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Human Immunodeficiency Virus Type 2 (HIV-2)

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Abstract

HIV-1 and HIV-2 are genetically and antigenically related viruses with distinct epidemiologic and biologic properties. In West Africa, many populations are at risk for both HIV-1 and HIV-2. Since its discovery in 1985, research on HIV-2 conducted in large part by West African researchers has amply demonstrated the unique biologic properties of this virus. Various studies suggest differences between HIV-2 and HIV-1 in geographic distribution, distinct temporal trends in the epidemic spread, and dramatic differences in perinatal and sexual transmission. Studies of HIV-2 infected individuals have shown a significantly slower progression to AIDS. Whereas most HIV-1 cohort studies have found 5-15% of their subjects fit a definition of long-term non-progression, 86-95% of HIV-2 infected individuals would be similarly classified. This dramatic difference in pathogenicity provides a unique opportunity to identify viral and host immune mechanisms involved in a closely related and relevant virus system that is predicted to have a significantly slower course of progression. In similar settings, HIV-2 shows lower infectivity and pathogenicity in comparison to that of HIV-1, suggesting that it may be viewed as a virus that is attenuated with respect to HIV-1. This view gave rise to the hypothesis that infection with HIV-2 might provide protection against subsequent infection with the more pathogenic HIV-1. The striking conclusion was that HIV-2 did provide ~60% protection against subsequent infection with HIV-1, now evaluated for over 13 years of study. This hypothesis has now been tested in a number of studies in other parts of West Africa. The 'natural experiment' of HIV-2's observed protection against HIV-1 infection represents an invaluable model in which important correlates of HIV-1 protection can be identified and characterized. We are hopeful that further comparative studies of these related immunodeficiency viruses will yield important information on the pathogenic mechanisms employed by HIV viruses and lead the way to the development of effective interventions for the prevention and control of the AIDS pandemic.

Key words

HIV-2. HIV. Africa. Natural history. Epidemiology.

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Introduction

Human Immunodeficiency Virus Type 2 (HIV-2) was first described in Senegal, West Africa in 1985, by its serologic cross-reactivity to the related simian immunodeficiency virus (SIV)[1]. Subsequent characterization of this new human virus and case reports of associated AIDS cases suggested to some, that a second AIDS epidemic was imminent, this being based on the belief that HIV-2 biology could be readily predicted from our knowledge of HIV-1[2]. However, almost 15 years since its discovery, research studies conducted both in the laboratory and in HIV-2 infected people have highlighted distinct biological differences between these related viruses[3,4]. Internationally based epidemiologic and natural history studies of HIV-2 have provided a wealth of biologic data that comprises much of our current appreciation of the unique properties of this related virus. Some of these unique properties include a distinct global distribution of the virus with limited spread, significantly reduced perinatal and sexual transmission, slower rates of progression to AIDS and the potential protective effect of HIV-2 from subsequent HIV-1 infection. A complete review and update of all aspects of HIV-2 infection are beyond the scope of this review, rather, I have chosen to highlight some of the biological aspects of HIV-2 which have been of most interest from a comparative perspective. Based on our current understanding, the distinct biological differences between these related viruses suggest that viral versus host determinants may be more responsible for the unique pathogenic mechanisms employed by HIV viruses in general. It is hoped that the further characterization of such determinants will be useful for the design of effective HIV interventions.

Geographic distribution of HIV-2

The discovery of HIV-2 in West Africa prompted numerous serologic surveys to further identify its geographic distribution. Over the past decade significant HIV-2 infection has been well documented in most West African countries[5]. Direct comparisons of prevalence rates in different countries are difficult because of differences in study design and diagnostic methodologies; this is particularly pertinent in comparing rates of HIV-dual infections, as described later. A second epidemiologic pattern of HIV-2 infection has been suggested from reports of HIV-2 in Portugal, Mozambique, Angola, southwestern India and Brazil, all areas with former ties to Portugal[6,7]. Case reports or exceedingly low HIV-2 prevalence rates have been documented in other parts of Africa, Europe, the Americas, the Middle East and Asia, however, its spread has been quite limited. This is further supported by the reduced sexual and perinatal transmission rate of the virus[8-11]. Thus, the current data suggest that HIV-2 has been present in certain populations for a long time in order to establish endemic infection and its spread outside of these endemic areas is limited by a low transmission potential. It therefore seems unlikely that this virus will cause a global pandemic similar to that of HIV-1.

HIV-2 Virology

Both HIV-1 and HIV-2 are human lentiviruses with a number of similar virologic properties. The viruses share 40-50% genetic homology, major antigenic cross-reactivity in viral structural gene products, similar genetic organization and cell tropism[12]. Although the CD4 molecule is the major cellular receptor for HIV-2, it has been shown to have lower affinity for the receptor compared with HIV-1[13-15], and its use and relative affinity for more recently described co-receptors for HIV-1 entry has been shown to be more promiscuous than that of HIV-1[16-18]. *In vitro* studies of HIV-2 isolates by a number of laboratories have described differences in cytopathicity of HIV-2 as compared with HIV-1[19-21]. In comparison with HIV-1, HIV-2 isolates demonstrate decreased cell killing, less syncytial cell formation, reduced virus replication, and differences in interaction with CD4, in some cases related to the clinical stage of the HIV-2-infected individuals[22].

