Human immunodeficiency virus type 2 (HIV-2) immunodeficiency is characterized by slow disease progression with limited impact on the survival of the majority of infected adults (20, 33, 45). The rate of CD4+ T-cell decline is much slower in HIV-2 than in HIV-1 disease, and there is a low plasma viral load irrespective of disease stage (2, 4, 9, 17, 20, 32, 41, 43). The factors contributing to the suggested decreased rate of virus production in HIV-2 infection remain largely unknown.

In spite of the promiscuity of coreceptor usage exhibited by HIV-2 in in vitro experimental settings (8, 13, 16, 22, 29, 39, 40), several lines of evidence show that CCR5 and CXCR4 are the major coreceptors for HIV-2 infection in vivo (6, 24, 25). Here we report a significantly increased proportion of memory-effector CD4 T cells expressing CCR5 in HIV-2-infected patients correlating with CD4 depletion. Moreover, HIV-2 proviral DNA was essentially restricted to memory-effector CD4, suggesting that this is the main target for HIV-2. Similar levels of proviral DNA were found in the two infection categories. Thus, the reduced viremia and slow rate of CD4 decline that characterize HIV-2 infection seem to be unrelated to coreceptor availability.

TABLE 1. Cohort characterization

| Characteristic              | Value for group                  |
|-----------------------------|----------------------------------|
|                             | Healthy controls | HIV-2-positive patients | HIV-1-positive patients |
| No. of subjects (no. male/no. female) | 21 (9/12)   | 22 (6/16)   | 23 (10/13)   |
| Age (yr)                     | 42 ± 4 (21–84) | 46 ± 3 (21–64) | 37 ± 3 (20–68) |
| Ethnicity                    |                   |                   |                |
| White                        | 17                 | 8                 | 13             |
| Other                        | 4                  | 14                | 10             |
| HIV transmission category    |                   |                   |                |
| Heterosexual                 | n.a.a              | 17                | 18             |
| Homosexual or bisexual       | n.a.               | 1                 | 3              |
| Intravenous drug user        | n.a.               | 1                 | 2              |
| Blood transfusion            | n.a.               | 3                 | 0              |
| CD3 count in cells/μl        | 1.844 ± 165 (767–3,488) | 1.305 ± 119 (427–2,629)* | 1.454 ± 158 (378–3,554)* |
| % CD3                        | 73 ± 1.8 (58–84)   | 71 ± 2.3 (48–87)  | 74 ± 1.9 (55–90) |
| CD4 count (cells/μl)         | 1,174 ± 108 (551–2,387) | 551 ± 73 (38–1,207)*** | 498 ± 61 (66–1,300)*** |
| % CD4                        | 46 ± 1.8 (33–64)   | 29 ± 2.8 (4–49)*** | 28 ± 2.4 (9–52)*** |
| CD8 count (cells/μl)         | 632 ± 71 (234–1,236) | 729 ± 76 (180–1,456) | 861 ± 100 (269–2,007) |
| % CD8                        | 24 ± 1.5 (13–38)   | 40 ± 2.9 (24–70)*** | 44 ± 2.4 (28–64)*** |
| Viremia (RNA; no. of copies/ml) | n.a.            | 409 ± 190 (200–4,006)f | 75,508 ± 30,429 (118–548,631)f |
| Proviral DNA (copies/10⁶ PBMC) | n.a.            | 1,760 ± 823 (5–10,725)f | 2,481 ± 863 (61–12,565)f |

* Data are means ± standard errors of the means with limits in brackets.

Significance in comparison with healthy control results is represented as follows: *, P < 0.05; ***, P < 0.0001. There were no significant differences between the HIV-2 and HIV-1 cohorts except for the viremia results (P = 0.0001).

a HIV-2 viremia was quantified by a reverse transcriptase PCR-based test (41); the results were below 200 RNA copies/ml (cutoff) for 19 out of the 21 patients studied. In these cases the cutoff value was used.

b HIV-1 viremia was quantified by reverse transcriptase PCR (Ultrasensitive Test; Roche Molecular Systems, Branchburg, NJ). The cutoff was 50 RNA copies/ml.

c Proviral DNA was quantified by real-time PCR and was detected in all 17 HIV-2-infected patients and all 16 HIV-1-infected patients investigated.

