptors. One of these factors is the effect of coreceptor engagement on the physiologic state of the cell. Several reports have mentioned that binding of HIV-1 SU envelope glycoprotein to chemokine receptors triggers the activation of signal transduction pathways [12, 49, 55, 69, 140, 146, 165, 198, 251] and could be responsible for chemo-attract activated CD4+ lymphocytes to sites of viral replication or to enhance viral replication *in vivo* by increasing the activation state of target cells. Although receptor signaling is not required for coreceptor function [10, 91, 98], these chemokine signaling cascades *in vivo* may prepare the target cells for viral replication and conceivably they could be responsible for some of the cellular responses to the virus. For instance, specific sequences in the envelope glycoprotein have been shown to direct not only envelope fusion, but also events in the intracellular viral life cycle after entry [168]. Viral envelope glycoproteins binding to chemokine receptors could also be potentially linked to several intracellular pathways that regulate cell growth, cell survival, and cell differentiation [40, 74, 77, 112, 142, 243]. In addition, ligand binding to chemokine receptors (and considering HIV glycoproteins as unnatural ligands for chemokine receptors) has been shown to induce modifications in cytoskeletal structure [173] that, in HIV infection, may facilitate viral transmission from infected to uninfected cells [40, 112].

Even though viral entry into primary lymphocytes and macrophages via CCR5 does not depend on G-coupled signaling [7], and mutations in CCR5 that reduce or eliminate signal transduction do not affect coreceptor activity [5, 10, 91, 98], some indirect evidences suggested that HIV coreceptor binding-mediated signaling may modulate HIV infection in primary cells. Pertussis toxin- or protein kinase C-dependent desensitization of CCR5 prevents cell entry of R5 HIV-1 primary isolates into primary activated T lymphocytes without disturbing CCR5 or CD4 cell surface expression [2, 100]. Moreover, the ability of R5 HIV-1 strains to replicate in macrophages, correlates with the capacity of the virus to induce signal transduction through CCR5, suggesting that coreceptor activation is essential for HIV replication cycle be accomplish in these cells [12]. Other authors however, using a different approach, found that the HIV-1 infection of both primary lymphocytes and macrophages are not dependent on the activation triggered by chemokine signaling cascades as a consequence of SU glycoprotein interaction with CCR5 [7]. Therefore, although controversial, and apparently cell type- and/or viral strain-dependent, it seems that the simple existence of appropriate coreceptors at cell membrane is not sufficient, in some circumstances, to guarantee a productive infection.

Another factor that may account for a successful viral entry process is the relative concentration of cellular receptors and their co-localization in specific sites of plasma membrane [128, 129, 194, 262]. Different cell types show different plasma membrane concentrations of CD4 and coreceptors [138, 139]. Natural variation in their levels is also observed during activation/differentiation of T lymphocytes and macrophages that directly correlates with cellular susceptibilities to HIV-1 infection [177, 192, 245, 260]. Quantitative studies have shown that CCR5 functions

more efficiently as HIV coreceptor when CD4 concentration at cell membrane is increased [194]. Apparently, higher concentrations of CD4 could compensate for decreased quantities of CCR5 [194]. Conversely, lower CD4 concentrations require larger amounts of CCR5 for efficient R5 HIV-1 infection. Actually, and based on a study carried out with a mutant form of CCR5 with decreased affinity to bind HIV-1 Env glycoproteins, an estimate of 4 to 6 CCR5 molecules are needed to form a fusion pore [129]. This need for a localized synergy between cellular receptors to viral fusion has been also reported for influenza virus where it was estimated that 3 to 6 hemagglutinin trimers are required to form a fusion pore [68, 87]. This notion, that a threshold level of cellular receptors concentration must be present, in a localized region of the plasma membrane, is particularly important in primary cells as T-lymphocytes or macrophages. Viral coreceptor usage has been assessed *in vitro* by infectivity assays using cell lines that express several thousand copies of CD4, CCR5 and other coreceptors [139]. In these circumstances, concentrations of cellular receptors are far from limiting conditions for viral infection. However, in primary T-lymphocytes and macrophages the amount of CCR5 or CXCR4, are typically much lower, donor-dependent and reliant on the cellular activation/differentiation status [139].