The antigenic relatedness of both SIV and HIV-2 to the prototype HIV-1 virus prompted both the discovery and further classification of these related viruses[1,23,24]. Similar to HIV-1, restriction site polymorphism and sequence data indicate significant genetic variability among HIV-2 strains[25,26]. As more sequence data have become available from various HIV-2 and SIV strains, it has also become apparent that no branching order of divergence can be specified and that these virus types may in fact share a common ancestor[27,28]. By comparison to HIV-1, the genetic diversity of HIV-2 is less extensive and only two subtypes (A, B) have been well characterized, other studies have reported the existence of four additional subtypes (C, D, E and F), but different attempts to isolate viruses or obtain additional samples to sequence from these identified subtypes have been unsuccessful[29-31]. Thus far, HIV-2 subtype A is the most characterized subtype and appears to be the major variant circulating in West Africa[32-35]. Only a recent study from Ivory Coast suggests a predominance of HIV-2 subtype B in this country[36]. Similar to the situation with HIV-1 subtypes, the potential impact of subtype differences on the epidemiology, pathogenicity and transmission of HIV-2 is not yet well appreciated.

HIV-2 Diagnostics and HIV-1/HIV-2 Dual Infection

Studies of HIV-2 epidemiology and natural history are heavily dependent on accurate HIV-2 viral diagnosis. The same procedures for serologic testing, virus culture, and genetic diagnostics such as polymerase chain reaction (PCR) that were developed for HIV-1 have been modified for HIV-2 diagnosis and improved over the years. The close relationship of HIV-2 to HIV-1 on a genetic and antigenic level, has necessitated the development and implementation of type-specific diagnostic assays. Commercial HIV ELISA assays most commonly include both HIV-1 and HIV-2 antigens for screening purposes. Immunoblots demonstrating a profile of ma-

jor structural gene product recognition are typically used to confirm HIV-1 and HIV-2 diagnosis using standard criteria. HIV-2 specific diagnosis by immunoblot requires antibody reactivity to *env* ± *gag* ± *pol* antigens. In the absence of reactivity to *gag* or *pol* antigens, the presence of reactivity to two envelope antigens is required (gp120 and gp32, transmembrane protein)[37].

Since 1986, a number of West African countries have reported significant rates of HIV-1 and HIV-2 infections. In addition, individuals with a HIV-dual serologic profile have been described[38-41]. The HIV dual antibody profile is characterized by antibodies with equally strong reactivity to the *env* antigens of both HIV-1 and HIV-2 by immunoblot and/or radioimmunoprecipitation analysis (RIPA)[1,41]. A number of explanations for this type of serologic HIV-dual reactivity must be entertained including: extensive cross-reactivity by either of the HIVs, dual infection, infection by one type and exposure to a second type, or infection with an intermediate virus.

Isolation of both HIV-1 and HIV-2 has been reported from select HIV- dual cases[42]; and PCR evidence of HIV-1 and HIV-2 infection has been reported in similar populations . Two studies from the Ivory Coast described 21/34 (61.7%) serologically diagnosed HIV-duals were confirmed by PCR[39], whereas a second report demonstrated 12/36 (33.3%)[43]. We have found that appropriate serological testing and PCR amplification can be highly correlated, particularly when serologic[44] and PCR assays are well standardized and optimized for sensitivity[45]. We have utilized two sets of nested primers for each HIV type with southern blot hybridization to confirm the amplified product. With this methodology we had 100% detection of the appropriate proviral HIV in singly infected individuals and in healthy individuals with HIV dual serologic patterns, all individuals were found to carry both HIV proviruses. By contrast, we found that in serologically designated HIV dual individuals with low CD4+ counts (<400 cells/mm^3), PCR confirmation of HIV-2 was compromised[45]. We would hypothesize that when the CD4 cell count decreases the differential viral replication properties of the two viruses results in an overabundance of cells with HIV-1 provirus. The prospective evaluation of these superinfected individuals with sequential samples will give us a better understanding of the interaction between HIV-1 and HIV-2.

Population biology might also predict that a poorly transmissible and less virulent virus, such as HIV-2, might not perpetuate in populations with significant HIV-1[46]. Although the existence or generation of an intermediate virus in these populations cannot be unequivocably ruled-out, it is apparent that rates of dual-reactivity have been inflated in the past due to sub-optimal specificity of serologic methods employed. Improvement of serologic assays and newer genetic methods for distinguishing the two viruses have improved and this should improve our diagnostic capabilities and our ability to conduct valid studies of HIV-1/HIV-2 interactions.

Natural history of HIV-2 infection

During the late 1980s and early 1990s, natural history studies of HIV-1 infection conducted in the developed world provided important data on the pathogenesis of HIV-1 infection *in vivo*. Although numerous cross sectional studies of HIV-2 infection were conducted in the late 1980s, they were intrinsically limited in their ability to describe the natural history of HIV-2 infection, which required prospective studies[47]. Studies concerning the natural history of chronic infections such as HIV are difficult to achieve particularly with minimal loss to follow-up; not surprisingly such studies have been rare in developing countries, where viruses such as HIV-2 can be studied.