Published ahead of print on 11 October 2006.
In HIV-1-infected patients, CCR5 expression determines susceptibility to infection, cell tropism, and the rate of disease progression and is currently an important target of new antiretroviral drugs (10, 11, 21, 27, 34, 35).

There are scanty data available on CCR5 and CXCR4 expression in HIV-2-infected patients. A previous study of a Senegalese cohort reported lower CCR5 expression in HIV-2 than in HIV-1 infection, but as these patients, unlike our cohorts, were not stratified according to CD4 depletion or viremia, direct comparison is problematic (38).

We analyzed here CCR5 and CXCR4 expression in freshly isolated peripheral blood mononuclear cells (PBMC) from untreated HIV-2- and HIV-1-infected subjects who were currently living in Portugal and attending outpatient clinics in Lisbon and who exhibited no known ongoing opportunistic infections or tumors. The epidemiological and clinical features...
of these cohorts, as well as of healthy controls, are summarized in Table 1. Of note, HIV-2 and HIV-1 cohorts exhibited similar levels of CD4 depletion but striking differences in viremia.

CCR5 and CXCR4 expression were assessed by flow cytometry in freshly isolated PBMC as previously described (42). HIV-2-positive patients exhibited a higher frequency of CCR5<sup>+</sup> cells within the CD<sup>+</sup> subset that reaches statistical significance than that seen with healthy subjects (Fig. 1A). In HIV-2 patients CCR5 expression was also largely confined to the memory CD<sup>+</sup> population, as illustrated in the representative contour plot of Fig. 1B.

The frequencies of CXCR4<sup>+</sup> cells within CD4<sup>+</sup> T cells showed no significant differences among the three cohorts, although there was a trend to lower frequencies in the HIV-2 cohort in both the naive and memory subsets (Fig. 1C).

A significant correlation between the frequency of CCR5<sup>+</sup> cells within the CD4 subset and the degree of CD4 depletion was observed with the HIV-2 cohort that was not observed with HIV-1-positive patients (Fig. 1D).

We have previously shown that CD4 depletion is directly linked to immune activation in both HIV-2 and HIV-1 infections in spite of the striking differences in viremia (15, 42). Since CCR5 is up-regulated upon T-cell activation, we looked for a possible correlation between the frequency of CCR5<sup>+</sup> cells and the expression of HLA-DR, a marker widely used to quantify immune activation in HIV disease (15). A significant correlation was observed with the HIV-2 cohort (r = 0.68; P = 0.0009) that was not found with HIV-1-positive patients (r = 0.25; P = 0.2814).

These data illustrated the link between the expansion of CCR5<sup>+</sup> cells and immune activation in HIV-2 infection. The lower frequency of circulating CCR5<sup>+</sup> cells in HIV-1 infection compared to HIV-2 results despite the similarities in heightened immune activation may be related to a continuous depletion of the CCR5 pool in association with the high level of viremia (19, 23).

The frequency of CCR5<sup>+</sup> cells may be underestimated due to binding-induced receptor internalization (26, 30). In fact, the assessment of the median fluorescence intensity (MedianFI) of CCR5<sup>+</sup> CD4<sup>+</sup> T cells revealed similar and significant down-regulation results for both HIV-2- and HIV-1-infected cohorts in comparison with the results seen with healthy subjects (Fig. 1E). This contrasts with the absence of differences in MedianFI of CXCR4<sup>+</sup> CD4<sup>+</sup> T cells for the three cohorts (Fig. 1F). It is noteworthy that HIV-2 infection has been associated with high levels of production of RANTES, MIP-1α, and MIP-1β (1, 18, 28), possibly contributing to the CCR5 down-regulation.

In order to exclude the possibility that CCR5Δ32 mutations contribute to the low MedianFI of CCR5<sup>+</sup> cells (44), we screened the cohorts for the presence of this allele using the primers described in Table 2. None of the HIV-2- or HIV-1-infected patients exhibited the CCR5Δ32 allele. There were five healthy subjects heterozygous for CCR5Δ32. The exclusion of these individuals from the analysis resulted in an even more significant difference in the results of down-regulation of CCR5 MedianFI between HIV cohorts and healthy subjects (P = 0.0019 for HIV-2 and P < 0.0001 for HIV-1).

