REVIEW

Infection with the Human Immunodeficiency Virus Type 2

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■ *Purpose:* To review the clinical, epidemiologic, and biological features of infection with the human immunodeficiency virus type 2 (HIV-2).

■ *Data Identification:* Studies published since 1981 identified from MEDLINE searches, articles accumulated by the author, bibliographies of identified articles, and discussions with other investigators.

■ *Study Selection:* Information for review was taken from the author's own studies, data from other investigators that have been submitted for publication, and from 131 of the more than 200 articles examined.

■ *Data Extraction:* Pertinent studies were selected and the data synthesized into a review format.

■ *Results of Data Synthesis:* Infection with HIV-2 is prevalent in West Africa and is increasingly being identified elsewhere. The human immunodeficiency virus type 2 is spread through sexual contact and via contaminated blood but, unlike HIV-1, perinatal transmission is limited. Human immunodeficiency virus type 2 is genetically much more closely related to the simian immunodeficiency virus (SIV) than to HIV-1; biological and demographic data suggest that HIV-2 may have originally been transmitted from monkeys to man. Although HIV-2 causes the acquired immunodeficiency syndrome (AIDS), the asymptomatic incubation period after infection with HIV-2 appears to be substantially longer than that following HIV-1 infection. Consistent with these clinical observations, genetic regulation of HIV-2 differs from that of HIV-1. Therapeutic studies of patients infected with HIV-2 are lacking.

■ *Conclusions:* The human immunodeficiency virus type 2 is prevalent in West Africa and is now recognized on several other continents, including North America. Its epidemiology, biology, and clinical course differ from HIV-1. Therapeutic studies are needed.

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The human immunodeficiency virus type 2 (HIV-2), like HIV-1, can cause the acquired immunodeficiency syndrome (AIDS) and related illnesses. Infection with HIV-2 is well recognized in West Africa, but persons infected with this human retrovirus are now being identified more frequently in other parts of the world. Although infection with HIV-2 is still rare in the United States, the Food and Drug Administration (FDA) has recently made the prudent decision to mandate testing of the blood supply for this agent. The HIV-2, which is more closely related to the simian immunodeficiency virus (SIV) than to HIV-1, appears to be less virulent than HIV-1, and has less efficient perinatal transmission. Further, HIV-2 is regulated differently than HIV-1 at the genetic level.

Relationship to Other Human Retroviruses

Although it has been recognized for years that retroviruses cause tumors in animals, the first clear link between human disease and retroviruses was reported in the early 1980s, when Gallo's group at the National Institutes of Health and Hinuma and coworkers in Japan discovered the link between the human T-cell leukemia virus type I (HTLV-I) and adult T-cell leukemia (1-4). In addition, HTLV-I has subsequently been shown to be associated with tropical spastic paraparesis and similar myelopathies (5, 6). The closely related retrovirus HTLV-II was first isolated from cell lines originating from patients with hairy cell leukemia (7-9). However, although HTLV-II infection is now being recognized more frequently in the United States (particularly among groups such as intravenous drug abusers), HTLV-II has not yet been conclusively linked to any disease (10, 11). From 1983 to 1984, it was shown that a newly discovered human retrovirus was a causative agent of AIDS (12-14). This virus was first called HTLV-III by the American group and lymphadenopathy-associated virus (LAV) by the French group (15). These two viruses have subsequently been shown to be essentially identical, and this virus, which demonstrates essentially no similarity to HTLV-I or HTLV-II at the genetic level, is now called the human immunodeficiency virus type 1.

In 1985, Kanki, Essex, and coworkers described a group of healthy Senegalese whose sera demonstrated much stronger antibody responses to SIV than to HIV-1 (16, 17). In 1986, Montagnier's group isolated a new retrovirus from West African patients with AIDS or AIDS-related complex (18-20). The new virus belonged to the HIV group, but differed significantly from HIV-1 (18, 19). Whereas different isolates of HIV-1 showed relatively minor antigenic variation, the West African virus, HIV-2, showed significant antigenic variation

Figure 1. Distribution of HIV-2 in Africa. Shaded areas represent regions where significant rates of HIV-2 infection have been reported.

from HIV-1, with only limited serologic cross-reactivity (18, 19). Analysis of the nucleotide sequence of this isolate of HIV-2 showed only 42% similarity to HIV-1 but 75% similarity to certain strains of SIV (21). Although the genomic organization and the function of the gene products encoded by HIV-2 are very similar to HIV-1 (21), HIV-2 appears to differ in its biological properties when compared to HIV-1.

