HIV-2 Infection

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Module 6: Key Populations
Lesson 8: HIV-2 Infection

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Background

Comparison of HIV-1 and HIV-2

Human immunodeficiency virus (HIV) is categorized into two main types: HIV-1 and HIV-2. Although HIV-1 and HIV-2 have the same routes of transmission and both can cause acquired immunodeficiency syndrome (AIDS), important differences exist between the viruses in terms of epidemiology, natural history, diagnosis, and management.[1,2] Compared with individuals with HIV-1, persons with HIV-2 typically have attenuated clinical progression and lower rates of sexual and perinatal HIV transmission.[3,4,5,6] Significant differences exist in the antiretroviral management of HIV-1 and HIV-2.[2] Clinicians should become familiar with the differences between these HIV infections and maintain a high index of suspicion for HIV-2 in persons from high-risk regions. In regions where HIV-2 circulates, individuals can become infected with both HIV-1 and HIV-2.[7]

HIV-2 Globally and in the United States

Among the estimated 37.9 million individuals with HIV worldwide as of 2018,[8] approximately 1 to 2 million have HIV-2.[1,9,10] Most persons infected with HIV-2 reside in West Africa, or in countries that have strong colonial or socioeconomic ties with West Africa, most notably France, Spain, and Portugal; HIV-2 has been reported in significant numbers in several former Portuguese colonies, including Angola, Mozambique, Brazil, and India (mainly in the states of Goa and Maharashtra and to a lesser degree in some southern regions).[1] During approximately the last two decades, HIV-2 prevalence has declined in several West African countries, but reasons for this are unclear.[11] In the United States, it is estimated that fewer than 1% of persons with HIV have HIV-2. The first case of HIV-2 in the United States was reported in 1987.[12] The vast majority of persons diagnosed with HIV-2 in the United States have emigrated from an HIV-2 endemic region, or had exposure to a person from an HIV-2 endemic region (Figure 1).[13] In addition, most of the reported cases of HIV-2 in the United States have been clustered in the northeast, as highlighted by a 2010 report that described 62 persons diagnosed with HIV-2 in New York City.[13,14] The reported number of HIV-2 infections may significantly underestimate the actual number of cases, due to unrecognized or undiagnosed infections.
Pathogenesis and Natural History of HIV-2

Pathogenesis and Transmission of HIV-2

Relative to HIV-1, HIV-2 is less virulent and is characterized by lower plasma HIV RNA levels, slower decline in CD4 cell counts, lower AIDS-related mortality rates, lower rates of perinatal transmission, and lower rates of sexual transmission.[2,6,11,15,16,17] For example, in West Africa, investigators prospectively followed 133 persons with HIV-2 who were not receiving antiretroviral therapy from 1991 through 2009 and found HIV-2 RNA levels remained consistently low, with 36 to 42% of the HIV-2 RNA levels falling in the range of less than 100 copies/mL.[18] This same study showed the rate of disease progression and mortality rates correlated with the baseline plasma HIV-2 RNA levels obtained in 1991: individuals with baseline HIV-2 RNA levels less than 100 copies/mL had very low mortality, similar to that in the general population in West Africa (Figure 2).[18] Other studies have observed that a large proportion of persons with HIV-2 do not experience progression to AIDS and many meet criteria as long-term nonprogressors or elite controllers.[19,20,21] The exact reasons for the diminished pathogenicity of HIV-2 remain incompletely defined, but both intrinsic viral factors and innate and adaptive immunity likely play important roles.[16] The small proportion of persons with HIV-2 who suffer immunologic decline develop similar opportunistic infections as individuals with HIV-1.[16] In natural history perinatal studies conducted in West Africa (in the pre-antiretroviral era), the rate of perinatal transmission of HIV-2 was significantly lower than for HIV-1, typically less than 5% versus approximately 25%.[15] Sexual transmission and genital shedding is also less efficient in persons with HIV-2.[5,22,23,24]