Our prospective studies conducted in a registered female sex worker cohort in Dakar, Senegal have provided the unique opportunity of measuring the infection and progression rates of both HIV-1 and HIV-2 infections[48-50]. Kaplan-Meier analysis comparing HIV-2 (n=50) and HIV-1 (n=81) seroincident women were significantly different with HIV-2 infected women demonstrating a slower progression to AIDS (Wilcoxon-Gehan test; p value = 0.006). HIV-1 infected women with known time of infection had a 5 year AIDS-free survival of 66.9%, whereas in HIV-2 infected women the 5 year AIDS-free survival was 94.7% (Fig. 1). These differences in survival probabilities between HIV-2 and HIV-1, were also seen for CDC IV disease and CD4+ lymphocyte counts below 400 cells/mm^3 and CD4+ lymphocyte counts below 200 cells/mm^3, as outcomes[49,50].

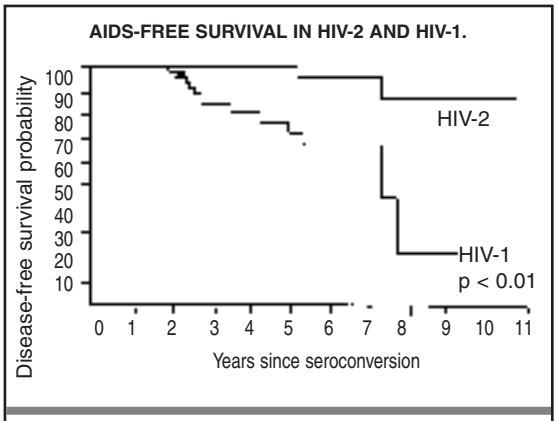

Fig. 1. Kaplan-Meier AIDS-free survival probability comparing incident HIV-1 and HIV-2 infected individuals. Wilcoxon-Gehan, p value <0.01.

In our prospective study of HIV-2 infected individuals, we have also identified individuals that fit a definition of long-term non-progression and can determine a rate of this phenotype in the studied population. The Kaplan-Meier analysis of HIV-2 incident infected individuals indicates that 85% (95%CI = 50 -96%) remain AIDS-free after 8 years of HIV-2 infection. We have also clinically followed a large number of HIV-2 positive prevalent individuals. Recent work by Alcabes *et al.*, indicates that confounding due to differential length-biased sampling in prevalent cohorts does not necessarily bias

Table 1. *Long-term progression in HIV-2 Infection.*

Definition	No. of HIV-2 Positives	No. of LTNPs	Percent LTNPs (%)
>8 yrs symptom free CD4+>500cells/mm^3	41	39	95.1%
>9 yrs symptom free CD4+>500cells/mm^3	22	19	86.4%
>10 yrs symptom free CD4+>500cells/mm^3	13	12	92.3%

Rates of long-term non-progression (LTNP) in HIV-2, dependent on different clinical definitions. Data from the cohort of commercial sex workers in Dakar, Senegal.

estimates of the impact of covariates on rates of progression to AIDS. Further, onset bias appears to decrease as study subjects' date of infection becomes more remote[51]. We have therefore combined our HIV-2 prevalent and incident individuals in estimating the rate of long-term non-progression in this virus infection. Using a definition of long-term non-progression of ≥ 8 years infection in the absence of AIDS or related symptoms, and stable CD4+ lymphocytes > 500 cells/mm^3, we have found 39 of 41 (95%) of our women would be classified as long-term non-progressors (Table 1). This dramatic difference in pathogenicity provides a unique opportunity to identify viral and host immune mechanisms involved in a closely related and relevant virus system that is predicted to have a significantly slower course of progression.

HIV-2 viral dynamics

Plasma viremia has become the standard surrogate marker of HIV progression in the HIV-1 system[52]. Studies of long-term non-progressors compared with rapid progressors during the early phases of their infection have consistently demonstrated lower plasma viral RNA and proviral burdens[53-55]. These individuals have also demonstrated lower seeding of virus in lymphoreticular tissues[56]. In addition, this quantitative assay has demonstrated utility in the SIV system, where plasma viremia at 6 weeks post-infection was predictive of disease outcome[57]. Unfortunately to date, a commercial HIV-2 plasma RNA assay is not available.

We have designed a quantitative internally-controlled RT-PCR that amplifies a portion of the gag region of HIV-2, using primers that we have previously shown to be highly sensitive and specific[45]. The assay has a lower limit of detection of 100 copies/mL, and is linear over 4 logs. We determined plasma viral load in individuals from the cohort of registered commercial sex workers in Dakar, Senegal[58]. HIV-2 viral RNA was detectable in 56% of all samples tested; the median load was 141 copies/mL. Levels of viral RNA in the plasma were inversely related to CD4+ cell counts. In a comparison of HIV-2 and HIV-1 viral loads from women in our cohort with known time of infection, we found that the median viral load was 30 times lower in the HIV-2-infected women ($p<0.001$, Wilcoxon rank-sum), irrespective of the length of time infected (Fig. 2). This suggests plasma viremia is linked to the differences in the pathogenicity of the two viruses.