Epidemiology of Human Immunodeficiency Virus Type 2 Infection

Infection with HIV-2 was first described in urban settings in West Africa (20). Indeed, HIV-2 appears to have been present in West Africa at least since 1966 (22, 23). Moderate to high rates of infection have been found (Figure 1) in urban areas of Senegal, Guinea, Guinea-Bissau, Burkina Faso, Ivory Coast, Gambia, and Cape Verde (24, 25). Interestingly, significant rates of HIV-2 infection have been reported in Angola and Mozambique (Figure 1), two countries located in southern Africa (25). These countries were formerly Portuguese colonies and maintain ongoing relationships with countries in Western Africa (Guinea-Bissau, Cape Verde), which were also Portuguese colonies (25). In Guinea-Bissau and Gambia, HIV-2 is the prevalent HIV, and HIV-1 is rare. In Ivory Coast and Burkina Faso, HIV-2 and HIV-1 are both present in an appreciable proportion of the population. In contrast, in Benin, infection with either virus is rare (26). Like HIV-1, HIV-2 is transmitted sexually and, in Africa, this appears to be largely due to heterosexual transmission. In certain urban centers in West Africa, 15% to 64% of female prostitutes are infected (24). Consistent with the idea that HIV-2 may be less virulent than HIV-1 and that HIV-2 has been present in West Africa for several generations, seropositivity increases with age in prostitutes in Dakar, Senegal, with almost 100% of 50-year-old prostitutes being infected (24, 25).

Infection with HIV-2 is now being recognized with increasing frequency in West Africa and other areas of the world (27-34). Infected individuals have been identified in Europe (28, 31), North America (34, 35), and South America (29), although, where a history was obtained, the infected individual was generally from West Africa or had sexual contact with such a person. More recently, a pocket of HIV-2 infection has been identified in Bombay, India (36, 37). Therefore, although HIV-2 infection probably originated in West Africa, it may, like HIV-1, come to pose a significant concern on other continents.

The prevalence of HIV-2 infection in the United States is still low, with 32 cases reported to the Centers for Disease Control (CDC) as of April 1992 (38). In all cases for which a history has been available, the infected individuals have previously lived in West Africa or have had sexual partners from that region. Until recently, the blood supply of the United States was not screened specifically for HIV-2. However, approximately 80% of sera from HIV-2 infected individuals cross-react in an HIV-1 enzyme immunosorbent assay (ELISA), and people from West Africa have been asked to refrain from donating blood. Indeed, no cases of transfusion-related HIV-2 infection have been discovered in the United States, consistent with these factors and the low prevalence of infection (39, 40). As of June 1992, the FDA has mandated that blood banks must screen the blood supply for HIV-2. This prudent measure will further protect against HIV-2 infection resulting from a transfusion. However, transmission of HIV-2 to a larger percentage of the American population through sexual contact and shared needles is possible.

Transmission

Human immunodeficiency virus type 2 appears to be transmitted in West Africa principally by sexual contact, with prostitutes being the most well-studied group (24, 25, 33, 41). The virus can also be spread by contact with infected blood, such as with transfusion (33). Early evidence indicates that the transmission pattern of HIV-2 differs in at least one significant manner from that of HIV-1: Whereas at least 30% of babies born to mothers infected with HIV-1 are infected, no more than 10% of infants born to HIV-2-infected mothers appear to be infected (25, 42-44). It has been theorized that the low rate of transmission may result from lower viral titers in the blood of HIV-2 patients compared with those infected with HIV-1. Preliminary data using polymerase chain reaction (PCR) and viral isolation indicates that viremia may be significantly lower in HIV-2 patients than in comparably staged HIV-1 patients (Kanki P. Personal communication). In addition, recent evidence indicates that only a particular subset of the subtypes of HIV-1 infecting a given mother are transmitted perinatally (45), but whether either of these findings will have a bearing on the issue of inefficient perinatal transmission of HIV-2 is also unknown.

