Perspectives CME

Clinically Significant Drug-Drug Interactions Between Hepatitis C Virus and HIV Treatments
Jennifer J. Kiser, PharmD

HCV Regimens in an Individual on Stable Antiretroviral Therapy • Other Drug-Drug Interactions

Sexually Transmitted Infections in the Context of HIV Disease: Clinical Implications
Dana W. Dunne, MD, FACP

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Topics in Antiviral Medicine is published 4 to 6 times a year. To obtain a subscription or notify the IAS–USA of a change in address, please create or update your user profile at www.iasusa.org.

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Website: http://www.iasusa.org

On the Web
Current and previous issues of Topics in Antiviral Medicine (as well as Topics in HIV Medicine) are available online at www.iasusa.org/pub.

ISSN 2161-5861 (Print)
ISSN 2161-5853 (Online)

Printed in USA on acid-free paper
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Grant Support
IAS–USA funding comes from a variety of sources. The largest single source of revenue is conference and participant registration fees.

This activity is part of the IAS–USA national educational effort that is funded, in part, by charitable contributions from commercial companies. Per IAS–USA policy, any effort that uses commercial grants must receive grants from several companies with competing products. Funds are pooled and distributed to activities at the sole discretion of the IAS–USA. Grantors have no input into any activity, including its content, development, or selection of topics or speakers.
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- Describe treatment and screening for sexually transmitted infections in the context of HIV disease
- Describe the elements of the HIV care continuum and strategies to improve engagement in care for HIV-infected individuals

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This enduring material is designed for physicians and other health care practitioners who are actively involved in the medical care of people with HIV or HCV infection.

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Financial affiliations with commercial entities: Dr Kiser has received research support awarded to the University of Colorado from Janssen Therapeutics and Viiv Healthcare. Her spouse has served on a speakers bureau for Astellas Pharma, Inc. Dr Dunne has no relevant financial affiliations to disclose. Dr Mugavero has served on advisory boards for Bristol-Myers Squibb, Gilead Sciences, Inc, and Janssen Therapeutics, and as a consultant or an advisor to Abt Associates, Gilead Sciences, Inc, and Merck & Co, Inc. Dr Richman has been a consultant to Antiva Biosciences, Chimerix, Gilead Sciences, Inc, and Monogram Biosciences, Inc.

Dr Benson serves on a data and safety monitoring board for Glaxo-SmithKline/Viiv Healthcare. She has received research grants awarded to her institution from AbbVie, Gilead Sciences, Inc, and Viiv Healthcare. Her spouse, Robert T. Schooley, MD, was awarded research grants, paid to his institution, from Boehringer Ingelheim Pharmaceuticals, Inc, and Bristol-Myers Squibb. Dr Hirsch has no relevant financial affiliations to disclose. Ms Jacobsen has no relevant financial affiliations to disclose.

Grant Support

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Independent educational grants for the 2016 Improving the Management of HIV Disease® CME program:

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Presenters: Harjot K. Singh, MD, ScM, Weill Cornell Medicine; Eugenia L. Siegler, MD, Weill Cornell Medicine—November 15, 2016

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New York, New York
- Full-Day HIV Course—February 24, 2017
- Half-Day HCV Workshop—Date to be confirmed (TBC)

Atlanta, Georgia
- Half-Day HCV Workshop—Date TBC
- Full-Day HIV Course—Date TBC

Los Angeles, California
- Half-Day HCV Workshop—Date TBC
- Full-Day HIV Course—Date TBC

Chicago, Illinois
- Half-Day HCV Workshop—Date TBC
- Full-Day HIV Course—Date TBC

Washington, DC
- Half-Day HCV Workshop—Date TBC
- Full-Day HIV Course—Date TBC

San Francisco, California
- Half-Day HCV Workshop—Date TBC
- Full-Day HIV Course—Date TBC

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Pneumocystis jirovecii Pneumonia in the HIV-Infected Patient
Authors: Anuradha Ganesan, MBBS, MPH, Uniformed Services University of the Health Sciences; Marc Siegel, MD, George Washington University School of Medicine; Henry Masur, MD, George Washington University School of Medicine

Initial Antiretroviral Therapy in the HIV-Infected Patient
Authors: Jameela J. Yusuff, MD, MPH, FACP, State University of New York; Katharine Kuntz, MD, State University of New York

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**Perspective**

Clinically Significant Drug-Drug Interactions Between Hepatitis C Virus and HIV Treatments

The potential for drug-drug interactions is an important consideration in the treatment of HIV/hepatitis C virus (HCV) coinfection. Regimens for HCV genotype 1 infection are discussed in the context of an individual on stable antiretroviral therapy, to determine which HCV treatments may be initiated without requiring a change in antiretroviral regimen or an increase in monitoring for potential drug-drug interactions. The effects of potential interactions between HCV drugs and other therapeutic classes of drugs are also discussed. This article summarizes a presentation by Jennifer J. Kiser, PharmD, at the IAS–USA continuing education program, Improving the Management of HIV Disease, held in Los Angeles, California, in April 2016.

