CULTURAL COMPETENCY FOR CLINICIANS WORKING WITH LESBIAN, GAY, BISEXUAL, AND TRANSGENDER PATIENTS

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Hi, I'm Dr. Ritu Pati, Director of Research and Attending Physician with the Spencer Cox Center for Health at St. Luke's and Roosevelt hospitals in New York City. Thank you for viewing the New York State Department of Health Clinical Education Initiative video on HIV-2. The guidelines presented in this video are based on guidelines from the New York State Department of Health AIDS Institute, updated as of May, 2013.

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In this video, I'll provide an introduction to HIV-2 in the United States, discuss HIV-2 screening and diagnosis as well as monitoring and treatment, and review HIV-1 and HIV-2 co-infection.

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Since HIV-2 is endemic to West Africa, it is no surprise that most diagnoses in the United States are made in persons from West Africa or from countries with colonial ties to West Africa like France and Portugal.

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HIV-2 is rarely diagnosed in the United States. The Centers for Disease Control and Prevention reported that 166 cases met the CDC case definition of HIV-2 infection from 1988 to June, 2010. As of December, 31 2012, New York City had 124 confirmed cases. 95 percent were born in Africa. HIV-1 and HIV-2 are closely related retroviruses of the same genus lentiviridae. Both are considered to have arisen from the introduction of simian immunodeficiency virus, or SIV, into the human population. HIV-1 and HIV-2 share the same modes of transmission but HIV-2 replicates and evolves more slowly than HIV-1.

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Though the majority of HIV-2 patients do not have progressive disease, HIV-2 can cause AIDS and HIV-2 infected patients with AIDS have the same signs, symptoms, and opportunistic infections as are seen in patients with HIV-1-associated AIDS. There are a host of challenges associated with the diagnosis and treatment of HIV-2.

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HIV-2 may be underreported because antibody cross reactivity frequently results in misdiagnosis of HIV-2 as HIV-1 infection. It is important to diagnose HIV-2 infection accurately, not only for public health monitoring but also because the choice of combination antiretroviral therapy for HIV-2 differs from that of HIV-1.

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HIV-2 infected individuals with progressive disease are less likely to respond as predictably to treatment as patients with HIV-1 infection. Until now, it has been difficult to monitor virologic response to
treatment because there have been no commercially available HIV-2 viral load assays. However, HIV-2 DNA PCR and HIV-2 viral load testing are available through the New York State Department of Health Wadsworth Institute laboratory of blood borne diseases.

Please refer to the PDF accompanying this video titled "New York City and State Public Health Laboratories and Help Lines" to contact the New York City Department of Health and Mental Hygiene to arrange for HIV-2 viral load testing.

In contrast to the detailed knowledge base for the management of HIV-1, no clinical trials have been conducted to guide decision making in the management of HIV-2. Studies of immunologic responses to combination antiretroviral therapy have demonstrated higher increases in CD4 cell counts in HIV-1 infected patients compared with HIV-2 infected patients after initiation of therapy. These factors, along with a lack of expertise in the area of HIV-1 and HIV-2 co-infection, contribute to the treatment challenges associated with HIV-2. The recommendations provided in this section are based on the opinions of the members of New York State Department of Health Medical Criteria Committee.

All specimens submitted for HIV testing should be screened by an enzyme immuno assay that detects antibodies to HIV-1, HIV-1 Group O, and HIV-2. All laboratories that perform HIV diagnostic testing, particularly those in areas known to have HIV-2 diagnoses or West African immigrant populations, should incorporate algorithms for differentiation of HIV-1 from HIV-2 in samples that are repeatedly reactive on screening. When HIV-1/HIV-2 combination screening yields a reactive result but is followed by an indeterminate or non-reactive HIV 1 western blot, clinicians should do the following: obtain a plasma HIV RNA assay to exclude acute HIV-1 infection. If acute HIV-1 infection has been excluded, test for HIV-2 antibodies using an FDA-approved HIV-1/HIV-2 type differentiating immunoassay. Currently, the only FDA-approved differentiation assay licensed in the U.S. is the bio Bio-Rad Multispot HIV-1/HIV-2 rapid test but others may be on the horizon. Consider specimens positive for HIV-2 if they are repeatedly reactive on an HIV-1/HIV-2 screening test and reactive for HIV-2 antibodies on the HIV-1/HIV-2 differentiation test. In order to determine whether a type differentiating immunoassay is indicated, providers should reevaluate the patient’s potential exposure to HIV-2 such as in this case, which occurred at a New York City hospital.