#### MOLECULAR DETERMINANTS OF CORECEPTORS USAGE

Different coreceptor usage is mainly determined, in HIV-1, by the envelope SU glycoprotein [52, 106, 108, 109, 234]. Specifically, the third variable (V3) region of HIV-1 has been highly associated with coreceptor usage: several data has ruled out that higher positive charges in V3 region are associated with CXCR4 usage and to the ability to induce syncytia formation in primary T-CD4 lymphocytes [70, 71, 197, 222]. Additionally, the first and second variable region (V1/V2) of HIV-1 gp120 have also been linked with coreceptor usage, apparently by a direct cooperation with V3 region [137, 176, 197]. Both regions seem also to be implicated in the replication rate phenotype of HIV-1 [197]. Alterations within N-linked glycosylation sites have been shown to alter coreceptor usage, CD4-binding and antibody neutralization profiles of HIV-1 [123, 151, 152, 182, 197, 250].

In HIV-2, the SU glycoprotein contains five variable regions (V1-V5) intercalated with five conserved domains (C1-C5). As for HIV-1, several N-linked glycosylation sites and conserved cysteine residues, involved in disulphide bonds, could be identified throughout the SU glycoprotein of HIV-2 [166, 239, 256]. Interestingly, residues that in HIV-1 SU glycoprotein are implicated in CD4 and coreceptor binding are highly conserved in HIV-2 and SIV [135, 211], suggesting that these regions might share a common structure and perhaps a similar function.

In comparison to HIV-1, fewer HIV-2 strains have been genetically characterized. However, the results of the studied strains have shown that viral variability seems to be limited [34, 67], probably as a consequence of the lower replication rate within the infected patient and the decreased transmission of HIV-2. Noteworthy, the V3 region of HIV-2 appeared to be highly conserved, in contrast to HIV-1.

Conversely, amino acid composition of the V1/V2 region is highly variable among HIV-2 strains [67, 130, 160]. This high mutation rate suggests the existence of a strong selective pressure on the V1/V2 region, similarly to that on the V3 loop of HIV-1 strains. Accordingly, the role of the V3 loop of HIV-2 as a neutralization target has been controversial [16, 28, 29, 158, 244]. Also in the close related SIV model, peptides representing the V3 loop did not induce neutralizing antibodies [115, 119]. These data might suggest that in HIV-2 and SIV the V3 region is less exposed than in HIV-1.

Determinants of coreceptor usage by HIV-2 strains have been attributed to the V3 region. Particularly, differences in amino acid composition of the C-terminal region of the V3 loop correlate with the shift of coreceptor usage between CCR5 to CXCR4 [110]. The SIV's V3 loop, which shares little sequence homology with its HIV-1 counterpart, is also important for viral tropism, although amino acids outside the V3 region can also determine coreceptor usage [85, 108, 120]. Particularly, amino acid 324 (isoleucine) in the V3 region of SIVmac has been reported to directly affect the usage of specific SIV coreceptors [120, 196]. Remarkably, this isoleucine residue (I324) is conserved in SIV and in the majority of HIV-1 strains [186, 196]. In HIV-2, only HIV-2UC1 has I324 whereas all other HIV-2 V3 sequences this amino acid is replaced by a valine (V324). This substitution (I324V) has been referred to have no effect on viral coreceptor usage, replicative capacity or infectivity of SIVmac [196].

Despite the obvious contribution of residues in the V3 loop for HIV-2 coreceptor usage, the absence of a significant variability in this region seems to be hardly concealed with the unpredictability in coreceptor usage detected in most HIV-2 strains, unless other more variable regions, such as V1/V2, directly influence the coreceptor engagement. Alternatively, the conformation of HIV-2 Env glycoproteins, particularly from those with promiscuous coreceptor usage, may be sufficiently relaxed to interact indifferently and with similar efficiencies with different coreceptors, somehow like a master key able to open several "doors" (i.e. coreceptors). Conversely, in HIV-1 the Envs conformation should be much more stringent in the way they interact with coreceptors.

#### HIV-2 INFECTION AND CELLULAR RECEPTORS ENGAGEMENT

Virtually, all the concepts and models regarding HIV coreceptors usage and viral pathogenesis were deduced from studies conducted with HIV-1. On the other hand, as noted above, HIV-2 infection *in vivo* reveals several unique characteristics when compared to HIV-1 infection; the most remarkable of which is the extraordinary long asymptomatic period. Several factors are obviously involved, but all of them are directly or indirectly related to the unique characteristics of HIV-2 as an inheritably attenuated pathogen. One of these factors should be the efficiency with which HIV-2 uses cellular receptors to enter susceptible cells.