On the other hand, despite differing levels of viremia, we did not find significant differences between HIV-2 and HIV-1 proviral DNA levels, suggesting the presence of similar numbers of infected cells in the two infection categories (Table 1), in agreement with previous reports (3–5, 14, 31). Proviral DNA was assessed by absolute quantitative real-time PCR using an ABI PRISM 7000 sequence detection system (Applied Biosystems) with a detection range of 7 orders of magnitude and a sensitivity of five copies. Reactions containing 150 ng of genomic DNA extracted from 10<sup>6</sup> PBMC by use of an ABI PRISM 6100 nucleic acid extractor (Applied Biosystems), 25 μl of Platinum quantitative PCR Supermix-UDG, 1 μl ROX reference dye (Invitrogen) (50×), 5 mM MgCl<sub>2</sub>, 300 nM primer (each), and 200 nM probe (Table 2) were run in duplicate. Albumin was used to standardize DNA input.

It is worth noting that no correlation was found between the

---

TABLE 2. Primer and probe sequences<sup>a</sup>

| Primer or probe | Sequence<sup>a</sup> |
|----------------|---------------------|
| HIV-2 Forward primer | 5′-CGC GAG AAA CTC CGT GTT G-3′ |
| HIV-2 Reverse primer | 5′-ACG ACA ATA TGT TTT AGC TGT TAC TTG TT-3′ |
| HIV-2 Probe | 5′-FAM-CCG GCC GGT AAT CAA CT-MGB-3′ |
| HIV-1 Forward primer | 5′-GGG AGA ATG AGA TCG ATG GGA AA-3′ |
| HIV-1 Reverse primer | 5′-CTG CTT GCC CAT ACT ATA TGT TTT AAT TTA-3′ |
| HIV-1 Probe | 5′-FAM-CCC TGG CCT TAA CCG AAT T-MGB-3′ |
| CCR5 Forward primer | 5′-TTC ATT ACA CCT GCA GCT CT-3′ |
| CCR5 Reverse primer | 5′-CAC AGC CCT GTG CTT CTT CTT ACT ATG C-3′ |
| CCR5 Primer or probe | Sequence<sup>a</sup> |
| Primer or probe | Sequence<sup>a</sup> |
| Primer or probe | Sequence<sup>a</sup> |
| Primer or probe | Sequence<sup>a</sup> |
| Primer or probe | Sequence<sup>a</sup> |
| Primer or probe | Sequence<sup>a</sup> |

---

TABLE 3. HIV-2 proviral DNA in CD4 naive and memory subsets

| Case | No. of copies of proviral DNA/10<sup>6</sup> PBMC | No. of CD4 cells/μl | No. of copies of proviral DNA/10<sup>6</sup> PBMC | % CCR5 | No. of copies of proviral DNA/10<sup>6</sup> PBMC | % CCR5 |
|------|----------------------------------|------------------|----------------------------------|--------|----------------------------------|--------|
| 1    | 57                               | 181              | 95                               | 7.45   | 5                               | 0.86   |
| 2    | 206                              | 629              | 1,541                            | 11.21  | 5                               | 2.08   |

---

<sup>a</sup> Freshly isolated PBMC were successively gated using CD4<sup>+</sup> and CD45RA<sup>+</sup> (naive) or CD45RA<sup>−</sup> (memory); the subsets were purified using FACSaria (BD Biosciences), with purity higher than 98%.
frequency of CCR5+ cells within the CD4 subset and the levels of HIV-2 proviral DNA (r = 0.08; P = 0.7483).

In order to evaluate the possibility that the similar levels of proviral DNA in the presence of the dissimilar HIV-1 and HIV-2 viremia results might be due to differences in cell targets, we purified the naïve and the memory CD4 T cells from PBMC of two HIV-2 patients with different levels of CD4 depletion by high-speed cell sorting using FACSaria (BD Biosciences).

As depicted in Table 3, the levels of HIV-2 proviral DNA documented in the naïve subset were minimal. Therefore, these data suggest that memory CD4 T cells are the major targets for HIV-2 infection in vivo, reinforcing the idea of a major role of CCR5 coreceptor in HIV-2 infection. This was consistent with data on HIV-1 infection in which integrated proviruses are preferentially detected within the memory subset (7, 12, 36).