Effect of HIV-2 Coinfection on HIV-1 Progression

Limited data exist on the natural disease progression in persons with concomitant HIV-1 and HIV-2 infection; in West Africa, up to 15% (approximately) of individuals have dual infection, though the proportion of persons with HIV-2 monoinfection has decreased as the prevalence of HIV-2 has decreased.[16,25] Unfortunately, initial infection with HIV-2 does not appear to protect against subsequent HIV-1 acquisition, as was initially reported in a cohort of female sex workers in Dakar, Senegal.[17,26,27] One study suggested that persons with both HIV-1 and HIV-2 have slower disease progression and delayed death when compared with those who have HIV-1 alone, with the greatest benefit occurring when infection with HIV-2 precedes HIV-1 infection.[25] Other studies, including a robust meta-analysis, found no survival benefit in persons dually infected with HIV-1 and HIV-2 when compared with persons who have HIV-1 alone.[26,28]
2014 Surveillance Case Definition for HIV-2 Infection

In 2014, the Centers for Disease Control and Prevention released a Revised Surveillance Case Definition for HIV Infection that added specific criteria for defining a case of HIV-2, which was not part of the 2008 case definition.[29] To classify an adult as having HIV-2, one or more of the following laboratory criteria are necessary:

- FDA-approved HIV-1/HIV-2 type-differentiating antibody test result positive for HIV-2 and negative for HIV-1
- Positive HIV-2 Western blot result and negative or indeterminate HIV-1 Western blot result
- Positive qualitative HIV-2 nucleic acid test (NAT)
- Detectable quantitative HIV-2 NAT (viral load)
- Laboratory results interpreted as consistent with HIV-2 infection by a laboratory expert experienced in differentiating HIV-2 from HIV-1 if laboratory evidence for HIV-2 is ambiguous

In addition, the 2014 Revised Surveillance Case Definition for HIV Infection classifies an individual as having dual infection (with HIV-1 and HIV-2) if both an HIV-1 NAT and an HIV-2 NAT are positive.[29]
Diagnostic Testing for HIV-2

Approach to Diagnostic Testing for HIV-2

In CDC screening guidelines for HIV issued prior to 2014, specific HIV-2 testing was recommended only for persons with known HIV-2 risk factors.[30] With this older HIV testing algorithm, which utilized HIV enzyme immunoassay (EIA) as the screening test and HIV-1 Western blot as the confirmatory test, the diagnosis of HIV-2 was often missed because HIV EIA testing detects both HIV-1 and HIV-2, but does not distinguish between them; in addition, the traditional HIV-1 Western blot fails to detect HIV-2 (or it indicates an indeterminate or false positive result for HIV-1).[13,30,31] It is important to note that HIV-1 RNA and DNA assays do not reliably detect HIV-2.[1,31] Use of tests as recommended in the CDC and Association of Public Health Laboratories (APHL) HIV diagnostic algorithm can reliably detect HIV-2; the HIV-1/HIV-2 antigen-antibody test is the recommended initial test, followed by an HIV-1/HIV-2 differentiation immunoassay if the initial test is positive (Figure 3).[31,32] With use of the CDC-recommended testing algorithm, all persons undergoing HIV testing are thus tested for both HIV-1 and HIV-2.[31,32] In some circumstances, such as an indeterminate HIV-2 test on the HIV-1/HIV-2 differentiation immunoassay, HIV-2 NAT diagnostic testing is recommended.[33] Diagnostic HIV-2 qualitative testing is now available for diagnostic purposes through two laboratories: University of Washington Laboratory Medicine (HIV-2 DNA/RNA Qualitative) and the New York State Department of Health (HIV-2 Qualitative RNA Detection). It is important to recognize that about 40% of persons with HIV-2 who are not receiving antiretroviral therapy have undetectable HIV-2 RNA levels; for this reason, HIV-2 RNA viral load testing is not a reliable diagnostic test.[34,35,36]