A general principle that emerged from several reports is that HIV-1 and HIV-2 use chemokines receptors as cofactors

for viral entry in different ways. An important feature observed in HIV-2 is the ability to enter into target cells through a CD4-independent pathway. Certain laboratory-adapted strains [88, 207] and particularly primary HIV-2 isolates [14, 206], have been shown to infect CD4-negative cells mainly via CCR5 or CXCR4, a characteristic only observed in highly adapted HIV-1 strains [83, 107]. Additionally, many primary HIV-2 strains use additional chemokine receptors for viral entry and, over all, they can exploit these alternative coreceptors as efficiently as they use CCR5 or CXCR4 [38, 99, 159]. Remarkably, some of these coreceptors are not or very rarely are used by HIV-1 strains [36].

Coreceptor usage, as well as CD4-independent entry are both related to oligomeric structure of envelope glycoproteins [82, 208] and what these two characteristic features of primary HIV-2 isolates suggests is that this oligomeric structure should be more flexible in HIV-2 than in HIV-1.

Apparently the ability to use a larger set of coreceptors and to enter cells independently from the CD4 molecule should constitute an advantage for HIV-2, since both contribute to a potentially broader cell tropism. Consequently, and not considering the probable *in vivo* consequences of these features (discussed below), HIV-2 should be a more efficient human pathogen, with the inherent ability to infect other cells in different compartments and to noticeably induce clinical and immunological signs *in vivo*. Well... it should be but, in fact it isn't, as we have previously shown.

This apparent paradox imposes a deeper and clarifying discussion. The first important question is why CCR5 usage is so important in HIV pathogenesis. Studies using sequential HIV-1 isolates, based on phenotypic assays, show that R5 variants predominate during the asymptomatic phase of infection [63, 214, 226, 227, 247, 267]. Throughout the course of the infection, X4 and X4/R5 viruses transiently emerge and, in some late stage HIV-1 infected individuals, these viruses will eventually predominate, preceding an accelerated CD4 T-cell decline and a more rapid disease progression [31, 64, 222, 261]. Nevertheless, the predominance of X4 or R5/X4 variants are clearly not required for AIDS progression [72], since a R5 population still predominates in many HIV-1 infected individuals in the late disease stage [48]. This transition from CCR5 to CXCR4 coreceptor usage is in general associated with a shift in the viral ability to induce syncytia formation. R5 viruses are usually unable to induce syncytia (non-syncytia-inducing or NSI) while X4 or R5/X4 show a syncytium-inducing (SI) phenotype.

In HIV-2 however, a correlation between coreceptor usage and viral phenotype was not consistently observed [13, 99, 169, 206]. In addition, a clear pattern of R5 to X4 evolution along with disease progression (as seen in HIV-1) was difficult to establish, although R5 viruses are observed in asymptomatic or early symptomatic patients and strains showing a restricted CXCR4 usage are only observed in late symptomatic individuals [13, 99, 159, 206].

The ability to use CXCR4 is associated with increased replication kinetics and with a more cytopathic phenotype

[25, 104, 209, 225]. Accordingly, the acquisition of CXCR4 usage should theoretically constitute a beneficial characteristic for the viral population existing in infected individuals, since this usage results in an expanded target cell population repertoire *in vivo* and in a more aggressive replicative ability [25, 32, 43, 246]. Paradoxically, and although only a few amino acid changes in the V3 loop of HIV-1 SU glycoprotein are needed to confer the ability to use CXCR4 [70, 93, 110], X4 variants emerge only in a limited number of infected patients and only in later stages of HIV infection, when some immune impairment already exists. It seems that a strong selective pressure restrain X4 variants from emerging. Some hypotheses to explain this paradox include a stronger immune control over X4 variants [126], increased levels of SDF-1 $\alpha$  (the ligand of CXCR4) [181], internalization of CXCR4 induced by SDF-1 $\alpha$  [6], or to a reduced fitness of evolutionary intermediates [131]. Another possible explanation could be related to CCR5/CXCR4 expression patterns in lymphocyte subsets. Typically, the chemokine receptor CXCR4 is present and functional in resting and stimulated T-lymphocytes (reviewed in [19]) whereas CCR5 expression is higher in memory T-CD4 lymphocytes (CD45RO+) and lower in naïve (non activated) T-CD4 subset (CD45RA+) [33, 260]. A similar activation-dependent expression is also observed for CCR1, CCR2 and CXCR3 chemokine receptors, in particular with Interleukin-2 (IL-2) [33, 148, 149, 260]. Furthermore, several *in vitro* studies suggested that the activation state of target cell is an important factor to establish a productive infection by HIV-1 [183, 240]. Notably, CD45RO+ lymphocytes are highly permissive to HIV-1 replication [213, 238], while HIV-1 entry into CD45RA+ lymphocytes requires cellular activation in a time-dependent manner after viral entry; otherwise, an abortive infection is observed [259]. So, apparently CCR5 usage is a hallmark of HIV pathogenesis and makes HIV able to infect stimulated, full-permissive cells, leading to the production of a significantly more infectious viral population and therefore must be considered as a fundamental prerequisite for HIV pathogenesis.