**Keywords:** HIV, HCV, hepatitis C, coinfection, drug-drug interactions, CYP3A4, tenofovir, HIV protease inhibitors, metabolic enzymes, drug transporters

An important consideration in the treatment of HIV/hepatitis C virus (HCV)-coinfected individuals is the potential for drug-drug interactions. Current HCV therapies generally have well-characterized pharmacology and manageable drug interaction profiles. However, there are a number of potential interactions for which clinicians should maintain vigilance.

**HCV Regimens in an Individual on Stable Antiretroviral Therapy**

Consider the case of a 60-year-old man with a history of injection drug use who was diagnosed with HIV and HCV infections in 1997. His HIV infection is well controlled; he has an undetectable HIV viral load and a CD4+ cell count of 506/µL. His past antiretroviral regimens were zidovudine/lamivudine (slash indicates a coformulation) plus indinavir; zidovudine/lamivudine/abacavir plus ritonavir-boosted lopinavir; and tenofovir disoproxil fumarate (TDF)/lamivudine, abacavir, and ritonavir-boosted lopinavir. His current regimen is TDF/emtricitabine, ritonavir-boosted darunavir twice daily, and raltegravir. The changes in his antiretroviral regimen were “upgrades” to emerging standard treatment and not due to virologic failure.

He has HCV genotype 1a infection, which relapsed after prior treatment with 72 weeks of peginterferon alfa and ribavirin. His current HCV RNA level is 7.3 log10 IU/mL, and recent transient elastography testing showed a liver stiffness measurement of 9.1 kPa. Clinical lab results include an estimated creatinine clearance of approximately 119 mL/min, indicating normal renal function; a platelet count of 175 x 10^9/L; and serum biomarker results consistent with the transient elastography result. His physicians want to start HCV treatment that does not require a change in his antiretroviral regimen or increased monitoring. Would an HCV regimen of any of: elbasvir/grazoprevir; paritaprevir/ritonavir/ombitasvir plus dasabuvir (PrOD) plus ribavirin; ledipasvir/sofosbuvir; sofosbuvir/daclatasvir; or sofosbuvir/velpatasvir meet this objective?

**Elbasvir/Grazoprevir**

With regard to effects on enzymes and drug transporters, elbasvir and grazoprevir are each metabolized by cytochrome P450 3A (CYP3A), posing risk of interaction with drugs that inhibit or induce this enzyme. Grazoprevir is also a mild inhibitor of CYP3A4 and is a substrate of the organic anion-transporting polypeptide 1B1 (OATP1B1) uptake transporter in the liver. Elbasvir and grazoprevir are each substrates of P-glycoprotein (P-gp). There are several inhibitors of OATP1B1 that would cause increased plasma concentrations of grazoprevir. Elbasvir and grazoprevir each inhibit breast cancer resistance protein (BCRP), an efflux transporter in the liver.

Boosting agents should not be used with elbasvir/grazoprevir, as they can inhibit CYP3A and OATP1B1, resulting in increased levels of grazoprevir and increased risk of toxic effects. Because this individual is taking boosted darunavir, he cannot take elbasvir/grazoprevir. Among other antiretroviral drugs, efavirenz also interacts with this HCV regimen, as it induces CYP3A and thus reduces levels of elbasvir and grazoprevir. Although etravirine has not been studied in this regard, a similar interaction is assumed.

**PrOD Plus Ribavirin**

Paritaprevir, ombitasvir, and dasabuvir are substrates of CYP3A4 and P-gp. Dasabuvir is also a substrate of CYP2C8 and CYP2D6. All 3 drugs inhibit UDP-glucuronosyltransferase 1A1 (UGT1A1), paritaprevir and ombitasvir inhibit CYP2C8, and ritonavir inhibits CYP3A4. Paritaprevir inhibits P-gp, OATP1B1/3, and BCRP, and dasabuvir also inhibits BCRP. Ribavirin is used for individuals with HCV genotype 1a infection. Ribavirin is not metabolized by CYP enzymes and has a low potential for interactions with antiretroviral drugs. However, it does have an intracellular interaction with didanosine, which is seldom used in the treatment of HIV infection, and this combination should be avoided. Zidovudine should also be avoided with ribavirin, as both drugs can cause anemia.

Data are available on interactions between PrOD and several antiretroviral drugs.1 There do not appear to be concerns

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Dr Kiser is Associate Professor at the University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences in Aurora, Colorado.
regarding use of PrOD with TDF, emtricitabine, dolutegravir, or raltegravir; however, increased levels of rilpivirine have been observed when coadministered with PrOD, which could theoretically increase the risk for prolongation of the corrected QT interval.

With regard to HIV PIs, atazanavir at a dose of 300 mg can be used with PrOD, but it should be administered simultaneously with the coformulated tablet of ritonavir-boosted paritaprevir and ombitasvir, and separate tablets of ritonavir as a boosting agent should be held for the duration of treatment with PrOD. Lopinavir should not be used with PrOD owing to the fact that it is coformulated with ritonavir, and PrOD already contains ritonavir as a boosting agent.

Use of PrOD with ritonavir-boosted darunavir resulted in an approximately 50% reduction in darunavir trough concentrations in individuals not infected with HIV or HCV. Based on this study, the prescribing information for PrOD in the United States as well as guidelines from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America do not recommend use of ritonavir-boosted darunavir with PrOD.