Although the regulation of viral gene expression in HIV-2 seems to resemble that observed in HIV-1, several differences have been described that may play a role in the differential pathogenicity and *in vivo* replication of these viruses. Sequence comparisons of HIV-1 and HIV-2 have demonstrated differences in the LTR structure. Whereas HIV-1 has two NF-kB enhancer binding sites, only one can be identified for HIV-2 or most SIVs[59]. The regulation and response to T-cell activation via the viral LTR also appears to be distinct in HIV-2 as compared to HIV-1[60-62]. Specific and unique elements in the HIV-2 LTR may regulate HIV-2 gene expression independently of the T-cell activation signals or cytokines that would normally modulate HIV-1 gene expression[60,61,63]. Mutational studies of the unique sites in the HIV-2 LTR responsible for inducible enhancer function demonstrate that this function is more readily disrupted in HIV-2 compared with HIV-1[63], perhaps explaining some of the distinct biological properties of the virus.

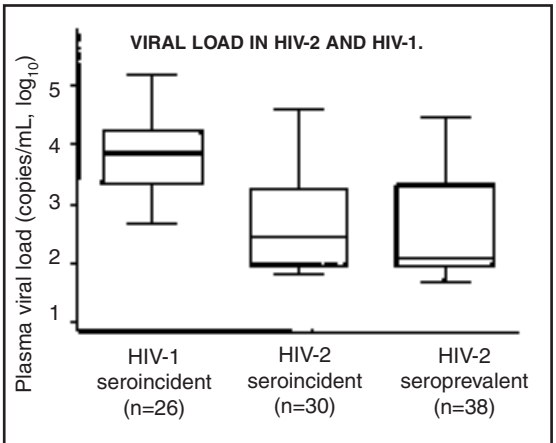

Fig. 2. Plasma viral load on HIV-1 and HIV-2 infected women (shaded). The interior line defines the median viral load, and the boxes cover the 25th to 75th percentile. The whiskers mark the full range of viral load values[58].

HIV-2 Protection from HIV-1

Given the observations of HIV-2 lower transmissibility[8,64,65] and pathogenicity[49,50] compared to HIV-1, one can easily draw parallels to other systems in which a related less pathogenic virus might induce immune responses that protect against subsequent infection with the more pathogenic virus. This type of interaction can be referred to as a Jennerian approach to vaccination, after Edward Jenner's demonstration that infection with the benign cowpox virus could protect the individual from subsequent infection with the more virulent smallpox virus. In 1995, it was documented in our cohort of commercial sex workers in Dakar, Senegal, that HIV-2 infection conferred a ~70% reduction in the subsequent risk of HIV-1 infection, when controlling for STD infection as a surrogate marker of sexual behavior and immunosuppression as measured by CD4+ counts[66]. We used a Poisson model to estimate the independent effect of demographic, behavioral, and biologic variables on the risk of HIV-1 infection in a cohort of HIV-2 seropositive and HIV seronegative women. Despite higher incidence of other STDs, HIV-2-infected women had lower incidence of HIV-1 than seronegatives, with an incidence rate ratio (IRR) of 0.32 (p=0.008). When immunosuppression was accounted for, the IRR associated with HIV-2 seropositivity was reduced further, to 0.23 (p=0.02), and the modelling indicated significant effect modification by CD4+ cell count. This analysis led to the conclusion that HIV-2 infection confers a significant reduction in the subsequent risk of HIV-1 infection. This study suggests that the diversity of HIV and SIV viruses previously considered a major stumbling block to vaccine development may have instead provided a natural model for HIV protection and control.

Continued analysis of the Dakar cohort has extended the observation period from the first published report to over 13 years[67,68]. These analyses yielded estimates of HIV-2's protective efficacy ranging from 52 to 74%, dependent on the study design[66,67] suggesting that further unbiased studies of the interaction of the two viruses, controlling for important confounders, are important to determine the generalizability of the noted protective effect (Table 2). It is clear that the protective effect initially noted continues to be documented in this longitudinal study, which is noteworthy for its statistical power generated by the large person-time of observation and narrow confidence intervals.

Other studies in West Africa have addressed the question of HIV-2 protection from a retrospective analysis. These various studies conducted in different populations and countries have distinct study designs and therefore can only address the question of how generalizable the HIV-2 protection will be in diverse settings[69-71]. Problems with insufficient statistical power, loss to follow-up and misclassification bias have been previously raised[68] and recent studies report point estimates that fail to achieve statistical significance[69-71]. Continued scientific discourse around this topic will no doubt continue, but it is hoped that this will be fueled by carefully designed studies that can clearly address this important research topic[67,68]. Unbiased, powerful studies, using sensitive and specific classification methods, will effectively address the generalizability of the observation of HIV-2 protective efficacy against subsequent HIV-1-infection. Also, they will be able to provide mechanistic insight into the population-based observation of protection. Molecular epidemiologic techniques may identify the host and viral characteristics that interact in those mechanisms.

Table 2. *Protective effect of HIV-2 on risk of subsequent HIV-1 infection.*

IRR	Fraction Protected	Yrs of Observation	p value
0.23-0.32[66]	68-77%	9 years	<0.05
0.26-0.36[67]	64-74%	11 years	<0.05
0.33-0.42[68]	58-67%	12 years	<0.03
0.34-0.44 [unpub.]	56-66%	13 years	<0.03

The protective effect of HIV-2 on risk of subsequent HIV-1 infection as documented over time in a cohort of commercial sex workers in Dakar, Senegal. The range of incidence rate ratios (IRR) and associated effect measurement, fraction protected results from inclusion or not of a variable accounting for CD4+ cell count in the Poisson regression model used to estimate the independent effects of potentially confounding variables. [xx] denotes reference.