The emergence of a CXCR4-using viral population could be seen as an additional consequence of an already deteriorated immune response that contributes to an accelerated disease progression. The infection of naïve T-cells by X4 strains, is likely to occur early in T-lymphocyte ontogeny and may thus contribute to the described enhancement of T-cells depletion by X4 strains. Studies of thymocyte development demonstrated that CXCR4 is highly expressed on immature T-cell progenitors resident to thymic cortex. During thymocyte differentiation, this chemokine receptor is down regulated, while CCR5 is expressed predominantly on mature thymocytes [26, 121, 241, 264]. As a result, infection of immature thymocytes by X4 strains may disrupt thymopoiesis leading to an impairment of T-cell development and to an accelerated T-cell depletion [26, 121, 241].

The widespread ability of HIV-2 strains to interact and efficiently use different chemokine receptors as viral entry factors, could lead to infection of inappropriate subsets of non-activated/non-permissive cells, in which HIV-2 is unable to complete the replication cycle due to intracellular blockades. Alternatively, since Env glycoproteins must

interact with a threshold number of cellular receptors to fusion with cell membrane, the HIV-2 interaction with cells expressing sub-optimal levels of a given coreceptor (besides CCR5 or CXCR4) should be a much more frequent event than with HIV-1.

As mentioned before, the entry pathway described for HIV imposes an initial binding event between Env SU glycoprotein with the CD4 molecule that may lead to formation and/or exposure of coreceptor binding site. However, this entry pathway can be bypassed in part by some HIV and SIV strains through a direct interaction with the coreceptor. The requirement of CD4 engagement to activate Env's membrane fusion mechanism restricts the tropism of HIV, since CD4-independence may enable viruses to infect CD4-negative/coreceptor positive cells *in vivo*. This notion is consistent with previous studies which demonstrate that a neuropathogenic SIV strain infects CD4-negative primary rhesus macaque brain capillary endothelial cells (BCECs) in a CD4-independent manner both *in vitro* and *in vivo* [85, 153]. CD4-independent infection of cells from central nervous system was also demonstrated for HIV-1 [18, 103, 105, 134, 171, 254]. Additionally, CD4-independence may enable viruses to infect more efficiently cells where CD4 expression is lower and consequently limiting. The identification of a neurovirulent primary HIV-1 isolate that shows a reduced CD4 dependence [97], suggests that an adaptative evolution may select for viral variants able to infect cells in the central nervous system expressing low levels of surface CD4, or even CD4-negative cells.

Despite the potential advantage of CD4-independency, naturally occurring HIV-1 strains are quite rare [83, 107, 125, 136] and only recently a group of 7 out of 12 isolates were selected from viral swarm capable to infect CD8+ lymphocytes in a CD4 independent manner [263]. In contrast, primary HIV-2 strains capable to shortcut the normal entry pathway have been frequently described *in vitro* [58, 145, 206, 257]. Although there are no reports demonstrating HIV-2 infection of CD4-negative cells *in vivo*, or even the relevance of lentiviral *in vivo* infection of CD4-negative cells, it is tempting to speculate that viruses with a CD4-independent phenotype could infect cells in different tissue compartments within an infected individual, besides haematopoietic CD4-positive cells. Infection of tissue compartments such as the brain, testes, lymphoid tissue or lungs [89, 97, 111, 220, 257], suggests that CD4-independent viruses might play an important role in some particular tissue settings.