Data from a small study indicate this combination may be acceptable for individuals taking once-daily ritonavir-boosted darunavir provided they have no darunavir-associated resistance mutations. Twenty-two HIV/HCV-coinfected individuals receiving once-daily darunavir were randomly assigned to continue once-daily or switch to twice-daily boosted darunavir, and were then treated with 12 weeks of PrOD plus ribavirin. When used concurrently with PrOD, the median darunavir trough concentrations among those taking once- and twice-daily darunavir were 1045 ng/mL and 2590 ng/mL, respectively. These trough concentrations are lower than historical estimates of approximately 2200 ng/mL and 3300 ng/mL with once- and twice-daily darunavir, respectively. However, the lower trough concentrations did not appear to compromise HIV suppression, as no participants required changes in their antiretroviral regimen during treatment with PrOD. Five participants had HIV RNA levels between 40 and 79 copies/mL during treatment with PrOD, but there was no clear association between darunavir trough concentrations and these HIV “blips.”

Use of PrOD in the individual under discussion would not be advisable, as he is HIV treatment experienced and is taking twice-daily ritonavir-boosted darunavir.

**Ledipasvir/Sofosbuvir**

Ledipasvir has a much lower potential for interactions with antiretroviral drugs than elbasvir/grazoprevir and PrOD, but it is not devoid of interactions. Ledipasvir does appear to undergo some metabolism by CYP3A4, as efavirenz reduces levels of ledipasvir by approximately 30%. Ledipasvir is a substrate of P-gp and an inhibitor of P-gp (eg, increasing digoxin levels), BCRP (involved in the transport of rosuvastatin), and OATP1B1/3.

Of note, absorption of ledipasvir is pH dependent. Antacid doses should be separated from ledipasvir/sofosbuvir doses by 4 hours. Doses of histamine type 2 receptor blockers should not exceed the equivalent of famotidine 40 mg twice daily. There are conflicting data on whether use of proton pump inhibitors (PPIs) with ledipasvir/sofosbuvir compromises SVR rates. If possible, PPIs should be discontinued during treatment with ledipasvir/sofosbuvir. If a PPI is given concurrently with ledipasvir/sofosbuvir, only doses comparable to omeprazole 20 mg given once daily should be administered simultaneously with ledipasvir/sofosbuvir under fasted conditions. However, the individual under discussion is not taking a PPI. This individual is receiving ritonavir-boosted darunavir and TDF, and ledipasvir/sofosbuvir may increase tenofovir levels. Increases in levels of tenofovir are observed with ledipasvir/sofosbuvir in many TDF-containing antiretroviral regimens, although increases are usually within established safety standards. However, increases in levels of tenofovir observed with ledipasvir/sofosbuvir in individuals receiving antiretroviral regimens that contain a booster (ie, ritonavir or cobicistat) may exceed those for which there are established safety data. Thus, ledipasvir/sofosbuvir likely should not be used for this individual without a change in his antiretroviral regimen or additional monitoring.

Current guidelines for HCV treatment state that concurrent use of ledipasvir/sofosbuvir and TDF should be avoided in individuals with a creatinine clearance below 60 mL/min and that use of ledipasvir/sofosbuvir with TDF and boosted antiretroviral regimens should be avoided (pending further data) unless the antiretroviral regimen cannot be changed and the urgency of treatment is high. For individuals in whom use of TDF and a boosted antiretroviral regimen cannot be avoided.

**Table 1. Daclatasvir Dosing With Concomitant CYP3A4 Inhibitors and Inducers**

<table>
<thead>
<tr>
<th>Drugs That Strongly Inhibit CYP3A (Decrease Daclatasvir Dose to 30 mg)</th>
<th>Drugs That Moderately Inhibit CYP3A (Standard Daclatasvir Dose of 60 mg)</th>
<th>Drugs That Strongly Induce CYP3A (Daclatasvir Contraindicated)</th>
<th>Drugs That Moderately Induce CYP3A (Increase Daclatasvir Dose to 90 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir-boosted atazanavir</td>
<td>Ritonavir-boosted darunavir</td>
<td>Rifampicins</td>
<td>Bosentan</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Ritonavir-boosted lopinavir</td>
<td>St John’s wort</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Ciprofloxacin</td>
<td>Anticonvulsants</td>
<td>Efavirenz</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Diltiazem</td>
<td></td>
<td>Etravirine</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Erythromycin</td>
<td></td>
<td>Modafinil</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Fluconazole</td>
<td></td>
<td>Nafcillin</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>Fosamprenavir</td>
<td></td>
<td>Rifapentine</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Verapamil</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CYP3A, cytochrome P450 3A.
estimated renal function, electrolyte levels (including phosphorus), and urinary protein and glucose levels should be assessed at baseline and monitored every 2 to 4 weeks during treatment. In a recent study of individuals receiving a ritonavir- or cobicistat-boosted antiretroviral regimen with TDF, average estimated glomerular filtration rate (eGFR) declined slightly with the initiation of ledipasvir/sofosbuvir; however, there was no difference in eGFR between those taking TDF plus a boosted antiretroviral regimen and those taking TDF without a boosted antiretroviral regimen, and no difference between the groups at end of treatment in those with eGFRs below 70 mL/min. Although the study includes only a small data set, it provides some reassurance that the increased tenofovir levels observed may not have a substantial clinical impact during the relatively short period of HCV treatment.