HIV-2 immunity and correlates of protection

A number of immune mediated host responses might be involved in the *in vivo* protection described. Available data is supportive of a variety of potential cross-immune effector mechanisms. An early study of MHC-restricted CD8+ CTLs demonstrated HIV-2 *gag*-specific CTL activity in 5 of 7 HIV-2 infected individuals, in the absence of *in vitro* restimulation[72]. Studies of cultured CTL responses have shown *gag* directed activity in 18/20 (90%) and *pol* directed activity in 14/20 (70%) HIV-2-infected subjects. The sum of specific lysis against HIV-2 *gag*, *pol* and *nef*, or specific lysis of the dominant CTL response, correlated strongly with HIV-2 proviral load[73]. HIV-2 neutralizing antibody activity has also been described in a significant proportion of individuals, the reactivity appears to be broadly reactive and in some cases cross-reactive to HIV-1[74-76] Therefore, in limited studies of HIV-2 specific immunity, there is good evidence for qualitatively superior responses that are detectable in a larger proportion of individuals, when compared with HIV-1 infected individuals.

β chemokines have now been identified as potent soluble suppressors of macrophage-tropic HIV infection *in vitro*. Studies of multiply exposed uninfected individuals have implicated the role of elevated β-chemokines in HIV resistance, in many cases, independent of genetic mutations in the chemokine receptor[77-79]. Macaque studies have

also suggested a role for β-chemokines in vaccine induced protective immunity using a variety of vaccine candidates and live virus challenge[80]. Recently, *in vitro* observations from our laboratory have suggested similar mechanisms for HIV-2 protection from subsequent HIV-1 infection (Kokkotou and Kanki, unpublished data). Using an *in vitro* HIV-1 challenge system, we were able to demonstrate that a significant percentage (~60%) of PBMCs derived from HIV-2-infected women could not support replication of a CCR5-dependent HIV-1 virus compared with CXCR4-dependent virus. Resistance was transferable, CD8 dependent and strongly correlated with β-chemokine production in the media. All resistant cultures were rendered susceptible by addition of antibodies to β-chemokines.

HIV-2 infection might dramatically influence β-chemokine production by enhancing it in magnitude and duration, thus enabling HIV-2-infected individuals to cope favorably with subsequent exposure to HIV-1. This is supported by the studies demonstrating that binding of the HIV-2 envelope to the alpha chain of CD8 stimulates dramatic levels of β-chemokine production in comparison to HIV-1 gp120 activity[81]. Not only does this implicate a novel viral suppressive mechanism but one that may be adapted for immunoprophylaxis. Antiretroviral vaccine strategies that incorporate β-chemokine induction or other receptor-blocking functions raise some encouraging possibilities for vaccine design and development.

Summary

Since the discovery of the second human immunodeficiency virus in 1985, considerable progress has been made in understanding the virology and epidemiology of HIV-2. The data suggests differences between HIV-2 and HIV-1 in geographic distribution, distinct epidemic trends, differences in perinatal transmission rates and incubation periods to the development of AIDS. The virologic determinants and mechanisms for these apparent biological differences are still unknown. However, an understanding of how HIV-2 differs from HIV-1 is essential for interpretations of comparative virologic studies. We are hopeful that such comparative studies will yield important information on the pathogenic mechanisms employed by HIV viruses and lead the way to the development of effective interventions for the prevention of AIDS. This is best exemplified in the studies that indicate that this close relative of HIV-1 infection, via its attenuated phenotype, may confer significant protection from subsequent HIV-1 infection. This further suggests that understanding HIV-2 immunity and cross-immunity may be useful for HIV vaccine design and development.