Clinical Course

Early case reports clearly showed that HIV-2 can cause AIDS (20, 28, 33). Because the period between

infection and development of AIDS appears to be substantially longer than that for HIV-1 (25, 27, 42), prospective cohort studies have only recently begun to confirm this link (46). Estimates indicate that the rate of progression to CDC stage IV disease is 3 to 4 times greater for HIV-1 than for HIV-2 and that the rate of progression to overt AIDS is 12 to 13 times greater (46). Individuals infected by HIV-2 are, therefore, less likely to develop AIDS or, at least, will have a much longer asymptomatic period (25). These estimated rates would further imply that progression of symptomatic disease to AIDS is slower for HIV-2 than for HIV-1. Once HIV-2-infected patients develop AIDS, progression to death may be slower than for HIV-1-infected AIDS patients (28), although this matter has not yet been thoroughly studied.

Consistent with the slower clinical progression, other objective measurements of immunity appear to decline more slowly with HIV-2 infection than with HIV-1. Prostitutes in Senegal who are infected with HIV-2 are approximately twice as likely to show skin test anergy than are seronegative prostitutes. Those with HIV-1 infection are six times more likely to be anergic than are seronegative prostitutes, or three times more likely than those infected with HIV-2 (46). Similarly, initial evaluation of HIV-2-infected persons has revealed T4 counts and T4/T8 ratios intermediate between those of uninfected individuals and those with HIV-1 infection (46, 47).

The symptoms resulting from infection with HIV-2 appear to be very similar to those caused by HIV-1 infection. As with HIV-1, HIV-2-related disease can be separated into two broad categories: symptoms caused primarily by the virus itself or symptoms caused by opportunistic infections or tumors resulting from the destruction of the immune system. Human immunodeficiency virus type 2 infection can cause diffuse lymphadenopathy, weight loss, and chronic diarrhea in the absence of any other identifiable pathogen (20, 27, 28, 33). As with HIV-1, HIV-2 infection alone can also cause both central and peripheral nervous system disease (20, 48, 49). The infectious mononucleosis-like syndrome of acute HIV-1 infection (50) has not yet been described for HIV-2, but this is probably due to the lack of formal study. Infection with HIV-2 is associated with many opportunistic infections that are also seen with HIV-1 infection, including esophageal candidiasis, cerebral toxoplasmosis, tuberculosis, herpes zoster rash, systemic salmonellosis, and diarrhea secondary to *Isospora belli* or *cryptosporidium* (20, 27, 28, 33, 34). Kaposi sarcoma has also been described (20). Pneumonia due to *Pneumocystis carinii* is rarely described in HIV-2 infected patients, but this is consistent with the paucity of this opportunistic infection in African patients with AIDS caused by HIV-1 (20). Infections with other opportunistic pathogens and "opportunistic" tumors are likely to be described as more HIV-2 patients are followed for a longer period. Despite the similar range of opportunistic infections and tumors, patients with HIV-2-related AIDS may live longer than those with HIV-1 (28).

Relationship of Human Immunodeficiency Virus Type 2 to Simian Immunodeficiency Virus

Sequencing of the initial isolate of HIV-2 revealed that this virus, although showing only 40% to 50% similarity to HIV-1 at the nucleic acid level, shows approximately 75% similarity to SIV_{MAC} and SIV_{SM}, two closely related strains of SIV found in macaque and sooty mangabey monkeys, respectively (21). It was subsequently shown that different isolates of HIV-2, like HIV-1, show substantial genetic variation (51-54). More recent work has shown that sequence data from a given viral isolate cannot be used to distinguish whether that isolate is from humans (HIV-2) or West African sooty mangabey monkeys (SIV_{SM}; [55-57]). This appears to be the case whether the *pol* (56, 57) or *env* (57) genes are sequenced. These data raise the provocative question of whether HIV-2 and SIV_{SM} are actually the same virus. This hypothesis is further made plausible by the shared geographic distribution (West Africa) of HIV-2 and SIV_{SM}. Because sooty mangabeys infected with SIV_{SM} appear to be relatively asymptomatic (56, 58), these primates might be a reservoir from which the virus could spread to humans. Although monkeys are hunted and eaten, it seems unlikely that ingestion of monkey meat could lead to infection because the virus would probably be destroyed by gastric acid. Monkey hunting is reported to be quite bloody, however, and the hunters are likely to have chronic sores on their hands. Therefore, monkey hunting could present an excellent opportunity for the transmission of virus from sooty mangabeys to humans. It must be noted, however, that this theory is not yet proven.