Tenofovir alafenamide (TAF) is an alternative to TDF. In the circulation, TDF is converted to tenofovir; tenofovir is a substrate of the OAT1 uptake transporter in the kidney, posing increased risk for nephrotoxic effects. In contrast, intact TAF transits directly into target cells, with only a minor amount being converted to tenofovir. Within cells, TDF and TAF are each converted to the active tenofovir diphosphate form. Because there is less systemically available tenofovir with use of TAF and because TAF is not a substrate of OAT1, there is less tenofovir interacting with the kidney and therefore a reduced risk of nephrotoxic effects. In a study of uninfected individuals given an antiretroviral regimen of TAF/emtricitabine/ cobicistat-boosted elvitegravir, the addition of sofosbuvir/ledipasvir resulted in a 27% increase in tenofovir levels, but the tenofovir area under the concentration time curve (AUC) was still only 20% of that seen with TDF administration.

### Table 2. Drug Classes That Can Be Used, Can Be Used With Dosing Modification, or Cannot Be Used With Hepatitis C Virus Regimens

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>Elbasvir/Grazoprevir</th>
<th>Ledipasvir/Sofosbuvir</th>
<th>Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir</th>
<th>Sofosbuvir/Daclatasvir</th>
<th>Sofosbuvir/Velpatasvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Analgesics</td>
<td>✓</td>
<td>✓</td>
<td>?</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Anxiolytics, sedative hypnotics, benzodiazepines</td>
<td>✓</td>
<td>✓</td>
<td>∆, x</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>✓</td>
<td>✓</td>
<td>?</td>
<td>✓</td>
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</tr>
<tr>
<td>Oral contraceptives</td>
<td>✓</td>
<td>✓</td>
<td>x</td>
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<tr>
<td>Immunosuppressants</td>
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<td>∆</td>
<td>✓</td>
<td>✓, ?*</td>
</tr>
<tr>
<td>Anticonvulsants (old)</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Statins</td>
<td>∆, x</td>
<td>?*</td>
<td>∆</td>
<td>∆</td>
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<tr>
<td>Calcium channel blockers</td>
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<td>x</td>
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</tbody>
</table>

* ✓ indicates lack of a clinically significant interaction; ∆ indicates that a dose change or reduction may be necessary for the concomitant medication; x indicates these drugs should not be used in combination; ? indicates lack of data. Regimens listed are all coformulations.

*Cyclosporine is acceptable; data on tacrolimus are lacking.
*Cyclosporine is not recommended; data on tacrolimus are lacking.
*Rosuvastatin is not recommended; other statins have not been studied.

### Sofosbuvir/Daclatasvir

Of the potential HCV regimens listed above, sofosbuvir/daclatasvir is the best choice for this individual, to avoid changes in antiretroviral regimen or additional monitoring. Daclatasvir is highly reliant on CYP3A for metabolism and it is also a substrate of P-gp and an inhibitor of P-gp, BCRP, and OATP1B1/3. Initial findings indicated that daclatasvir level was markedly increased when used concomitantly with ritonavir-boosted atazanavir, raising concerns over potential interactions with other ritonavir-boosted HIV PIs and suggesting the need to reduce doses of daclatasvir. However, in one study, it was found that 9 of 12 participants who experienced viral relapse were receiving ritonavir-boosted darunavir with daclatasvir 30 mg, a dose reduced from the standard 60 mg. In a study of HCV-uninfected individuals, daclatasvir maximum concentration when given at 60 mg was reduced by 62%, and daclatasvir AUC was reduced by 30% when given at 30 mg with ritonavir-boosted darunavir. It is now recommended that daclatasvir be used at the full dose when concurrently used with boosted darunavir or lopinavir, but that the daclatasvir dose be decreased to 30 mg when concurrently used with boosted atazanavir. The recommended dose of daclatasvir when used with strong or moderate CYP3A4 inhibitors or inducers is shown in Table 1.

### Sofosbuvir/Velpatasvir

Velpatasvir has pharmacologic characteristics similar to those of ledipasvir in that it exhibits pH-dependent absorption and results in increased tenofovir levels when used with TDF. Unlike ledipasvir/sofosbuvir, it is recommended that...
sofosbuvir/velpatasvir may require dose reduction or therapeutic substitution and should be avoided with all HCV regimens. Statins used. Anxiolytics, sedative hypnotics, and benzodiazepines may interact with PrOD, depending on the drug used. Buprenorphine do not interact with current HCV therapies. There are few data on interactions between selective serotonin reuptake inhibitors and PrOD, but they do not appear to interact with other HCV regimens. Oral contraceptives can be used with HCV regimens; however, when used with PrOD, ethinyl estradiol–based contraceptives increased levels of liver enzymes and thus should not be used, although norethindrone–only–containing oral contraceptives are acceptable.