Assuming that, theoretically, CD4-independence could constitute an advantage, and this phenotype can be easily generated as a consequence of a small number of mutations in Env glycoproteins [83, 86, 107, 125, 136, 208], then a critical question is why naturally occurring HIV-1 isolates with this phenotype are so infrequently found? Or why the occurrence of CD4-independent HIV-2 strains is not reflected by an increased pathogenic outcome in the human host? Unless in the presence of a strong counter selecting pressure, we can expect that, given the replication rate of HIV and the mutability associated to it *in vivo*, CD4-independent variants would appear and eventually predominate. One of the hindrances associated with CD4-independence is related with

a less fitted interaction and infection of target cells. In all studies reporting CD4-independent strains the replication rate in the absence of CD4, either cell-associated or in soluble form, was reduced compared to replication in the presence of CD4. This indicates that either the coreceptor binding site is only partially exposed/formed in CD4-independent strains or that mere exposure of the coreceptor binding site alone is not sufficient enough for an efficient infection. The prior interaction with CD4 should be important to induce further conformational changes, increasing the affinity and stability of SU glycoprotein-coreceptor complex. Additionally, the CD4 interaction might also influence the way these or other conformational changes are triggered and consequently modulating post-coreceptor binding events, that lead to membrane fusion and viral entry [86, 94, 161].

Another consequence of CD4-independence is associated with neutralization sensitivity. HIV CD4-independent strains are far more sensitive to neutralizing antibodies and to human sera from HIV-infected individuals than CD4-dependent viruses. The conformation of Env glycoproteins that allows direct interaction with coreceptor molecule, as frequently observed in HIV-2, might consequently expose epitopes that are usually revealed only after CD4 interaction. If these variants exist *in vivo* we might predict that the premature exposure of the coreceptor binding site could elicit neutralizing antibodies targeting this critical region for viral replication, favoring the host immunological response. In fact, monoclonal antibodies directed to these epitopes are much more efficient in CD4-independent derivatives than in CD4-dependent counterparts [86, 107, 124, 204]. Hence, the more relaxed conformation of HIV-2 Env glycoproteins, responsible for CD4-independence and broader coreceptor usage, may partially contribute to the better immunological control observed throughout HIV-2 infection and could explain why HIV-2 infected individuals show lower virus load in peripheral blood and such a marked delay in disease progression and immunological failure. Supporting this hypothesis is the fact that sera from HIV-2 infected individuals shows higher and broader neutralizing capacity [30, 212, 253] than HIV-1 positive sera.

Noteworthy, although HIV-2 is markedly less pathogenic *in vivo* than HIV-1, HIV-2 cytopathic potential in *ex vivo* culture of human tonsillar or adenoid tissue, seems to mirror the pattern typically found for HIV-1 infections in lymphoid tissue. An analysis carried out with R5, X4 and multitropic HIV-2 strains revealed striking differences regarding the cytopathic potential among these different viruses [224], segregating them into two distinct phenotypes: one with a mildly depletion of CD4+ T-lymphocytes, and the other where an aggressive depletion of those cells could be observed. This remarkable difference in cytopathic potential is related to the coreceptor usage by HIV-2 strains: milder cytopathic effect was observed for the R5 strain while CXCR4 usage (exclusively or not) is associated with the more aggressive phenotype. Moreover, this depletion seems to be similar either for HIV-1 or HIV-2 X4 strains [224]. Thus, in both HIV-2 and HIV-1 models [95, 190, 224], the acquisition of CXCR4 coreceptor usage is directly related with an increased cytopathic ability to induce an aggressive CD4 depletion with comparable kinetics. These data supports the notion that when an obvious immunodeficiency

is installed and consequently X4 strains arise (and in some cases predominates), the host clinical and immunological status rapidly deteriorates for both HIV-1 or HIV-2 infected individuals.