A 51-year-old black male presented to a major New York City hospital with altered mental status, dizziness, and confusion. He had no fever and denied any history of seizures, cough, and recent weight loss. The differential diagnosis included CVA, viral encephalitis, CNS lymphoma, CNS toxoplasmosis, cryptococcal and TB meningitis, brain abscess, PML, AIDS dementia complex, vacuolar myelopathy, and progressive radiculopathy. The labs were positive for Epstein-Barr virus, Hepatitis A, and Hepatitis B antibodies. The HIV Western Blot Test was indeterminate and the ELISA was non-reactive. An MRI revealed two focal lesions and white matter edema. The patient was diagnosed with CNS toxoplasmosis
and started treatment with pyrimethamine, sulfadiazine, and leucovorin. HIV was reconsidered after considerable discussion between neurologists and infectious disease experts as to the underlying causes of the toxoplasmosis. The HIV Western Blot was repeated and again indeterminate. The CD4 count was 32. Two weeks later, the HIV-1 viral load was undetectable and the CD4 was 20. After another two weeks, the HIV-1 viral load was repeated and again undetectable. The CD4 count was 27. Amid the frustrated deliberations between the attending and consult services as to the correct diagnosis, a determined first year infectious disease fellow assisting with the case finally asked the one question that no one had: where is the patient from? It was discovered that the patient was born in the Ivory Coast and lived in France 10 years prior to his arrival in the United States.

This case illustrates some of the challenges associated with diagnosis of HIV-2. In retrospect, the clinicians should have placed HIV-2 in the differential diagnosis because of the patient’s origin from an endemic region, his typical clinical presentation, immunodepletion, undetectable HIV-1 viral load, and equivocal HIV-1 antibody results. Medical providers who are knowledgeable of the usual course of HIV-2 infection might have dismissed it in this patient because the overwhelming majority of HIV-2 infected persons do not have progressive illness. Whereas this patient presented with severe immunodepletion and opportunistic infection. Nevertheless, HIV-2 can progress to AIDS and does so in approximately 15 percent of infected individuals. Any equivocal HIV-1 antibody test result in a person with immunologic deterioration in the context of an undetectable HIV-1 viral load should raise suspicion of HI-2, especially in a person from West Africa or a country with colonial ties to West Africa.

Clinicians should HIV-1/HIV-2 type differentiating amino assays and nucleic acid testing protocols when screening for HIV in patients who: originated from or traveled to an HIV-2 endemic area; received medical care, injections, immunizations, phlebotomy, surgery, or blood products or participated in vaccine trials in an HIV-2 endemic area; had sexual or needle sharing contact with persons who are infected with HIV-2 or are from an HIV-2 endemic area; were born to a mother with HIV-2 infection; had opportunistic infections or other clinical symptoms of HIV/AIDS but tested negative or indeterminate for HIV-1; received multiple HIV-1 indeterminate antibody test results; or have a confirmed diagnosis of HIV-1 but an undetectable viral load that is incompatible with the clinical or immunological status.

And alternative HIV diagnostic algorithm has been proposed that uses fourth generation combination antigen antibody testing to screen for HIV followed by a supplemental confirmatory test that differentiates between HIV-1 and HIV-2 antibodies.

This differentiating test called the Bio-Rad Multispot rapid HIV-1/HIV-2 type differentiation immunoassay would take the place of the traditional Western Blot test. With this new algorithm, a sample that is repeatedly reactive on an HIV-1/HIV-2 screening test and reactive for only HIV-2 antibodies on the HIV-1/HIV-2 type differentiating immunoassay would be considered positive for HIV-2
infection. An HIV-2 RNA or DNA detection test may be obtained for further confirmation such as in cases where there are equivocal results or there is antibody reactivity to both viruses. In cases where HIV-1 or HIV-2 antibodies are not detected by the type differentiating immunoassay, it is imperative that the laboratory perform a nucleic acid test for HIV-1 RNA to rule out acute HIV-1 infection.

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If the original sample has been exhausted, laboratories must follow up with clinicians to obtain a second specimen as soon as possible.

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For more information on HIV testing, diagnosis, and differentiating between HIV-1 and HIV-2, see the PDF accompanying this video titled "New York City Department of Health 2009 Health Advisory FAQs on HIV-2.

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Or contact one of the public health laboratories listed in the PDF titled "New York City and State Public Health Laboratories and Help Lines."

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All New York State public health laboratories and all major commercial laboratories now perform screening for antibodies to HIV-1 group M, HIV-1 group O, and HIV-2. And many are already using fourth generation combination HIV-1 antigen and HIV-1 and 2 antibody screening. Most of the FDA-approved clinical laboratory improvement amendment or CLIA-waived HIV rapid tests also detect HIV-1 and HIV-2 antibodies. A limited number of laboratories offer in-house HIV-2 western blot tests. HIV-2 western blots in use in the US have not received FDA approval and interpretation of results is complicated by the absence of standardized procedures and algorithms and by the failure of most laboratories to do side by side comparisons of HIV-1 and HIV-2 Western Blots. There is significant cross reactivity between HIV-1 and HIV-2 antibodies so differential diagnoses can be challenging.

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The New York City Department of Health and Mental Hygiene offers a comprehensive diagnostic algorithm that differentiates between HIV-1 and HIV-2 and can confirm or rule out HIV-2 diagnoses through a combination of tests that detect antibody and viral antigen.