There are data available on how to modify doses of tacrolimus and cyclosporine in individuals receiving PrOD. These immunosuppressants can be used with ledipasvir/sofosbuvir and sofosbuvir/daclatasvir. Sofosbuvir/velpatasvir can be used with cyclosporine; however, there are currently no data on the effects of velpatasvir on tacrolimus. Levels of grazoprevir are substantially increased when coadministered with cyclosporine owing to its inhibition of CYP3A and OATP1B1 transporter.

Other anticonvulsants (eg, phenytoin, carbamazepine, or phenobarbital) are potent inducers of enzymes and drug transporters and should be avoided with all HCV regimens. Statin therapy may require dose reduction or therapeutic substitution in the case of simvastatin and lovastatin, as statins rely on CYP3A, OATP1B1, or BCRP for metabolism, and all of the HCV drugs above interact with at least 1 of these pathways. Calcium channel blockers also require adjustment or increased monitoring when used with elbasvir/grazoprevir or PrOD. Amiodarone should not be used with sofosbuvir-containing HCV regimens because of the risk of bradycardia.

**Conclusion**

The most important consideration in the treatment of HIV/HCV coinfection is the potential for drug interactions. In general, current HCV therapies have well-characterized pharmacology and manageable drug interaction profiles. A systematic approach to the identification and management of drug-drug interactions is essential. Although there are data available to inform treatment decisions, there are some interactions that should be committed to memory (more information on interactions is available from the University of Liverpool,14 Toronto General Hospital,15 and US Department of Health and Human Services16).

Presented by Dr Kiser in April 2016. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Kiser in October 2016.

Financial affiliations in the past 12 months: Dr Kiser has received research support awarded to the University of Colorado from Janssen Therapeutics and ViHIV Healthcare. Her spouse has served on a speakers bureau for Astellas Pharma, Inc.

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**Perspective**

**Sexually Transmitted Infections in the Context of HIV Disease: Clinical Implications**

Universal screening and frequent retesting are required to reduce the burden of sexually transmitted infections in the HIV-infected population. Dual treatment is available for gonorrhea, expedited partner therapy is effective and legal in most states, sexually transmitted infection rates are high in the context of preexposure prophylaxis, and there is a continuing rise in rates of syphilis, particularly early neurosyphilis. This article summarizes a presentation by Dana W. Dunne, MD, FACP, at the IAS–USA continuing education program, Improving the Management of HIV Disease, held in New York, New York, in March 2016.

**Keywords:** HIV, sexually transmitted disease, STD, sexually transmitted infection, STI, preexposure prophylaxis, PrEP

Clinicians must be highly vigilant regarding sexually transmitted infections (STIs). HIV incidence remains high, and STIs indicate high-risk behaviors and increase the risk of HIV transmission, which represents an individual and a public health concern. The goal of reaching zero HIV transmissions requires more-effective STI screening and treatment of HIV-infected individuals.

To illustrate the relevance and practical points of STI testing and treatment in this population, the case of the following typical patient will be presented throughout.

**Case:** A 40-year-old man with well-controlled HIV infection who describes himself as bisexual and is currently in a relationship with an HIV-seropositive woman presents for care. He has no symptoms.

Common questions practitioners ask in such a case are: 1) if STI rates are high enough after initial clinic intake to warrant continued screening; 2) if screening can be limited to exposed anatomic areas; and 3) if a urine sample alone is enough.

STI rates are high in HIV clinics. In a study based in HIV primary care clinics in 4 large US cities, approximately 13% of participants had STIs at the time of enrollment, and the incidence of new STIs at 6 months was 7%. Men who have sex with men (MSM) accounted for 94% of STIs (excluding trichomoniasis) and 20% of incident infections at 6 months. The most common STIs were rectal *Chlamydia trachomatis* and pharyngeal gonococcal infections. Rates of screening were suboptimal, with only 39% of HIV-infected individuals screened for *C trachomatis* and gonococcal infections and only 10% of MSM screened at extragenital sites.1,2

Thus, it is important to remember the principles of routine STI testing in the era of HIV disease. The initial visit to establish care should include a syphilis serology, nucleic acid amplification tests (NAATs) for *C trachomatis* and gonococcal infections at exposed sites, testing for trichomoniasis (via NAAT or antigen detection) and cervical Papanicolaou testing for women, and testing for hepatitis A, B, and C virus infections. More-frequent testing should be performed based on risk behaviors, including for individuals with a new sex partner, a partner who has concurrent partners, more than 1 partner, or a partner who engages in behaviors that put them at high risk for STIs.

**Screening: Where and What**

Data indicate that selective screening or screening based on symptoms can miss up to half of STIs3 and that screening urine only misses the majority of STIs in MSM.4 Thus, universal STI screening should be performed every 3 to 6 months for at-risk individuals regardless of symptoms or of site exposed. Screening should include urine and rectal NAATs for *C trachomatis* and gonococcal infections and a pharyngeal NAAT for gonococcal infection, as well as syphilis serology. In male genital testing, first void urine is as effective as endourethral swabbing. For women, urine testing is typically less sensitive than vaginal swabbing, which is slightly more sensitive than endocervical swabbing; swabs can be practitioner or patient collected. For extragenital testing, individuals should undergo pharyngeal and rectal swabbing, and samples may be practitioner or patient collected.