Interpretation of Diagnostic Tests in HIV-2

- **Enzyme Immunoassay (EIA):** A person with HIV-2 will likely have a positive HIV enzyme immunoassay (EIA) regardless of which test is used because most, but not all, EIA tests detect both HIV-1 and HIV-2.[30] Commercially available EIAs do not generally differentiate between HIV-1 and HIV-2, although there is a specific HIV-2 EIA that is FDA-approved (Genetic Systems HIV-2 EIA).
- **Point-of-Care Tests:** Several point-of-care HIV tests are FDA-approved for the detection of HIV-2, including the OraQuick Advance Rapid HIV-1/2 Antibody Test, Clearview HIV 1/2 STAT-PAK, Clearview COMPLETE HIV 1/2, INSTI HIV-1/HIV-2 Rapid Antibody Test, Architect HIV Ag/Ab Combo Assay, and Alere Determine HIV-1/2 Ag/Ab. These point-of-care tests do not distinguish HIV-1 from HIV-2 infection.
- **Differentiation Assays for HIV-1/HIV-2:** In the United States, the Geenius HIV 1/2 Supplemental Assay, and BioPlex 2200 HIV Ag-Ab are FDA-approved for differentiating HIV-1 from HIV-2 infection.[37,38,39] The Geenius test can detect four antibodies to HIV-1 (p31, gp160, p24, and gp41) and two antibodies to HIV-2 (gp36 and gp140) (Figure 4).[37,40] The CDC recommended algorithm for HIV testing utilizes the HIV-1/HIV-2 differentiation assay as the second step in the algorithm.[31] The CDC has issued a technical update on HIV-1/HIV-2 differentiation assays that provide guidance for three results that may occur in the Geenius assay that were not previously seen with the Multispot HIV differentiation assay: HIV-2 positive with HIV-1 cross reactivity, HIV-2 indeterminate, and HIV indeterminate.[33] If the result is HIV-2 positive with HIV-1 cross reactivity, the CDC recommends considering this result as positive for HIV-2 infection. For specimens with a result of HIV-2 indeterminate or HIV indeterminate results, additional testing is required (often including HIV-2 nucleic acid testing) and guidance in the technical update should be followed carefully; ideally, expert consultation is obtained in this setting.
- **HIV Western Blot:** The HIV Western blot is no longer routinely used for HIV diagnosis and is not recommended in the CDC HIV testing algorithm. Infection with HIV-2 may cause a negative, indeterminate, or positive HIV-1 Western blot due to cross-reacting antibodies. Persons with HIV-2 infection often have an indeterminate HIV-1 Western blot pattern, with the presence of Gag bands (p55, p24, or p17) and Pol bands (p66, p51, or p31), but absence of Env bands (gp160, gp120, or gp41) (Figure 5).[1,14] The Western blot pattern in persons with HIV-2 occurs because HIV-1 and HIV-2 have 60% similarity in the regions encoding gag and pol, compared with only 30 to 40% similarity in the region encoding env.[41] In the United States, HIV-2 Western blot tests are not FDA-
approved but some HIV-2 supplemental HIV-2 antibody tests are commercially available through reference laboratories.[1]

- **Qualitative Plasma HIV-2 RNA:** An HIV-2 nucleic acid test is typically utilized to confirm a positive HIV-2 differentiation assay or to provide additional information in the setting of an indeterminate result on the HIV Geenius differentiation assay. A positive qualitative HIV-2 RNA will confirm a diagnosis of HIV-2. A negative HIV-2 plasma RNA test, however, does not rule out HIV-2, since approximately 40% of persons with untreated chronic HIV-2 have undetectable plasma HIV-2 RNA levels.[34,35,36] To address this issue, investigators have developed a qualitative assay that detects HIV-2 total nucleic acid in patient peripheral blood mononuclear cells; this assay can detect HIV-2 DNA and RNA in persons with HIV-2 who have undetectable plasma HIV-2 RNA levels.[42]

**Quantitative HIV-2 RNA Testing**

The HIV-1 nucleic acid amplification tests (NAAT) do not reliably detect or quantitate HIV-2. Quantitative HIV-2 RNA viral load assays for monitoring response to therapy are available through the University of Washington Laboratory Medicine (HIV-2 RNA Quantitation) and the New York State Department of Health (HIV-2 Quantification).[2]
Antiretroviral Susceptibility and Resistance

The following summarizes what is known related to HIV-2 susceptibility and resistance to medications in specific antiretroviral medication classes.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