Human Immunodeficiency Virus Type 2 Proteins

Despite the sequence divergence noted above, HIV-2 encodes largely the same gene products as HIV-1 (Figure 2). The exception is that whereas HIV-2 lacks the *vpu* gene of HIV-1, it encodes the *vpx* gene, which is not found in HIV-1. The *vpx* gene product appears to be necessary for efficient viral replication under certain circumstances (59-61). Other structural and regulatory genes of HIV-2 are very similar in function to those of HIV-1. Like all retroviruses, HIV-2 encodes *gag* (nucleocapsid), *pol* (polymerase), and *env* (envelope) genes. The *env* gene, which demonstrates considerable variation from isolate to isolate (54, 62-65), encodes the gp160/140 precursor of the gp120 outer membrane glycoprotein and the gp32-40 transmembrane glycoprotein. As is the case for HIV-1, gp120 binds the CD4 receptor of T cells, macrophages, and possibly other cells and is, therefore, one of the determinants of tissue tropism and pathogenicity (25, 64, 66-69). The *gag* gene encodes the p55 precursor of the nucleocapsid proteins p24-26 and p15 (17, 25, 70). The *pol* gene encodes p64 and p53, which make up the reverse transcriptase, p34 (integrase), and p11 (protease), the latter of which is essential for the processing of the *gag* and *pol* gene products (25, 71-73). The genes *gag* and *pol* are well conserved in HIV and SIV and account for most of the cross-reactivity seen in ELISA assays for HIV-1 (25). In

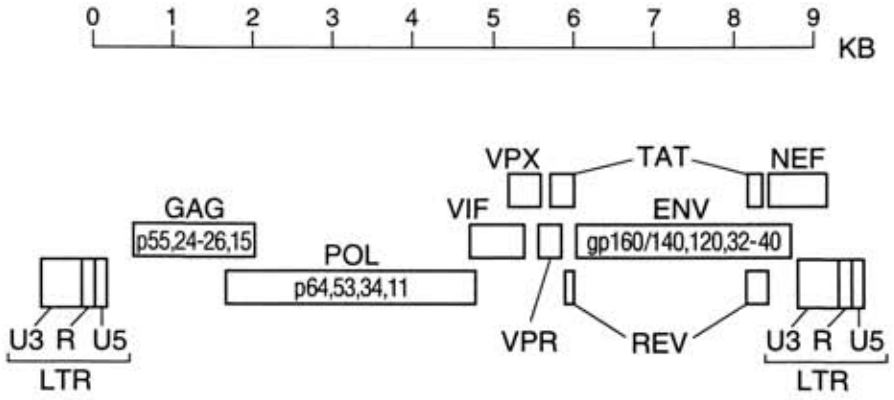

Figure 2. The HIV-2 genome. The enhancer/promoter region is located in the long terminal repeat (*LTR*). Major structural proteins encoded by *gag*, *pol*, and *env* are indicated. p55 is the precursor of the nucleocapsid proteins p24-26 and p15. gp160/140 is the glycoprotein precursor of the gp120 outer membrane and gp32-40 transmembrane envelope proteins. p64 and p53 make up the reverse transcriptase, p34 is the integrase, and p11, the protease. The products of the *vif*, *vpx*, *vpr*, *nef*, *tat*, and *rev* genes are described in the text. KB = kilobases.