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References

1. Barin F, Mboup S, Denis F, *et al.* Serological evidence for virus related to simian T-lymphotropic retrovirus III in residents of West Africa. Lancet 1985; 2: 1387-90.
2. Clavel F, Guetard D, Brun-Vezinet F, *et al.* Isolation of a new human retrovirus from West African patients with AIDS. Science 1986; 233: 343-6.
3. Essex M, Kanki P. Human immunodeficiency virus type 2 (HIV-2). In: Merigan T, Bartlett J, Bologenesi D (eds.). Textbook of AIDS Medicine. Baltimore: Williams & Wilkins, 1997.
4. Markovitz D. Infection with the human immunodeficiency virus type 2. Ann Intern Med 1993; 118: 211-8.
5. Kanki P, DeCock K. Epidemiology and natural history of HIV-2. AIDS 1994; 8: S1-S9.
6. Smallman-Raynor M, Cliff A. The spread of human immunodeficiency Virus Type 2 into Europe: A geographical analysis. Intl J of Epi 1991; 20: 480.
7. Kanki P. Epidemiology and natural history of HIV-2. In: DeVita VJ, Hellman S, Rosenberg S (eds.). In AIDS: Etiology, diagnosis, treatment and prevention. Philadelphia: J. B. Lippincott Co 1997:127-35.
8. Kanki P, Travers K, Hernández-Ávila M, *et al.* Slower heterosexual spread of HIV-2 compared with HIV-1. Lancet 1994; 343: 943-6.
9. Andreasson P, Dias F, Naucler A, Anderson S, Biberfeld G. A prospective study of vertical transmission of HIV-2 in Bissau, Guinea-Bissau. AIDS 1993; 7: 989.
10. Ngagne M, Diouf A, Kebe F, *et al.* Histoire Naturelle de la transmission verticale VIH1 et VIH 2 a Dakar, IXth International Conference on AIDS and Associated Cancers in Africa, December 1995 Kampala, Uganda.
11. Adjorlolo-Johnson G, DeCock K, Ekpini E, *et al.* Prospective comparison of mother-to-child transmission of HIV-1 and HIV-2 in Abidjan, Ivory Coast. JAMA 1994; 272: 462-6.
12. Kanki P. Virologic and Biologic Features of HIV-2. In: Wormser GP (ed.). AIDS and other manifestations of HIV infection. New York: Raven Press, Ltd., 1997.
13. Clapham P, McKnight A, Weiss RA. Human immunodeficiency virus type 2 infection and fusion of CD4-negative human cell lines: Induction and enhancement by soluble CD4. J Virol 1992; 66: 3531-7.
14. Moore J. Simple methods for monitoring HIV-1 and HIV-2 gp120 binding to soluble CD4 by enzyme-linked immunosorbent assay: HIV-2 has a 25-fold lower affinity than HIV-1 for soluble CD4. AIDS 1990; 4: 297-305.
15. Mulligan M, Ritter GD, Chaikin MA, *et al.* Human immunodeficiency virus type 2 envelope glycoprotein: Differential CD4 interactions of soluble gp120 versus the assembled envelope complex. Virology 1992; 187: 233-41.
16. Bron R, Klasse P, Wilkinson D, *et al.* Promiscuous use of Cc and Cxc chemokine receptors in cell-to-cell fusion mediated by a human immunodeficiency virus type 2 Envelope Protein. J Virol 1997; 71: 8405-15.
17. Endres M, Clapham P, Marsh M, *et al.* CD4-independent infection by HIV-2 is mediated by fusin/CXCR4. Cell 1996; 87: 745-56.
18. Feng Y, Broder C, Kennedy P, Berger EA. HIV-1 entry cofactor: Functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. Science 1996; 272: 872-7.
19. Evans L, Moreau J, Odehouri K, *et al.* Characterization of a noncytopathic HIV-2 strain with unusual effects on CD4 expression. Science 1988; 240: 1522-5.
20. Kong L, Lee S, Kappes J, *et al.* West African HIV-2-related human retrovirus with attenuated cytopathicity. Science 1988; 240: 1525-9.