In summary, HIV-2-infected patients showed an increase in the proportion of CCR5+ cells within the memory-effector CD4+ T cells in correlation with the degree of CD4 depletion and immune activation. In contrast, in HIV-1 infection there was dissociation between CCR5 and other markers of immune activation which could be interpreted as an indirect evidence of depletion of the CCR5+ cells by HIV-1. However, the HIV-2 proviral load was also mainly restricted to memory-effector CD4 T cells, suggesting these are the major HIV-2 targets, which is consistent with CCR5 being the main HIV-2 coreceptor in vivo. Moreover, the levels of HIV-2 proviral load were similar to those observed in untreated HIV-1-infected individuals, suggesting equivalent numbers of infected cells resulting from the two diseases in spite of viremia being undetectable in the majority of the HIV-2 patients.

The presence of reduced HIV-2 viremia seems to be unrelated to coreceptor availability. Since HIV-2 is no less cytopathic per se than HIV-1 (37), other host factors must be implicated in the control of viral replication in spite of significant proviral DNA levels in HIV-2-positive patients. The further investigation of the mechanisms contributing to this control of HIV-2 viremia in the absence of antiretroviral therapy may prove to be useful in defining complementary therapeutic strategies to control viral reservoirs in HIV-1.

This work was supported by grants from Fundação para a Ciência e a Tecnologia (FCT) and Comissão Nacional de Luta Contra a SIDA to A. E. S. R. S. R. F., and C. C. received scholarships from FCT.

We gratefully acknowledge Perpétua Gomes for the quantification of HIV-2 viremia, Ana Caetano for cell sorting technical assistance, and the clinical collaboration of the following colleagues: E. Valadas, F. Antunes, L. Pinheiro, M. Doroana, M. Lucas, and R. Marçal.

REFERENCES

1. Ahmed, R. K., H. Norrgren, Z. da Silva, A. Blaxhult, E. L. Fredriksson, G. Biberfeld, S. Andersson, and R. Thorstensson. 2005. Antigen-specific beta-chromatome infection and CDS-T cell noncytotoxic antiviral activity in HIV-2-infected individuals. Scand. J. Immunol. 61:653–71.

2. Andersson, S., H. Norrgren, Z. da Silva, A. Blaxhult, S. Bamba, S. Kwo, C. Christopherson, G. Biberfeld, and J. Albert. 2000. Plasma viral load in HIV-1 and HIV-2 singly and dually infected individuals in Guinea-Bissau, West Africa: significantly lower plasma virus set point in HIV-2 infection than in HIV-1 infection. Arch. Intern. Med. 160:3286–3293.

3. Ariyoshi, K., N. Berry, A. Wilkins, D. Ricard, P. Aaby, A. Naucler, P. T. Ngom, O. Jobe, S. Jaffar, S. Sabally, T. Corrah, R. Tedder, and H. Whittle. 1998. Low peripheral blood viral HIV-2 RNA in individuals with high CD4 percentage differentiates HIV-2 from HIV-1 infection. J. Hum. Virol. 1:457–468.

4. Berry, N., K. Ariyoshi, D. Jaffe, P. T. Ngum, T. Corrah, A. Wilkins, H. Whitehead, and R. Tedder. 1994. HIV-2 infection and other infections in Western Africa: a community-based study of human immunodeficiency virus type 2 and simian immune deficiency virus infection. J. Virol. 68:173–245.

5. Brenchley, J. M., B. J. Hill, D. R. Ambrozak, D. A. Price, F. J. Guennaga, J. P. Casasaza, J. Kuruppu, J. Zaylasani, S. A. Migueles, M. Conners, M. Roederer, D. T. Douek, and R. A. Koup. 2004. T-cell subsets that harbor human immunodeficiency virus (HIV) in vivo: implications for HIV pathogenesis. J. Virol. 78:1160–1168.

6. Bron, R. P. J. Klasse, D. Wilkinson, P. R. Clapham, A. Pelchen-Matthews, C. Power, T. N. Wells, J. Kim, S. C. Peiper, J. A. Hoxie, and M. Marsh. 1997. Promiscuous use of C and CXC chemokine receptors in cell-to-cell fusion mediated by a human immunodeficiency virus type 2 envelope protein. J. Virol. 71:8405–8415.