**Case cont.:** STI screening results are returned. The patient has pharyngeal gonorrhea, but *chlamydia* testing results at all anatomic sites (using NAATs) are negative.

**Dual Treatment for Gonorrhea**

The Centers for Disease Control and Prevention (CDC) recommends that dual therapy with a single dose each of ceftriaxone 250 mg intramuscularly and azithromycin 1 g orally be used for treatment of uncomplicated genital, rectal, or pharyngeal gonorrhea.5 Azithromycin should be used in this setting regardless of *C trachomatis* test results. Dual therapy is advocated by the CDC as a strategy to hinder emergence of antimicrobial resistance. If ceftriaxone is unavailable, a single dose of cefixime 400 mg orally may be substituted for treatment of anorectal infection. If cefixime is used for pharyngeal infection, it must be accompanied by a test of cure in 2 weeks. Azithromycin 2 g is no longer recommended as an alternative treatment for individuals who are allergic to cephalosporins, owing to concern about emerging macrolide resistance.

To break the cycle of reinfection, retesting for STIs is crucial. Women with *C trachomatis* infection, gonococcal...
infection, or trichomoniasis, and men with *C. trachomatis* or gonococcal infection should be rescreened at 3 months after treatment. Individuals diagnosed with syphilis should undergo follow-up serology per current recommendations. Retesting is not the same as a test of cure but, rather, acts as a surrogate for assessing whether sex partners have also been treated.

**Case cont.:** The patient is informed about his gonococcal pharyngitis and is treated with ceftriaxone and azithromycin. The clinician should now consider partner notification and treatment.

**Expedited Partner Therapy**

Expedited partner therapy (EPT), in which individuals provide medicines to their sex partners (otherwise known as patient-delivered partner therapy) is now permissible in 40 states and “potentially allowable” (subject to additional actions or policies) in 8 states. The only states that currently prohibit EPT are Kentucky and West Virginia (visit the CDC website for frequent updates on the legal status of expedited partner therapy). Studies have demonstrated reduced rates of reinfection in index patients when partners were offered EPT compared with traditional partner referral. Expedited partner therapy is currently only recommended for heterosexual couples. Because MSM have high rates of undiagnosed HIV infection and syphilis, it is advisable for their sex partners to present to care for a full examination and workup. It should be noted that not every state allows expedited partner therapy for both chlamydia and gonorrhea, as treatment for the latter involves intramuscular ceftriaxone.

**Case cont.:** The patient tells his female partner about EPT, but she prefers to visit the clinic. The clinician orders routine STI screening and she is treated, based on her contact with gonorrhea, with ceftriaxone and azithromycin. Her Trichomonas vaginalis antigen test result is positive.

**Trichomoniasis: New Tests and Longer Treatment**

Microscopy for diagnosis of trichomoniasis is inferior to newer options, including rapid antigen testing and a transcription-mediated amplification *T. vaginalis* assay. For transcription-mediated amplification testing for *T. vaginalis* infection, the same specimen types used in NAATs for *C. trachomatis* and gonococcal infections can be used (ie, vaginal swab, endocervical swab, and urine). Rapid antigen testing is reported to have 90% sensitivity and 100% specificity. Transcription-mediated amplification testing is reported to have 98% sensitivity and 98% specificity. The recommended regimen for trichomoniasis in HIV-infected women is twice-daily metronidazole 500 mg orally for 7 days, with rescreening (ideally with an NAAT) at 3 months.

**Case cont.:** The patient advises one of his male sex partners of his STI, and this partner visits the clinic for gonorrhea screening and treatment.

**Screening for Bacterial STIs in a PrEP Clinic**

This is an excellent opportunity to screen this partner for chlamydia and gonorrhea at all 3 anatomic sites, perform serologic testing for syphilis and HIV, assess viral hepatitis status, and vaccinate if he is not protected against hepatitis A and B viruses or human papillomavirus (the latter depending on age). This is also an opportunity to discuss preexposure prophylaxis (PrEP) to prevent HIV infection.

Recent studies of PrEP have shown a high burden of bacterial STIs: the PROUD (Preexposure Option for Reducing HIV in the UK) study showed a baseline rate of 63% and an incidence at 6 months of 51% to 57%, the IPERGAY (Action to Prevent Risk Exposure By and For Gay Men) study showed a baseline rate of 25% to 31% and a 6-month incidence of 20%, and the Partners PrEP study showed a baseline rate of 10% to 15%. Accordingly, the CDC provided an interim guideline recommending screening for bacterial STIs every 6 months, including oral and rectal screening. More-frequent testing is supported by recent findings. For example, a community PrEP demonstration project in which there was a 21% incidence of STIs in the 6 months prior to initiation of PrEP asked participants about symptoms of STIs along with screening every 3 months. Reliance on symptoms alone to prompt testing would have missed 77% of STIs at 3 months and 68% of STIs at 9 months (Figure 1); repeat patients accounted for the bulk of incident infections. In another study of PrEP among MSM with STIs, at 3 months 90% had engaged in unprotected anal intercourse and had a mean of 3 sex partners. Both studies suggest that, given the high incidence of bacterial STIs in this population receiving PrEP, the currently recommended testing interval of 6 months may result in missed opportunities to mitigate the personal and public health sequelae of untreated STIs.