21. Albert J, Naucler A, Bottiger B, *et al.* Replicative capacity of HIV-2, like HIV-1, correlates with severity of immunodeficiency. AIDS 1990; 4: 291-5.
22. Albert J, Stalhandske P, Marquina S, *et al.* Biological phenotype of HIV type 2 isolates correlates with V3 genotype. AIDS Res Hum Retroviruses 1996; 12: 821-8.
23. Kanki P. West African Human Retroviruses Related to STLV-III. AIDS 1987; 1: 141-5.
24. Biberfeld G, Brown F, Esparza J, *et al.* Meeting Report, WHO working group on characterization of HIV-related, retroviruses: Criteria for characterization and proposal for a nomenclature system. AIDS 1987; 1: 189-90.
25. Franchini G, Gurgo C, Guo H, *et al.* Sequence of simian immunodeficiency virus and its relationship to the human immunodeficiency viruses. Nature 1987; 328: 539-43.
26. Boeri E, Giri A, Lillo F, *et al. In vivo* genetic variability of the human immunodeficiency virus type 2 V3 region. J Virol 1992; 66: 4546-50.
27. Kirchhoff F, Jentsch K, Bachmann B, *et al.* A novel proviral clone of HIV-2: Biological and phylogenetic relationship to other primate immunodeficiency viruses. Virology. 1990; 177: 305-11.
28. Gao F, Yue L, White A, *et al.* Human infection by genetically diverse SIVSM-related HIV-2 in West Africa. Nature 1992; 358: 495-9.
29. Gao F, Yue L, Robertson D, *et al.* Genetic diversity of human immunodeficiency virus type 2: Evidence for distinct sequence subtypes with differences in virus biology. J Virol 1994; 68: 7433-47.
30. Chen Z, Luckay A, Sodora D, *et al.* Human immunodeficiency virus type 2 (HIV-2) seroprevalence and characterization of a distinct HIV-2 genetic subtype from the natural range of simian immunodeficiency virus-infected sooty mangabeys. J Virol 1997; 71: 3953-60.
31. Heredia A, Vallejo A, Soriano V, Epstein J, Hewlett I. Chemokine receptors and HIV-2. AIDS 1997; 11: 1198-9.
32. Sankalé JL, Sallier de la Tour R, Renjifo B, *et al.* Intra-patient Variability of the human immunodeficiency virus type-2 (HIV-2) Envelope V3 Loop. AIDS Res Hum Retroviruses 1995; 11: 617-23.
33. Norrgren H, Marquina S, Leitner T, *et al.* HIV-2 genetic variation and DNA load in asymptomatic carriers and AIDS cases in Guinea-Bissau. J of Acquir Imm Deficiency Syndr 1997; 16: 31-8.
34. Peeters M, Koumare B, Mulanga C, *et al.* Genetic subtypes of HIV type 1 and HIV type 2 strains in commercial sex workers from Bamako, Mali. AIDS Res Hum Retroviruses 1998; 14: 51-8.
35. Xiang Z, Ariyoshi K, Wilkins A, Dias F, Whittle H, Breuer J. HIV type 2 pathogenicity is not related to subtype in rural Guinea Bissau. AIDS Res Hum Retroviruses 1997; 13: 501-5.
36. Pieniazek D, Ellenberger D, Janini L, Ramos A, Nkengasong J, *et al.* Predominance of human immunodeficiency virus type 2 subtype B in Abidjan, Ivory Coast. AIDS Res Hum Retroviruses 1999; 15.
37. Anonymous. AIDS: Recommendations for interpretation of HIV-2 western blot results. WHO Weekly Epidemiol Rec 1990; 65: 74-5.
38. Denis F, Barin F, Gershy-Damet G, *et al.* Prevalence of human T-lymphotropic retroviruses type III (HIV) and type IV in Ivory Coast. Lancet 1987; 1: 408-11.
39. George JR, Ou CY, Parekh B, *et al.* Prevalence of HIV-1 and HIV-2 mixed infections in Cote d'Ivoire. Lancet 1992; 340: 337-9.
40. Tedder R, O'Connor T, Hughs A, N'Hjie H, Corrah T, Whittle H. Envelope cross-reactivity in western blot for HIV-1 and HIV-2 may not indicate dual infection. Lancet 1988; 2: 927-30.
41. Essex M, Kanki P, Marlink R, Chou M-J, Lee TH. Antigenic characterization of the human immunodeficiency viruses. J. Am Acad Dermatol 1990; 22: 1206-9.
42. Evans L, Moreau J, Odehouri K, *et al.* Simultaneous isolation of HIV-1 and HIV-2 from an AIDS patient. Lancet 1988; 2: 1389-91.
43. Peeters M, Gershy-Damet GM, Fransen K, *et al.* Virological and polymerase chain reaction studies of HIV-1/HIV-2 dual infection in Cote d'Ivoire. Lancet 1992; 340: 339-40.
44. Gueye-Ndiaye A, Clark R, Samuel K, *et al.* Cost-effective diagnosis of HIV-1 and HIV-2 By recombinant-expressed env peptide (566/966) dot blot analysis. AIDS 1993; 7: 481-95.
45. Dieng-Sarr A, Thior I, Kokkotou E, Sankale J, Marlink R, Coll-Seck E, *et al.* HIV-1 and HIV-2 dual infection: Lack of HIV-2 provirus correlates with low CD4+ lymphocyte counts. AIDS 1998; 12: 131-7.
46. Anderson R, May R. The population biology of the interaction between HIV-1 and HIV-2: Coexistence or competitive exclusion? AIDS 1996; 10: 1663-73.
47. Romieu I, Marlink R, Kanki P, M'Boup S, Essex M. HIV-2 link to AIDS in West Africa. J Acq Immune Def Syn 1990; 3: 220-30.
48. Marlink R, Ricard D, M'Boup S, *et al.* Clinical, hematologic, and immunologic cross-sectional evaluation of individuals exposed to human immunodeficiency virus type 2 (HIV-2). AIDS Res Hum Retroviruses 1988; 4: 137-48.
49. Marlink R, Kanki P, Thior I, *et al.* Reduced Rate of Disease Development with HIV-2 Compared to HIV-1. Science 1994; 265: 1587-90.
50. Traore I, Marlink R, Thior I, *et al.* HIV-2 as a model for long-term non-progression, XI International Conference on AIDS, 1996 Vancouver, Canada.
51. Alcabes P, Pezzotti P, Phillips A, N Rezza G, Vlahov D. Long-term perspective on the prevalent-cohort biases in studies of human immunodeficiency virus progression. Am J of Epi 1997; 146: 543-51.
52. Mellors J, Kingsley L, Rinaldo CJr, *et al.* Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. Ann Intern Med 1995; 122: 573-9.
53. Mellors JWJrCRR, Gupta P, White R, Todd JA, Kingsley L. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. Science 1996; 272: 1167-70.
54. Cao Y, Qin L, Zhang L, Safrit J, Ho D. Characterization of long-term survivors of human immunodeficiency virus type 1 infection. Immunology Letters 1996; 51: 7-13.
55. Vesanen M, Steven C, Taylor P, Rubinstein P, Saksela K. Stability in controlling viral replication identifies long-term non-progressors as a distinct subgroup among human immunodeficiency virus type 1-infected persons. J Virol 1996; 70: 9035-40.
56. Pantaleo G, Menzo S, Vaccarezza M, *et al.* Studies in subjects with long-term non-progressive human immunodeficiency virus infection [see comments]. New Eng J Med 1995; 332: 209-16.
57. Hirsch V, Fuerst T, Sutter G, *et al.* Patterns of viral replication correlate with outcome in simian immunodeficiency virus (SIV)-infected macaques - effect of prior immunization with trivalent SIV vaccine in modified vaccinia virus Ankara. J Virol 1996; 70: 3741-52.
58. Popper S, Dieng-Sarr A, Travers K, *et al.* Lower HIV-2 viral load reflects the difference in pathogenicity of HIV-1 and HIV-2. J Inf Dis (in press).
59. Arya S. Human and simian immunodeficiency retroviruses: Activation and differential transactivation of gene expression. AIDS Res Hum Retroviruses 1988; 4: 175-86.
60. Markovitz D, Hannibal M, Pérez V, Gauntt C, Folks T, Nabel G. Differential regulation of human immunodeficiency viruses (HIVs): A specific regulatory element in HIV-2 responds to stimulation of the T-cell antigen receptor. Proc Natl Acad Sci USA 1990; 87: 9098-102.
61. Tong-Starksen S, Welsh T, Peterlin M. Differences in transcriptional enhancers of HIV-1 and HIV-2 response to T-cell activation signals. J Immunol 1990; 145: 4348-54.
62. Hannibal M, Markovitz D, Clark N, Nabel G. Differential activation of human immunodeficiency virus type 1 and 2 transcription by specific T- cell activation signals. J Virol. 1993; 67: 5035-40.
63. Markovitz D, Smith M, Hilfinger J, Hannibal M, Petryniak B, Nabel G. Activation of the human immunodeficiency virus type 2 enhancer is dependent on purine box and kappa B regulatory elements. J Virol 1992; 66: 5479-84.
64. Kanki P, Mboup S, Marlink R, *et al.* PrevaletType 2 (HIV-2) and human immunodeficiency virus type 1 (HIV-1) in West African female prostitutes. Amer J Epid 1992; 136: 895-907.
65. Donnelly C, Leisenring W, Kanki P, Awerbuch T, Sandberg S. Comparison of transmission rates of HIV-1 and HIV-2 in a cohort of prostitutes in Senegal. Bull of Math Bio 1993; 55: 731-43.
66. Travers K, Mboup S, Marlink R, *et al.* Natural protection against HIV-1 infection provided by HIV-2. Science 1995; 268: 1612-5.
67. Kanki P, Eisen G, Travers K, *et al.* HIV-2 and natural protection against HIV-1 infection. (Technical Comment). Science 1996; 272:1959-60.
68. Travers K, Eisen G, Marlink R., Kanki P, MBoup S. Protection from HIV-1 infection by HIV-2. AIDS 1998; 12: 224-5.