addition to these three standard structural genes found in all retroviruses, HIV-2, as a member of the family of "complex retroviruses" (74), encodes several other genes that contribute to the sophisticated regulation of these relatively small viruses. In addition to *vpx*, HIV-2 encodes the *vif* gene that, by analogy to HIV-1, is likely to be an infectivity factor (75). The *nef* gene, originally thought (on the basis of tissue culture experiments) to encode a negative regulatory element, is now known to encode a protein that actually increases SIV (and presumably HIV-2) replication in vivo (76). The product of the *vpr* gene appears to be a virion-associated structural protein that has been shown to modestly increase HIV-1 replication (77-79). The tat protein of HIV-2, like that of HIV-1, acts in *trans* to stimulate viral production and, by analogy to HIV-1 (80), is assumed to be essential for viral replication. The tat proteins are unusual viral *trans*-activators in that their action is mediated through a site or sites downstream (3′) of the RNA start-site (81, 82). Although it is generally believed that the primary role of tat is to permit the elongation of properly initiated viral transcripts (anti-termination), the exact mechanism of action is still being actively investigated (83-88). Whereas the RNA target for HIV-1 tat has only one stem loop structure, the HIV-2 tat target sequence has two (81). However, it appears that the distal site may be used only when the proximal site cannot be used (89). In addition to tat, another regulatory protein with a complex mechanism of action, rev, is required for HIV replication (90). Rev acts through its RNA target in the *env* gene to increase the number of transcripts for the HIV structural genes found in the cytoplasm (91). Rev performs this function by increasing the transport of unspliced (structural gene) viral RNA from the nucleus or by regulating RNA splicing, or both (91-98). Although it is much less well studied, HIV-2 rev appears to function in a similar manner to HIV-1 rev (99).

Activation of Human Immunodeficiency Virus Type 2 by Cellular Factors: Implications for "Latency"

After T cells are infected by HIV, the virus may not replicate to any significant degree until the T cell has been activated (stimulated) by antigen or substances that mimic this effect (100-104). Although the idea that HIV is truly "latent" (nonreplicating) in asymptomatic patients appears to be an oversimplification, disease progression is clearly associated with significant increases in viral replication (105). Therefore, extensive research has gone into identifying viral regulatory elements and cellular proteins which, following T-cell activation, might "trigger" HIV to go from the relatively "latent" state to one of increased replication, with resultant illness. The period from initial infection until clinically apparent disease is considerably longer for HIV-2 than for HIV-1. Therefore, our group has examined the regulation of the HIV-2 transcriptional enhancer/promoter, located in the long terminal repeat (LTR) of the virus, by cellular factors in activated T cells. We and others have found that, consistent with the clinical differences, a different set of cellular proteins is involved in induction (stimulation) of the HIV-2 enhancer than with HIV-1 (101, 106-108). NF-κB, the dominant protein involved in stimulating the HIV-1 enhancer in activated T cells (102, 109), also plays a role in the induction of the HIV-2 enhancer (101). Even when the single binding site for NF-κB is intact, however, the HIV-2 enhancer cannot be induced by T-cell stimulation when two purine-rich sites upstream of κB, PuB1, and PuB2 are mutated (107, 110). Interestingly, both of these sites are responsive to stimulation of the T-cell receptor and bind the cellular protein Elf-1, a member of the *ets* proto-oncogene family, which is very similar to the Drosophila development factor E74 (107, 110-112). Therefore, it appears that closely related proteins, conserved over approximately 600 million years of evolution, probably participate in the regulation of the pathogenic human retrovirus HIV-2 and in the developmental regulation of fruit flies. Members of the *ets* family of proteins often require co-factors to activate transcription (113) and, in keeping with this motif, a site proximal to the PuB2 *ets* site (pets), which is essential to optimal enhancer function, appears to bind a distinct nuclear factor (107). As mutation of the κB, PuB1, PuB2, or pets site greatly affects enhancer induction in activated T cells (107), it appears that inducible enhancer function is more readily disrupted in HIV-2 than in HIV-1, perhaps offering a partial explanation for the differential pathogenesis of the two viruses.

Diagnosis of Human Immunodeficiency Virus Type 2 Infection

Diagnostic tests for HIV-2 have recently been reviewed (38). Infection with HIV-2 must be strongly

considered in patients who either come from endemic areas, particularly West Africa, or have sexual partners from those regions. Approximately 80% of HIV-2-infected patients will test positive with an HIV-1 ELISA (depending on the specific kit used) and Western blots are weakly cross-reactive (25, 114). Therefore, HIV-2 infection may be the cause of an indeterminate HIV-1 Western blot (115). Diagnosis is made more complicated by reports of dual infection with HIV-1 and HIV-2 in individual patients (116-118).