**Case cont.:** A full STI screen and baseline HIV test are performed for the patient’s male partner, and he receives treatment for gonorrhea as well as daily PrEP with tenofovir disoproxil fumarate and emtricitabine. He returns for an evaluation 3 months later and STI screening is repeated. He reports blurriness in vision in his left eye. Two days later, his enzyme immunoassay for syphilis returns a positive result, with a reflex rapid plasma regain test result of 1:256. He also reports having a suspicious rash that resolved. His NAAT result for rectal chlamydia is positive.

**Neurologic Complaints and Suspicion of Neurosyphilis**

Rates of syphilis continue to increase among MSM. As of 2011, prevalence of primary or secondary syphilis was 2.6% among HIV-seronegative MSM and 10.1% among HIV-seropositive MSM. Data reported in 2014 showed that among MSM with syphilis who attended STI clinics, rates of coinfection with HIV ranged from 10% in Los Angeles, California, to 55% in Philadelphia, Pennsylvania, with intermediate rates in Seattle, Washington; San Francisco, California; Baltimore,
ner and he is started on treatment for neurosyphilis with lumbar puncture is performed for the patient’s male part-
(blurriness in left eye) and reactive syphilis serology, a Case cont.: Given his concerning neurologic symptoms of proctitis, treatment for a presumed lymphogranuloma venereum strain with twice-daily doxycycline 100 mg orally for 21 days is appropriate. Polymerase chain reaction (PCR) testing for lymphogranuloma venereum strains is not currently commercially available.

The male partner referenced above received azithromycin 1 g for his asymptomatic rectal chlamydial infection in addition to a 14-day course of intravenous penicillin for neurosyphilis. His suspected ocular syphilis is reported to the health department. He remains on daily PrEP with tenofovir disoproxil fumarate and emtricitabine and continues to be screened for STIs every 3 months along with his HIV testing and counseling regarding high-risk behaviors.

Online Resources

There are a number of resources for HIV clinicians to access the latest STI testing and treatment recommendations. The CDC offers a free mobile app that provides access to its STI treatment guidelines. The National Network of Sexually Transmitted Disease (STD) Clinical Prevention Training Centers (NNPTC) offers the STD Clinical Consultation Network (STDCCN), an online system that provides free STI clinical consultation services within 1 to 5 business days, depending on urgency, to health care practitioners nationally. Through the STDCCN, practitioners’ consultation requests are linked to regional NNPTC STI experts.

Summary

Given the prevalence and the personal and public health ramifications of STIs in HIV-seropositive individuals, it is important to screen individuals for STIs when they visit the HIV clinic. MSM and at-risk heterosexual individuals should be frequently screened at all anatomic sites regardless of symptoms or exposure. Dual treatment with a single dose of ceftriaxone 250 mg intramuscularly and azithromycin 1 g orally is the recommended treatment for gonorrhea. To ensure that reinfection has not occurred, individuals who test positive for chlamydia, gonorrhea, or trichomonias should be rescreened 3 months after treatment. To help limit the likelihood of reinfection, effective partner notification and treatment strategies are necessary. EPT is effective and is legal in a number of states and should be utilized, although state-by-state recommendations should be reviewed for guidelines regarding target patient populations in which this strategy has been proven safe and effective. Newer testing methods

Treatment for Rectal C trachomatis Infection

If rectal C trachomatis NAAT results are positive in an asymptomatic individual, treatment for uncomplicated C trachomatis infection with a single dose of azithromycin 1 g orally or twice-daily doses of doxycycline 100 mg orally for 7 days is appropriate; there is some evidence that doxycycline may be better in this setting, but randomized controlled trials are necessary to definitively answer this question.\textsuperscript{17,18} If NAAT results are positive for C trachomatis in an individual with symptoms of proctitis, treatment for a presumed lymphogranuloma venereum strain with twice-daily doxycycline 100 mg orally for 21 days is appropriate. Polymerase chain reaction (PCR) testing for lymphogranuloma venereum strains is not currently commercially available.

Figure 2. Sexually transmitted infection diagnoses, by time point and routine or symptom-based screening. PrEP indicates preexposure prophylaxis. Adapted with permission from Golub et al.\textsuperscript{13}

Maryland; and New York, New York.\textsuperscript{16} Because of the synergy between HIV infection and syphilis and the high rates of transmission among MSM, vigilance in screening and disease detection in this population is paramount.

Neurosyphilis can occur at any stage of syphilis infection. The spirochete disseminates through the spinal fluid early on, and early neurologic symptoms can often be seen at the time a syphilis-associated rash appears or shortly thereafter. Symptoms can include visual changes, hearing loss, facial weakness, and those associated with stuttering stroke. Given the rise in cases of syphilis, symptomatic early neurosyphilis (SENS) is seen more frequently. In SENS, ocular manifestations, including uveitis and chorioretinitis, are most common and occur in approximately 50% of cases. Otic manifestations include tinnitus and sensorineural hearing loss. Other early neurologic manifestations include cranial nerve involvement, aseptic meningitis, and stuttering stroke symptoms (meningovascular syphilis). Lumbar puncture is indicated if there are neurologic manifestations including cranial nerve involvement, aseptic meningitis, and stuttering stroke symptoms (meningovascular syphilis). Lumbar puncture is frequently performed to ascertain whether the increase in reported cases of ocular syphilis is attributable to case-finding bias or to changes in ocular tropism or neurotropism of the spirochete.