In general, nucleoside reverse transcriptase inhibitors (NRTIs) are active against HIV-2, but due to naturally occurring polymorphisms in HIV-2, may have less activity and a lower genetic barrier of resistance to HIV-2 than to HIV-1.\[43]\ \[44]\ Although HIV-1 and HIV-2 share some classic NRTI resistance mutations, such as the M184V mutation, which causes high-level resistance to lamivudine and emtricitabine, HIV-2 often follows different resistance pathways than HIV-1. For example, HIV-2 resistance to zidovudine occurs through the Q151M mutation rather than through the common thymidine analog mutation (TAM) pathways typically observed with HIV-1.\[44]\ Studies have produced conflicting results regarding the frequency of the K65R mutation in HIV-2 and its impact on susceptibility to tenofovir and abacavir.\[43,45,46]\ Available data suggest the development of the Q151M mutation in combination with a K65R or M184V mutation results in resistance to zidovudine, lamivudine, and emtricitabine; the presence of all three mutations together causes broad NRTI class resistance.\[47]\ 

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Multiple studies have shown that HIV-2 has intrinsic resistance to non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs.\[43,48]\ This intrinsic resistance occurs because the Y181I and Y188L substitutions are natural polymorphisms present in HIV-2 strains and these mutations alter the NNRTI binding pocket in the reverse transcriptase enzyme, rendering it less receptive to NNRTI medications.\[49]\ 

Integrase Strand Transfer Inhibitors (INSTIs)

Accumulating evidence suggests INSTIs usually have activity against HIV-2.\[2,50,51]\ The resistance that affects susceptibility of HIV-2 to INSTIs shares some similarities with those of HIV-1, though some key differences exist.\[52,53,54]\ For example, the integrase mutations N155H or Q148R confer resistance to raltegravir in both HIV-2 and HIV-1, but for HIV-2 the Y143 pathway requires secondary mutations to cause significant resistance (contrary to what is observed with HIV-1).\[52]\ Elvitegravir has activity against HIV-2 and, as in HIV-1, there is a high degree of cross-resistance between raltegravir and elvitegravir.\[51]\ As seen with HIV-1, raltegravir and elvitegravir have a relatively low barrier to resistance to HIV-2, perhaps even lower with HIV-2 than with HIV-1 due to intrinsic polymorphisms at secondary integrase sites.\[55]\ Dolutegravir has in vitro activity against HIV-2, and a small study has shown modest efficacy with dolutegravir in persons with HIV-2 who had resistance to first-generation INSTI.\[56]\ A recent study revealed a new resistance pathway of HIV-2 to INSTIs that involves a 5-amino acid insertion at codon 231 of the HIV-2 integrase, which is a region in the integrase C-terminal domain.\[57]\ This insertion mutation results in high-level resistance to elvitegravir and raltegravir and moderate-level resistance to dolutegravir.\[57]\ Resistance to bictegravir was observed in several isolates, but overall it retained the most potent INSTI in isolates with the codon 231 insertion mutation (231INS).\[57]\ 

Protease Inhibitors

Several studies have reported that HIV-2 has inherent partial or full resistance to some protease inhibitors, with only lopinavir-ritonavir, darunavir, and saquinavir having clinically useful activity against HIV-2.\[43,58,59,60,61]\ Investigators have identified four residues at amino acid positions—32, 47, 76, and 82—in the protease binding cleft that differ between HIV-2 and HIV-1 and predict protease inhibitor sensitivity; changes at these four amino acids can confer class-wide resistance to PIs.\[62]\ Studies have shown that fewer HIV protease mutations are necessary for resistance to develop in HIV-2 compared with HIV-1. Due to innate polymorphisms, a lower number of mutations are required for HIV-2 to become
resistant to PIs as compared to HIV-1. Similar to treatment for HIV-1, if a protease inhibitor is used to treat HIV-2, boosting with ritonavir or cobicistat is recommended. Based on available data, the recommended protease inhibitor-based regimens for HIV-2 consist of boosted darunavir, lopinavir, or saquinavir, in combination with two NRTIs.[2] Notably, atazanavir is not recommended for the treatment of HIV-2.