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Please contact the New York City Department of Health and Mental Hygiene for assistance with differential diagnosis of HIV-2.

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For additional information regarding HIV-1/HIV-2 combination rapid tests, please refer to the PDF titled "Diagnostic Monitoring and Resistance Laboratory Tests for HIV: Characteristics of FDA-Approved Rapid HIV Tests."
Monitoring of HIV-2 infection can be challenging. Until recently, CD4 count was the most readily available laboratory means for monitoring disease progression in HIV-2 infected patients. Commercially available HIV-1 viral load assays do not detect or quantify HIV-2. CLEP-approved HIV-2 viral load testing is now available through the New York State Department of Health Wadsworth Institute laboratory of blood borne diseases.

Please contact the New York City Department of Health and Mental Hygiene to arrange for specimen collection, pickup, and transfer to The New York State Wadsworth Institute.

For more information or to contact the Wadsworth Laboratory, access the PDF titled "New York City and State Public Health Laboratories and Help Lines." The steering methods and interpretation protocols that are used to monitor combination antiretroviral therapy for HIV-1 infected patients do not apply to HIV-2 infection.

Antiretroviral therapy for HIV-2 differs in important ways from treatment for HIV-1. Clinicians should note that even in advanced HIV-2 disease, viral loads tend to be lower than in HIV-1. Nonetheless, virologic response to antiretroviral therapy can be less successful than that seen with HIV-1. Furthermore, CD4 response treatment can be slower than HIV-1 and less robust.

The following factors should be considered when deciding whether or not to initiate treatment in HIV-2 infected patients. The majority of HIV-2 infected patients are long-term nonprogressors. While type HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors, or NNRTIs, NNRTIs should not be used in any combination antiretroviral regimen for HIV-2 infection. Pathways for the development of drug mutations and resistance barriers differ between the two viruses. Data have shown a significant reduction in HIV-1 transmission risk between serodiscordant heterosexual couples when the positive partner was receiving combination therapy. Similarly, lower viral load level may also reduce HIV-2 transmission risk.

However, patients with HIV-2 who do not have progressive disease generally have very low, if not undetectable, viral loads in the absence of treatment.

Refer to the PDF titled "Efficacy of Antiretroviral Therapy Against HIV-2 Infection" for more information.
When prescribing combination antiretroviral therapy for HIV-2 infection, clinicians should include two nucleosite reverse transcriptase inhibitors, or NRTIs, and ritonovir-boosted protease inhibitor, or PI, such as lopinavir, saquinavir, or darunavir or consider using cobicistat.

Clinicians should not prescribe NNRTIs or the protease inhibitors nelfinavir, atazanavir, amprenavir, or fosamprenavir as part of a combination antiretroviral regimen against HIV-2. The addition of an integrase strand transfer inhibitor, such as raltegravir, has been shown to improve virologic response in some patients in New York City. It is also possible that the new agent cobicistat will be an effective booster for PI therapy against HIV-2. Finally, clinicians should use caution in decisions to prescribe maraviroc.

Since HIV-2 uses either R5 or X4 code receptors to enter the host cell, the trofile assay does not apply to HIV-2 and HIV-2 may not respond to a CCR5 blocker. In view of the absence of established guidance on treatment for HIV-2, medical providers should review the risks and benefits of the available treatment options and work with their patients to make decision on whether and when to initiate treatment. Clinicians should consult with a provider with experience in the management of HIV-2 before initiating antiretroviral therapy in HIV-2 infected patients.

Please see the PDF titled "New York City and State Public Health Laboratories and Help Lines" for relevant contact information.

HIV-1/HIV-2 co-infection has been reported in the U.S. Among the 166 cases of HIV-2 reported by the CDC, 19 patients, or 11 percent, tested positive for possible HIV-1/HIV-2 co-infection.

Mortality appears to be higher among HIV-1/HIV-2 co-infected individuals than HIV-1 mono-infected individuals but this may be dependent on which infection occurred first. Over time, HIV-1 seems to outcompete HIV-2 as the primary virus behind disease progression in co-infected persons. Data also suggest that the mortality associated with HIV-1/HIV-2 co-infection is dependent on CD4 count and is higher than in HIV-2 mono-infected individuals matched for disease stage. HIV-1/HIV-2 co-infection is difficult to diagnose due to the cross reactivity of antibodies as well as viral antigens, making treatment decisions based on co-infection difficult to determine. To confirm a suspected dual diagnosis, it is best to perform genotyping at a specialty laboratory that can sequence and compare the two viruses.

Contact the New York City Department of Health and Mental Hygiene to arrange for this testing.
Thank you for watching this important update. With proper guidance and support from the New York State Department of Health, providers can feel more comfortable and confident engaging and providing care for persons with HIV-2.

For more information on each of you to please refer to the PDF accompanying this video titled "HIV-2 Guidelines."

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