7. Damond, F. M., G. Gouaidi, S. Pueyo, I. Farfara, D. L. Robertson, D. Descamps, G. Chêne, S. Matheron, P. Campa, F. Brun-Vezinet, and F. Simon. 2002. Plasma RNA viral load in human immunodeficiency virus type 2 subtype A and subtype B infections. J. Clin. Microbiol. 40:3654–3659.

8. Dean, M., M. Carrington, C. Winkler, G. A. Huttley, M. W. Smith, R. Allibert, J. J. Goedert, S. P. Buchbinder, E. Vittinghoff, E. Gomart, S. Donfield, D. Vlahov, R. Kaslow, A. Saah, C. Rinaldo, R. Detels, and S. O’Brien. 1996. Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CCR5 structural gene. Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Monolocular Cohort Study, San Francisco City Cohort, ALIVE Study. Science 275:1856–1862.

9. de Roda Husman, A. M., H. Blaak, L. Brouwer, and H. Schuitemaker. 1999. CC chemokine receptor 5 cell-surface expression in relation to C: chemokine receptor 5 genotype and the clinical course of HIV-1 infection. J. Immunol. 163:4597–4603.

10. Douek, D. C., J. M. Brenchley, M. R. Bettis, D. R. Ambrozak, B. J. Hill, Y. Okamoto, J. P. Casasaza, J. Kuruppu, K. Kunsmann, S. Wolinsky, Z. Grossman, M. Dvbil, A. Ozsim, D. A. Price, M. Conners, and R. A. Koup. 2002. HIV preferentially infects HIV-specific CD4+ T cells. Nature 417:95–98.

11. Endres, M. J., P. R. Clapham, M. Marsh, M. Ahuja, J. D. Turner, A. McKnight, J. F. Thomas, B. Stoebenau-Haggarty, S. Choe, P. J. Vance, T. N. Wells, C. A. Power, S. Sutterwala, R. W. Doms, N. R. Landau, and J. A. Hoxie. 1996. CD4-independent infection of HIV-2 is mediated by fusin/CCXCR4. Cell 87:745–756.

12. Gomes, P. N., C. Taveira, J. M. Pereira, F. Antunes, M. O. Ferreira, and M. H. Lourenço. 1999. Quantity of human immunodeficiency virus type 2 DNA in peripheral blood mononuclear cells by using a quantitative-competitive PCR assay. J. Clin. Microbiol. 37:435–436.

13. Grossman, Z., M. Meier-Schellersheim, A. E. Sousa, R. M. Victorino, and W. E. Paul. 2002. CD4 depletion in HIV infection: are we closer to understanding the cause? Nat. Med. 8:319–325.

14. Guillou, C., M. E. van der Ende, P. H. Boers, R. A. Gruters, M. Schutten, and A. D. Osterhaus. 1998. Coreceptor usage of human immunodeficiency virus type 2 primary isolates and biological clones is broad and does not correlate with their syncytium-inducing capacities. J. Virol. 72:6260–6262.

15. Jafrar, S., A. Wilkins, P. T. Ngom, S. Sabally, T. Corrah, J. E. Bangali, M. Rolfe, and H. C. Whittle. 1997. Rate of decline of percentage CD4+ cells is faster in HIV-1 than in HIV-2 infection. J. Acquir. Immune Defic. Syndr. 16:327–332.

16. Kokkotou, E. G., J. L. Sankale, I. Mani, A. Guye-Ndiaye, D. Schwartz, M. E. Essex, S. Mboup, and P. J. Kanki. 2000. In vitro correlates of HIV-2-mediated HIV-1 infection. Proc. Natl. Acad. Sci. USA 97:6860–6862.

17. Krzyzek, R., A. Rudent, L. Bouchet-Delbos, A. Foussat, C. Boutillon, A. Portier, D. Ingard, D. Sereni, P. Galanaud, L. Grangeot-Keros, and D. Emile. 2001. Preferential and persistent depletion of CCR5+ T-helper lymphocytes with nonlymphoid homing potential despite early treatment of primary HIV infection. Blood 98:3169–3177.

18. Marlink, R., P. Kanki, I. Thior, K. Travers, G. Eisen, T. Siyy, I. Traore, C. Hsieh, M. Dia, E. H. Guye, J. Hellingier, A. Guye-Ndiaye, J. L. Sankale, I. Ndoye, S. Mboup, and M. Essex. 1994. Reduced rate of disease development after HIV-2 infection as compared to HIV-1. Science 265:1587–1590.