**Fusion Inhibitors**

In vitro data have shown HIV-2 has intrinsic resistance to the fusion inhibitor, enfuvirtide.[48] Resistance to enfuvirtide correlates with genetic diversity at the target regions for the drug, namely the HR1 domain of the viral gp41 region.[63]

**CCR5 Inhibitor**

The efficacy of the CCR5 inhibitor, maraviroc, is uncertain since HIV-2 can use several different co-receptors to enter cells, and there is no commercial HIV-2 co-receptor tropism screening assay that would determine whether the patient has pure CCR5-tropic HIV-2.[1,2,64,65]
HIV-2 Treatment Studies

Clinical Trials for the Treatment of HIV-2

There are limited data from clinical trials that inform guidance on the optimal timing or regimen for initial antiretroviral therapy of persons with HIV-2, though several clinical trials are in progress, including a trial comparing tenofovir DF-emtricitabine plus raltegravir versus tenofovir DF-emtricitabine plus lopinavir-ritonavir. The lack of data on HIV-2 treatment is due to a combination of factors, including the low prevalence of HIV-2 (especially in the United States and Europe) and the lower virulence of HIV-2 compared with HIV-1, which has made investigation of antiretroviral therapy for HIV-2 less of a priority than for those with HIV-1.[1]

Observational Studies and In Vitro Data

Up to this point, most of the data on HIV-2 treatment have come from small observational studies.[66] A case series involving 5 patients with HIV-2 reported very good virologic and CD4 treatment responses with a raltegravir-based regimen.[50] Similar promising preliminary results were seen in a pilot trial of raltegravir plus tenofovir DF-emtricitabine.[67] There are no clinical data on the use of bictegravir-tenofovir alafenamide-emtricitabine for the treatment of HIV-2, but in vitro data suggest that HIV-2 is highly sensitive to bictegravir.[68] One case report and data from one clinical trial have shown favorable results with cobicistat-boosted elvitegravir (in a single tablet regimen of elvitegravir-cobicistat-emtricitabine-tenofovir DF).[51,69]
HIV-2 Treatment Recommendations

Timing of Initiating Antiretroviral Therapy with HIV-2

Although individuals with HIV-2 generally have a slower disease progression than persons with HIV-1, they generally have a less robust CD4 count increase in response to antiretroviral treatment.\[66,70,71,72\] This poor CD4 cell count response to antiretroviral therapy in persons with HIV-2 suggests that persons with HIV-2 should start antiretroviral therapy without delay. In addition, early treatment of HIV-2, in theory, would reduce transmission of HIV-2 to others.

**Recommendation:** The Adult and Adolescent ARV Guidelines recommend starting antiretroviral therapy at or soon after HIV-2 diagnosis to prevent disease progression and transmission of HIV-2 to others.\[2\]

Recommended Antiretroviral Regimens for Treatment of HIV-2

Based on experience with the treatment of HIV-1, a three-drug antiretroviral regimen should be used to treat HIV-2 in order to maintain viral suppression and to avoid development of resistance from suboptimal therapy. Since resistance testing is not commercially available for HIV-2, baseline resistance testing is not an option to guide initial therapy. Transmitted HIV-2 drug resistance has been reported, but to date, appears to be rare.\[73,74\]

**Recommendation:** The Adult and Adolescent ARV Guidelines recommend treating persons with HIV-2 using two NRTIs in combination with an INSTI (bictegravir, dolutegravir, elvitegravir, or raltegravir).\[2\] The alternative regimen is two NRTIs plus a boosted protease inhibitor (darunavir or lopinavir) active against HIV-2.\[2,72,75\] The NNRTIs should not be used to treat HIV-2.\[2\]

Treatment of Persons with HIV-1 and HIV-2 Dual Infection

Individuals with HIV-1 and HIV-2 coinfection should undergo baseline genotypic resistance testing for HIV-1; resistance testing for HIV-2 is not commercially available in the United States.\[2,75\] In this setting, if possible, monitoring of both HIV-1 and HIV-2 plasma RNA levels should be performed.\[76,77\]

**Recommendation:** The Adult and Adolescent ARV Guidelines recommend treatment of persons with HIV-1 and HIV-2 coinfection with 2 NRTIs in combination with an INSTI, even if the baseline HIV-2 plasma viral load is low or undetectable.\[2\] All of the preferred regimens in the Adult and Adolescent ARV Guidelines for the treatment of HIV-1 have good activity against both HIV-1 and HIV-2.\[2\]