The main differences between HIV-1 and HIV-2 pathogenesis are particularly striking during the asymptomatic stage of infection where a significantly slower clinical progression is in general observed. During this period very few isolates were studied due mainly to the inherent difficulty to detect HIV-2 asymptomatic infected individuals and also to a technical hindrance concerning *in vitro* HIV-2 isolation from asymptomatic individuals. Despite CCR5 and/or CXCR4 seem to be used by the majority of the described HIV-2 strains, there are some evidences that indicate an important role of additional coreceptors in HIV-2 infection and pathogenesis. Some studies had suggested the existence of HIV-2 strains that used CCR5 and CXCR4 less efficiently. In one of those studies [265], was reported an HIV-2 isolate only inhibited by high concentrations of AMD3100, a potent CXCR4 inhibitor [78] and totally insensitive to CXCR4 ligand, SDF-1 $\alpha$ , and to the CCR5 inhibitors, TAK-779 [15] and AOP-RANTES [231]. Also Sol and co-workers [235] described another interesting HIV-2 strain, obtained from an asymptomatic individual, that was unable to use CCR5, CXCR4 or CCR3 coreceptors present in U87MG-CD4 and HeLa-CD4 cell lines. More recently, we identified and characterized two primary isolates that do not use CCR5, CXCR4, CCR1, CCR2b, CCR3, CXCR6 or GPR15 coreceptors to enter into GHOST-CD4+ cell lines [13]. Furthermore, these strains, also obtained from asymptomatic patients, readily infect peripheral blood mononuclear cells (PBMC) even in the presence of high concentration of CCR5 or CXCR4-targeted inhibitors although infection is completely blocked by an anti-CD4 monoclonal antibody. The leading results from this paper are shown in (Fig. 1) with details, but collectively the data presented indicate that the non-usage of CCR5 or CXCR4 may be associated to a significant lack of replicative fitness when compared to other CCR5- and CXCR4-using HIV strains, revealed by a major impairment in viral entry and replication kinetics in PBMC. Analysis on Env amino acid composition of these viruses showed an extraordinary divergent V1/V2 sequence. Phylogenetic analysis showed that these V1/V2 regions are clustered together much more close to SIV isolates than with the other HIV-2 strains<sup>2</sup>. A report from Morner and co-workers [170], also described some HIV-2 strains that were able to productively infect PBMC from homozygous  $\Delta 32ccr5$  donors. Remarkably, in this report, 7 out of 8 HIV-2 R5 viruses were able to infect CCR5-deficient PBMC although with a delayed replication kinetics than in wild type PBMC. Another evidence suggesting the use of alternative coreceptors by HIV and SIV was reported by Willey and co-workers. These authors identified a subset of R5, R5X4 and X4 strains of HIV-1, HIV-2 and SIV that are able to infect untransformed human brain and lymphoid cells, lacking CCR5 and CXCR4, via an alternative

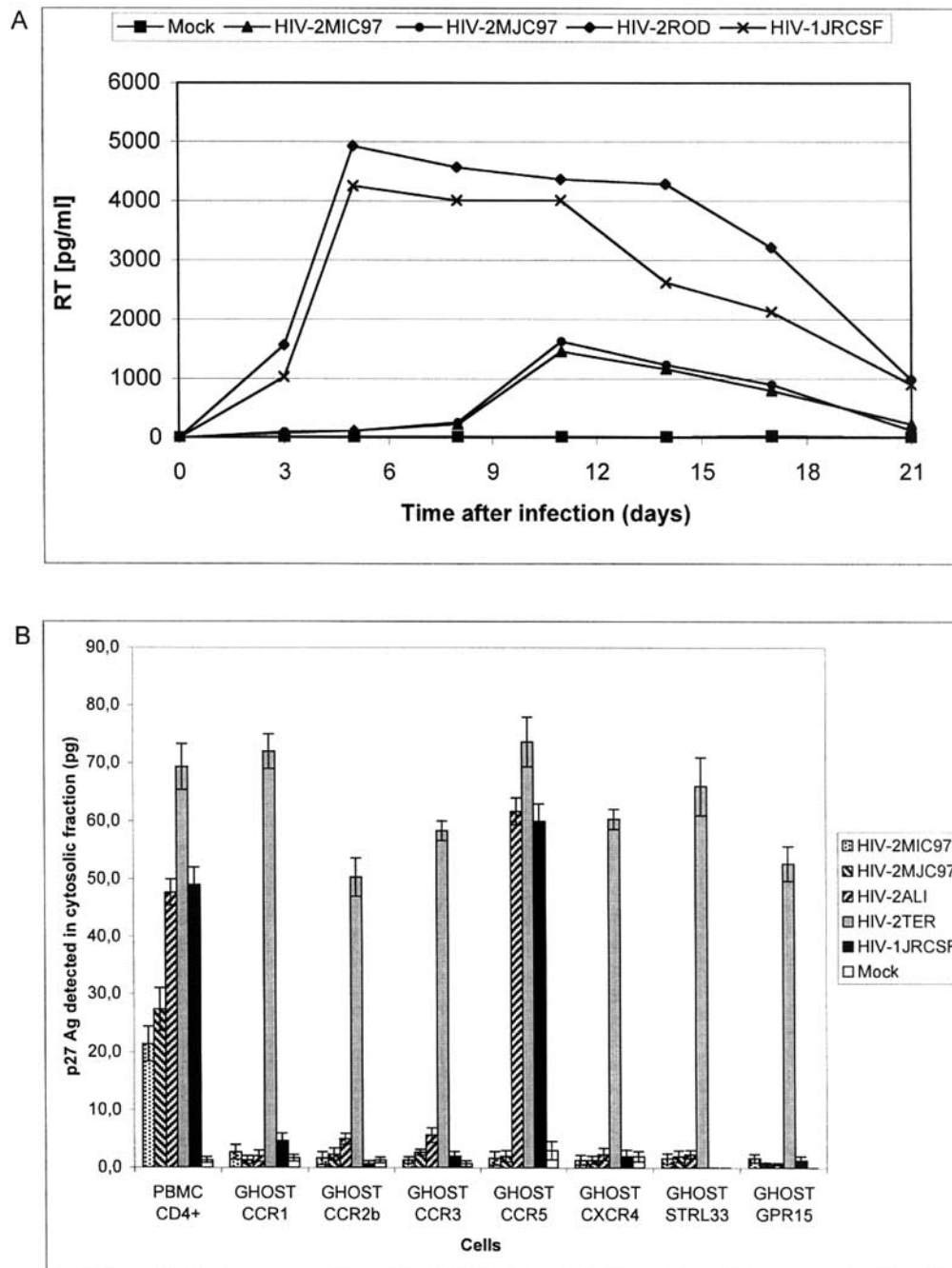
coreceptor [258]. The authors suggested a possible involvement of an unidentified receptor for vMIP-I (a chemokine encoded by HHV-8) since this chemokine was able to block infection of  $\Delta 32ccr5$  PBMC by some of the studied strains.