19. Martin, M. P., M. D. Smith, C. Winkler, B. Gerrard, N. L. Hibbitts, D. Whitby, E. Aarons, A. E. Proudfoot, H. Whittle, and P. R. Clapham. 1998. A broad range of chemokine receptors are used by primary
isolates of human immunodeficiency virus type 2 as coreceptors with CD4.
J. Virol. 72:4065–4071.
23. Mehadrus, S., M. A. Poles, K. Tenner-Racz, A. Horowitz, A. Hurley, C.
Hogan, D. Boden, P. Racz, and M. Markowitz. 2004. Primary HIV-1 infec-
tion is associated with preferential depletion of CD4+ T lymphocytes from
effector sites in the gastrointestinal tract. J. Exp. Med. 200:761–770.
24. Morner, A., A. Bjorndal, J. Albert, V. N. Kewalramani, D. R. Littman, R.
Inoue, R. Thorstenson, E. M. Fenyo, and E. Björnling. 1999. Primary human
immunodeficiency virus type 2 (HIV-2) isolates, like HIV-1 isolates, fre-
cently use CCR5 but show promiscuity in coreceptor usage. J. Virol. 73:
2343–2349.
25. Morner, A., A. Bjorndal, A. C. Leandersson, J. Albert, E. Björling, and M.
Jansson. 2002. CCR5 or CXCR4 is required for efficient infection of pe-
ripheral blood mononuclear cells by promiscuous human immunodeficiency
virus type 2 primary isolates. AIDS Res. Hum. Retrovir. 18:193–200.
26. Mueller, A., E. Kelly, and P. G. Strange. 2002. Pathways for internalization
and recycling of the chemokine receptor CCR5. Blood 99:785–791.
27. Mummidi, S., S. S. Ahuja, E. Gonzalez, S. A. Anderson, E. N. Santiago, K. T.
Stephan, F. E. Craig, P. O’Connell, V. Tryon, R. A. Clark, M. J. Dolan, and
S. K. Ahuja. 1998. Genealogy of the CCR5 locus and chemokine system gene
variants associated with altered rates of HIV-1 disease progression. Nat.
Med. 4:786–793.
28. Neoh, L. P., H. Akimoto, H. Kaneko, T. Hishikawa, H. Hashimoto, S. Hirose,
Y. Kaneko, N. Yamamoto, and I. Sekigawa. 1997. The production of beta-
chemokines induced by HIV-2 envelope glycoprotein. AIDS 11:1062–1063.
29. Owen, S. M., D. Ellenberger, M. Rayfield, S. Wiktor, P. Michel, M. H.
Grieco, F. Gao, B. H. Hahn, and R. B. Lal. 1998. Genetically divergent
strains of human immunodeficiency virus type 2 use multiple coreceptors for
viral entry. J. Virol. 72:5425–5432.
30. Pastori, C., B. Weiser, C. Barassi, C. Uberti-Foppa, S. Ghezzi, R. Longhi, G.
Calori, H. Burger, K. Kemal, G. Poli, A. Lazzarin, and L. Lopalco. 2006.
Long-lasting CCR5 internalization by antibodies in a subset of long-term
nonprogressors: a possible protective effect against disease progression.
Blood 107:4825–4833.
31. Popper, S. J., A. D. Sarr, A. Gueye-Ndiaye, S. Mboup, M. E. Essex, and P. J.
Kanki. 2000. Low plasma human immunodeficiency virus type 2 viral load
is independent of proviral load: low virus production in vivo. J. Virol. 74:
1554–1557.
32. Popper, S. J., A. D. Sarr, K. U. Travers, A. Gueye-Ndiaye, S. Mboup, M. E.
Essex, and P. J. Kanki. 1999. Lower human immunodeficiency virus (HIV)
type 2 viral load reflects the difference in pathogenicity of HIV-1 and HIV-2.
J. Infect. Dis. 180:1116–1121.
33. Poulsen, A. G., P. Aaby, O. Larsen, H. Jensen, A. Naucler, I. M. Lisse, C. B.
Christiansen, F. Dias, and M. Melbye. 1997. 9-year HIV-2-associated mor-
tality in an urban community in Bissau, west Africa. Lancet 349:911–914.