69. Aaby P, Poulsen A-G, Larsen O, *et al*. Does HIV-2 protect against HIV-1 infection? AIDS 1997; (letter) 11.
70. Ariyoshi K, van der Loeff M, Sabally S, *et al*. Does HIV-2 infection provide cross-protection against HIV-1 infection? AIDS 1997; (letter) 11.
71. Norrgren H, Andersson S, Biague A, *et al*. Trends and interaction o fhIV-1 and HIV-2 in Guinea-Bissau, West Africa: No protection of HIV-2 against HIV-1 infection. AIDS 1999; 13: 701-7.
72. Ariyoshi K, Cham F, Berry N, *et al*. HIV-2-specific cytotoxic T-lymphocyte activity is inversely related to proviral load. AIDS 1995; 9: 555-9.
73. Bertoletti A, Cham F, McAdam S, *et al*. Cytotoxic T cells from human immunodeficiency virus type 2 infected patients frequently cross-react with different human immunodeficiency virus type 1 clades. J Virol 1998; 72: 2439-48.
74. Bjorling E, Scarlatti G, von Gegerfelt A, *et al*. Autologous neutralizing antibodies prevail in HIV-2 but not in HIV-1 infection. Virology 1993; 193: 528-30.
75. Fenyo E, Putkonen P. Broad cross-neutralizing activity in serum is associated with slow progression and low risk of transmission in primate lentivirus infections. Immunology Letters 1996; 51: 95-9.
76. Robert-Guroff M, Aldrich K, Muldoon R, *et al*. Cross-neutralization of human immunodeficiency virus type 1 and 2 and simian immunodeficiency virus isolates. J Virol 1992; 66: 3602-8.
77. Paxton W, Martin S, Tse D, *et al*. Relative resistance to HIV-1 infection of CD4 lymphocytes from persons who remain uninfected despite multiple high-risk sexual exposure. Nature Med 1996; 2: 412-7.
78. Cocchi F, DeVico A, Garzino-Demo A, Arya S, Gallo R, Lusso P. Identification of RANTES, MIP-1 alpha, and MIP-1 beta as the major HIV-suppressive factors produced by CD8+ T cells. Science 1995; 270: 1811-5.
79. Zagury D L, Chams V, Fall L, Bernard J, Zagury J-F, Bizzini B, *et al*. C-C chemokines, pivotal in protection against HIV type 1 infection. Proc Natl Acad Sci USA 1998; 95: 3857-61.
80. Lehner T, Wang Y, Cranage M, *et al*. Protective mucosal immunity elicited by targeted iliac lymph node immunization with a subunit SIV envelope and core vaccine in macaques. Nature Med 1996; 2: 767-75.
81. Neoh L, Akimoto H, Kaneko H, *et al*. The production of beta-chemokines induced by HIV-2 envelope glycoprotein [letter]. AIDS 1997; 11: 1062-3.