In SIVmac model, a single amino acid substitution (I324L) at the V3 loop within the context of SIVmac Env [196], allowed the SIVmac239 strain to productively infect a rhesus macaque epithelial cell line (sMagi) which expresses very little if any CCR5 and no CXCR4 [235, 236]. Remarkably, I324L SIV variants show a clearly reduced CCR5 usage when compared to wild type viruses and are relatively insensitive to CCR5 inhibitor TAK-779. Both features indicate that I324L variants may enter sMagi cells via an unidentified coreceptor. Surprisingly this change in viral phenotype was observed as a result of a single substitution by a structurally related amino acid (I324L for example), stressing the delicate conformational organization of Env glycoproteins needed for coreceptor engagement and the fact that even minor changes in amino acid sequences can dramatically alter coreceptor usage.

All these observations also emphasize the outstanding plasticity of HIV and SIV envelope glycoproteins and remind us the enormous capacity of both lentiviruses to adapt to host-driven pressure. Chen and co-workers described one paradigmatic example of this when a natural infection by a CCR2b-using SIV was demonstrated in red-capped mangabey [50] homozygous for a deletion of 24 nucleotides ( $\Delta 24$ ) in the fourth transmembrane region of the *ccr5* gene product. The selective pressure that induced the coreceptor switch in the homozygous deleted mangabeys can be mirrored by the selection pressure imposed by CCR5-directed drug therapy and may cause viral adaptation to other coreceptors resulting in drug resistance.

It is particularly noticeable that strains able to infect target cells in a CCR5-independent way show important impairments in their ability to interact and infect target cells. The less efficient replication observed in HIV-2 strains from both reports [13, 170] could constitute a consequence of a later and/or minor expression of alternative coreceptors being used by these strains. Otherwise, the way these Env glycoproteins engage the unidentified coreceptors may require more receptor-binding events to elicit membrane fusion or to induce conformational changes more slowly than the interaction with CCR5 or CXCR4 coreceptors. Regardless the reason, it is obvious that the type of coreceptors engaged by a specific Env glycoprotein and how these Env engage those coreceptors are factors that can influence viral tropism but, more importantly, viral pathogenesis. Overall, we may stress that CCR5 usage seems to be crucial in viral fitness and to perform an efficient chronic infection in human host. Another important and fundamental issue that emanates from these reports is that an HIV-2 infection could be established without the strict need of CCR5 or CXCR4 coreceptors usage. Since the non-usage of CCR5 and CXCR4 coreceptors (among others), was observed in HIV-2 strains obtained from asymptomatic and immunologic competent individuals [13], and despite strains from well characterized HIV-2 asymptomatic individuals are scarce, these data raise the possibility that, *in vivo*, CCR5 usage ability, required for an