34. Reyes, J., P. Portales, M. Segundo, V. Baillat, P. Andre, O. Avinens, M. C.
Picot, J. Clot, J. F. Eliaou, and P. Corbeau. 2001. CD4 T cell surface CCR5
density as a host factor in HIV-1 disease progression. AIDS 15:1627–1634.
35. Ribeiro, R. M., M. D. Hazenberg, A. S. Perelson, and M. P. Davenport. 2006.
Naïve and memory cell turnover as drivers of CCR5-to-CXCR4 tropism
switch in human immunodeficiency virus type 1: implications for therapy.
J. Virol. 80:802–809.
36. Schnittman, S. M., H. C. Lane, J. Greenhouse, J. S. Justement, M. Baseler,
and A. S. Fauci. 1990. Preferential infection of CD4+ memory T cells by
human immunodeficiency virus type 1: evidence for a role in the selective
T-cell functional defects observed in infected individuals. Proc. Natl. Acad.
Sci. USA 87:6058–6062.
37. Schramm, B., M. L. Penn, E. H. Palacios, R. M. Grant, F. Kirchhoff, and
M. A. Goldsmith. 2000. Cytopathicity of human immunodeficiency virus type
2 (HIV-2) in human lymphoid tissue is coreceptor dependent and com-
parable to that of HIV-1. J. Virol. 74:9594–9600.
38. Shea, A., D. A. Sarr, N. Jones, I. Penning, G. Eisen, A. Gueye-Ndiaye, S.
Mboup, P. Kanki, and H. Cao. 2004. CCR5 receptor expression is down-
regulated in HIV type 2 infection: implication for viral control and protec-
tion. AIDS Res. Hum. Retrovir. 20:630–635.
39. Shi, Y., E. Brandim, E. Vincic, M. Jansson, A. Blaxhult, K. Gyhlensten, L.
Moberg, C. Broström, E. M. Fenyo, and J. Albert. 2005. Evolution of human
immunodeficiency virus type 2 coreceptor usage, autologous neutralization,
envelope sequence and glycosylation. J. Gen. Virol. 86:3385–3396.
40. Sol, N., F. Fercial, J. Braun, O. Pleskoff, C. Treboute, I. Ansart, and M.
Alizon. 1997. Usage of the coreceptors CCR-5, CCR-3, and CXCR-4 by
primary and cell line-adapted human immunodeficiency virus type 2. J. Virol.
71:8237–8244.
41. Soriano, V., P. Gomes, W. Heneine, A. Holguín, M. Doruana, R. Antunes, K.
Mansinho, W. M. Switzer, C. Araujo, V. Shanmugam, H. Lourengo, J.
Gonzalez-Lahoz, and F. Antunes. 2000. Human immunodeficiency virus type
2 (HIV-2) in Portugal: clinical spectrum, circulating subtypes, virus isolation,
and plasma viral load. J. Med. Virol. 61:111–116.
42. Sousa, A. E., J. Carneiro, M. Meier-Schellersheim, Z. Grossman, and R. M.
Victorino. 2002. CD4 T cell depletion is linked directly to immune activation
in the pathogenesis of HIV-1 and HIV-2 but only indirectly to the viral load.
J. Immunol. 169:3400–3406.
43. Sousa, A. E., A. F. Chaves, A. Loureiro, and R. M. Victorino. 2001. Com-
parison of the frequency of interleukin (IL)-2, interferon-gamma,- and
IL-4-producing T cells in 2 diseases, human immunodeficiency virus types
1 and 2, with distinct clinical outcomes. J. Infect. Dis. 184:552–559.
44. Venkatesan, S., A. Petrovic, D. I. Van Ryk, M. Locati, D. Weissman, and
P. M. Murphy. 2002. Reduced cell surface expression of CCR5 in
CCR5Delta 32 heterozygotes is mediated by gene dosage, rather than by
receptor sequestration. J. Biol. Chem. 277:2287–2301.
45. Whittle, H., J. Morris, J. Todt, T. Corrah, S. Sabally, J. Bangali, P. T. Ngom,
M. Rolle, and A. Wilkins. 1994. HIV-2-infected patients survive longer than
HIV-1-infected patients. AIDS 8:1617–1620.