Clinical follow-up and Laboratory Monitoring for HIV-2

Until further HIV-2 treatment data are available, clinicians should follow recommendations for HIV-1 clinical management and HIV primary care, including opportunistic infection prophylaxis and laboratory monitoring on antiretroviral therapy.\[2\] Traditionally, because of limited availability of HIV-2 RNA assays, response to antiretroviral therapy in most individuals with HIV-2 has been gauged only by regular clinical monitoring and repeated CD4 cell count monitoring. Since several laboratories are now capable of performing quantitative HIV-2 RNA levels, the management of persons with HIV-2 on antiretroviral therapy should include routine monitoring of quantitative HIV-2 levels, similar to what is done for persons with HIV-1.
Summary Points

- Compared with HIV-1, HIV-2 is a less virulent and less transmissible virus.
- Infection with HIV-2 should be considered in persons with risk factors for HIV-2 acquisition and in persons with a clinical illness (such as an AIDS-associated opportunistic infection) that suggests HIV infection but in whom testing for HIV-1 is negative.
- Use of the CDC and APHL HIV diagnostic testing algorithm (1) detects HIV-1 and HIV-2 infection in the initial screening test and (2) distinguishes HIV-1 and HIV-2 with the HIV differentiation assay used in the second step. A positive HIV-2 qualitative RNA or DNA confirms infection, but HIV-2 RNA alone is not reliable to rule out infection since approximately 40% of persons with HIV-2 have undetectable HIV-2 RNA levels.
- Persons with HIV-2 have poorer CD4 cell count responses to antiretroviral treatment relative to persons with HIV-1, so early diagnosis and early initiation of therapy for HIV-2 should be emphasized.
- HIV-2 has intrinsic resistance to all NNRTI drugs, some PIs, and to the fusion inhibitor, enfuvirtide.
- HIV-2 is generally susceptible to NRTIs, INSTIs, and certain PIs, although naturally occurring polymorphisms may result in a lower genetic barrier to resistance for HIV-2 than to HIV-1. Among the protease inhibitors, lopinavir and darunavir have the best activity against HIV-2.
- The preferred antiretroviral treatment of HIV-2 infection is two NRTIs plus an INSTI. The alternative regimen is two NRTIs plus a boosted PI (darunavir or lopinavir).
- Individuals with HIV-1 and HIV-2 coinfection should receive an antiretroviral regimen that can effectively treat both viruses, ideally two NRTIs plus an INSTI.
- In the event of clinical or virologic failure on antiretroviral therapy, consultation with an expert in HIV-2 management is recommended.
- Laboratory diagnostics for HIV-2 are available through two laboratories: University of Washington Laboratory Medicine (HIV-2 DNA/RNA Qualitative and RNA Quantitative) and the New York State Department of Health (HIV-2 RNA Qualitative and Quantitative).
Citations


8. UNAIDS. HIV/AIDS. Data and statistics: 2018. [UNAIDS]


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HIV-1 and can this explain the distinct natural history of infection with these two human retroviruses? Immunol Lett. 2015;163:69-75. [PubMed Abstract] -


Figures

Figure 1 Number (N = 164*) and percentage of persons receiving diagnoses of HIV-2 infection, by country of birth—United States, 1987-2009

A total 164 cases of HIV-2 were included in this analysis.

Figure 2 Association Between Baseline HIV-2 RNA Levels and Mortality Over an 18-Year Follow-Up Among Persons Living with HIV-2

In this study, 138 individuals diagnosed with HIV-2 in a rural West African village had plasma HIV-2 RNA levels measured in 1991 and investigators tracked mortality over an 18-year period. The group that had a baseline HIV-2 RNA level less than 100 copies/mL had a very low mortality rate 18 years later, similar to that of the general population in West Africa.

Figure 3 2018 CDC AHPL Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens

This graphic shows the HIV testing algorithm as recommended in 2014 and updated in 2018 by the Centers for Disease Control and Prevention and Association of Public Health Laboratories.

Figure 4 Geenius HIV-1/HIV-2 Supplemental Assay

The Geenius HIV-1/HIV-2 Supplemental Assay is a single-use immunochromatographic test that utilizes multiple recombinant or synthetic peptides to detect HIV-1 and HIV-2. Note the HIV-2 antibodies detected include gp36 and gp140 (marked by yellow color).

**Figure 5 HIV-1 and HIV-2 Gene Products, Proteins, and Glycoproteins**

Note the differences between some of the HIV-1 and HIV-2 proteins; this difference explains why HIV-1 Western blot tests fail to detect HIV-2 infection or give an indeterminate result.

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