<sup>2</sup> Santos-Costa, Q, Collman R, Moniz-Pereira J, and Azevedo-Pereira JM. Molecular Characterization of env Genes From Primary HIV-2 Strains Unable to Use CCR5 or CXCR4 Coreceptors. 11<sup>th</sup> Conference on Retroviruses and Opportunistic Infections, 2004. S. Francisco.



**Fig. (1).** Replication of several HIV-2 strains in PBMC and coreceptor-expressing GHOST CD4+ cells. (A) The remarked lower replication kinetics of HIV-2<sub>MIC97</sub> and HIV-2<sub>MJC97</sub> in PHA-activated PBMC, when exposed to 10 ng of RT activity of each virus, followed during a 21-day period. (B) The detection of p27 protein in the cytosolic fraction obtained from cells (4 x10<sup>6</sup>) exposed to different HIV-2 isolates (400 ng of p27 for each virus) shows the incapacity to use, for instance, CCR5 or CXCR4 coreceptors. The background obtained in each cell line was subtracted from the final result. These data are expressed as means of at least three independent experiments ± standard deviations.

efficient *in vitro* and apparently *in vivo* infection, could be acquired, from an initial population of CCR5- and CXCR4-non-using viruses, in addition or in alternative to the initial receptors used. This implies that in asymptomatic HIV-2 infected individuals, during a variable period of time, a less fitted population may exists that needs to evolve in order to exploit CCR5 coreceptor and consequently become more virulent. Furthermore, and assuming the HIV as a non-natural ligand of chemokine receptors, it is also tempting to

suggest that the interaction of HIV-2 with alternative receptor(s) could induce signals that counterbalance the immune destruction due to viral replication.

Another open question is how these viruses were transmitted to a human host, due to the well-documented importance of CCR5 usage in the HIV transmission. Since there is little (if any) selective advantage for an isolate to be transmitted using alternative coreceptors, one possibility is

that the CCR5/CXCR4-independent strains might result as a cross-species viral transmission rather than human-human transmission. The exposure of humans to a enormous diversity of highly divergent SIV strains was well documented in a study carry on in Cameroon [189], suggesting that zoonotic episodes may be far more frequent than expected [102, 228]. Natural infection of nonhuman primates lacking a functional CCR5 molecule with CCR5-independent SIVs [50] could constitute a potential source of zoonotic infections of humans by unusual virus strains. An evolution to CCR5 usage may have been acquired during the adaptation process to human host. Otherwise, and less speculative, the alternative coreceptor used by these HIV-2 strains could be expressed in high levels in some subsets of PBMCs, thus enabling viral transmission despite the non-CCR5 usage. Of note is the fact that CXCR5 chemokine receptor, expressed in PBMCs, has been referred as a coreceptor for HIV-2 but not to HIV-1 or SIV [116]. Additional studies on CCR5/CXCR4-independent strains are warranted and could shed some light on several aspects of HIV-2 evolution and on HIV-2 pathogenesis in human host.

### CONCLUDING REMARKS

Due to its peculiar and in some cases divergent characteristics, HIV-2 infection constitutes a remarkable interesting model to study immune control and HIV pathogenesis. The capacity to infect cells independently of CD4, the potential to infect cells through a broader range of coreceptors and the existence of strains, during asymptomatic stage, unable to use CCR5 and CXCR4 coreceptors, constitute important clues to understand the complex mechanisms involved in virus-cell and pathogen-host interactions responsible for the reduced virulence of HIV-2. Important areas for future investigation include the study of primary HIV-2 strains, particularly those obtained from asymptomatic patients. It will be important to determine the role of CCR5- and CXCR4-independent strains in those patients, the coreceptor evolution from this initial less-fitted viral population as well as the molecular determinants of this phenotype. Focus must therefore be extended to understand the role of initial events involved in HIV-2-target cell interaction, to clarify the mechanisms responsible for some of the differences observed in the pathogenic potential between HIV-2 and HIV-1, and en route to assist in HIV vaccine development.

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