An HIV-2/HIV-1 combination ELISA and an HIV-2-specific ELISA (38, 119) are commercially available. Although most patients infected with HIV-1 seroconvert within 3 months, the interval to HIV-2 seroconversion has not yet been determined. Infection with HIV-2 is confirmed by Western blot, with World Health Organization (WHO) diagnostic criteria requiring the presence of two *env*-encoded proteins for specific diagnosis (25, 120). Unfortunately, HIV-2 Western blot kits are not well standardized from manufacturer to manufacturer, and none are FDA approved. Therefore, the WHO criteria may not always be appropriate. In addition, interpretation of Western blots is complicated by the great variability in the outer envelope protein (gp120) and the propensity of the transmembrane protein (gp32-40) to form oligomers that can then be confused with gp120 (121, 122). A synthetic peptide immunoassay may prove useful in making the diagnosis of HIV-2 infection in certain cases (123). In patients with equivocal serology (or those infected too recently to have seroconverted), the polymerase chain reaction (124, 125) might prove helpful in making the diagnosis of HIV-2 infection.

Counseling and Treatment of Infected Patients

Human immunodeficiency virus type 2 is sensitive to zidovudine and other nucleoside analogs in vitro (126-128), but it may be less susceptible than HIV-1 (128). Efficacy studies, particularly in asymptomatic patients, may prove difficult to perform because of the relatively long incubation period seen with HIV-2. By analogy to HIV-1, it appears appropriate to withhold antiretroviral therapy from asymptomatic patients with T4 counts greater than 500/mm^3 and to initiate therapy in patients with symptoms or fewer than 200 T4 cells/mm^3. For the asymptomatic patient with 200 to 500 T4 cells/mm^3, the divergent natural histories of HIV-2 and HIV-1 infection make it difficult to draw any conclusions concerning the efficacy of antiretroviral therapy. It should also be noted that the range of normal T4 counts is different in African and North American populations (46, 47), making extrapolation of data from West African patients to North American patients more difficult. In addition to reverse transcriptase, which is inhibited by the nucleoside analogs, the HIV-2 protease is a potential target for future antiretroviral therapy (71-73, 129). Treatment of opportunistic infections in HIV-2-infected patients is similar, although perhaps more effective, than in AIDS associated with HIV-1 (28). Although little effort has thus far been specifically spent on developing an HIV-2 vaccine, the fact that the closely related SIV is being used as a model for AIDS vaccines should increase the prospects for an HIV-2 vaccine (130, 131).

As HIV-2 spreads from West Africa, more physicians will be faced with counseling and caring for patients infected with this virus. Infection may be diagnosed in either the appropriate clinical setting or in asymptomatic prospective blood donors. Although the natural history of HIV-2 infection is not as well described as that of HIV-1, it seems likely that a more optimistic tenor can be adopted when counseling HIV-2-infected patients. As with an HIV-1-infected person, the patients must be cautioned to inform any prospective sexual partner of their status, use condoms, and avoid anal intercourse. They should also be counseled not to donate blood or participate in any activity that would expose others to their blood (sharing needles or razors, for example).

Conclusions

Infection with HIV-2 poses a serious concern in West Africa and is becoming recognized more frequently in other parts of the world. The recent decision to test the blood supply for HIV-2 should bring more infected patients to the attention of physicians in the United States. Although it is clear that HIV-2 can cause AIDS, the incubation period appears to be considerably longer than for HIV-1 and maternal-fetal transmission of HIV-2 appears to be limited. The natural history of HIV-2 infection will need to be studied further to assess more accurately the length of the asymptomatic period and the percentage of infected persons in whom AIDS or related syndromes eventually develop. Appropriate therapy for patients infected with HIV-2 has not been studied systematically. Further work must be done to determine whether the divergent mechanisms of transcriptional regulation seen with HIV-2 and HIV-1 contribute to the decreased pathogenicity of the former and whether these differences can be exploited therapeutically. The very close genetic relationship and similar geographic distribution seen with HIV-2 and SIV_{SM}, as well as a plausible mechanism of transmission, offers the strongest evidence to date that human immunodeficiency viruses may have been transmitted from monkeys to man. As HIV-2 infection is increasingly recognized throughout the world, further studies of the epidemiology, natural history, therapy, and biology of this complex human pathogen will be needed.

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