Case cont.: Given his concerning neurologic symptoms (blurriness in left eye) and reactive syphilis serology, a lumbar puncture is performed for the patient’s male partner and he is started on treatment for neurosyphilis with high-dose intravenous penicillin G.
(eg, NAATs) are available for diagnosis of trichomoniasis and should be used when possible, as better identification of this infection, which is known to increase HIV viral load in cervicovaginal secretions, could play an important role in limiting HIV transmission. STIs are common among individuals taking HIV PrEP and should be screened more often in this setting. Rates of syphilis remain high among MSM, and practitioners should be aware of the neurologic symptoms associated with neurosyphilis. For individuals with rectal C trachomatis infection, appropriate treatment should be selected based on the presence or absence of symptoms. Useful online resources to guide STI treatment are now available to practitioners and should be utilized.

Presented by Dr Dunne in March 2016. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Dunne in August 2016.

Financial affiliations in the past 12 months: Dr Dunne has no relevant financial affiliations to disclose.

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References


Consider the case of a 21-year-old man diagnosed with HIV infection in June 2009. He entered care at the HIV clinic in August 2009, with a plasma HIV RNA level of approximately 100,000 copies/mL and a CD4+ cell count of 78/µL. He initiated antiretroviral therapy, and his viral load was undetectable in November 2009 and February 2010; his CD4+ cell count increased to 376/µL and 455/µL, respectively, at these visits. From a global perspective of the HIV care continuum, he rapidly and successfully spanned the successive steps from diagnosis through viral suppression. However, he then missed several visits and returned to the clinic in November 2010 with an HIV RNA level of 22,700 copies/mL and a CD4+ cell count of 248/µL, after which he was lost to care for approximately 2 years despite clinic efforts to contact and locate him. At a visit for laboratory evaluation in November 2012, he had an HIV RNA level of 80,300 copies/mL and a CD4+ cell count of 108/µL. It was not until April 2013, 5 months later, that he returned to the clinic for a visit with his practitioner, with an HIV RNA level of 200,000 copies/mL and a CD4+ cell count of 64/µL. He presented with a cough, weight loss, night sweats, and cutaneous Kaposi sarcoma–associated lesions; a chest x-ray showed bilateral opacification of the lungs. There was no response to empiric treatment for *Pneumocystis jiroveci* pneumonia. He was admitted to the hospital, and a bronchoscopy revealed pulmonary Kaposi sarcoma. This picture is encountered too commonly in clinical practice, in which as many as 50% of individuals diagnosed with HIV infection are lost to care.

**The Continuum of HIV Care**

The global process of HIV care is often referred to as a continuum, but in practice, it is more of a cascade—from a population-level health perspective—from higher to lower levels of success from the starting point of diagnosis of HIV infection to retention in care and achievement of viral suppression (Figure 1).\(^1\) However, individuals routinely shift within the framework of the cascade of HIV care, sometimes engaged...
in care for a prolonged period and then lost to care or only intermittently engaged in care, retained in care and adherent to antiretroviral therapy then nonadherent, and virally suppressed then unsuppressed (Figure 2).²

In practice, an individual does not simply, sequentially move from HIV diagnosis to linkage to care, retention in care, adherence to antiretroviral treatment, and then to viral suppression. Further, as shown in Figure 3,³,⁴ the continuum of care in practice is dynamic at the population and individual levels and includes the crucial component of reengagement in care, emphasizing the relationships that a clinic must forge with individuals and agencies in the community and public health to coordinate the efforts that must be made to reconnect individuals to care.

The National HIV/AIDS Strategy 2020 goals are shown in Figure 3.³,⁴ The goal for linkage to care from time of HIV diagnosis is 85% of HIV-infected individuals within 1 month, an ambitious target. The goals for retention in care and viral suppression are 90% and 80%, respectively, of individuals with diagnosed HIV infection.

Many factors influence the ability to successfully engage individuals in HIV care.³ These factors include individual risk or predisposing factors such as stigma, resilience, insurance status, and others. Beyond the individual, there is the influence of relationships (eg, with a spouse, significant other, or partner, or with peer mentors, practitioners, and clinicians), community-related factors (eg, education level, employment status, and income), health care system–related factors (eg, fragmentation and ease or difficulty of navigation), and health care policy–related factors (eg, the availability of needle-exchange programs and if there are waiting lists for the AIDS Drug Assistance Program). Some of these factors, at each level of this socioecologic framework, are targets for interventions that may improve the success of care.

According to one study, in 2009, approximately 90% of cases of HIV transmission in the United States were attributable to HIV-infected individuals who were undiagnosed or diagnosed but not retained in care, with the latter category accounting for approximately twice as many cases as the former (Figure 1).⁵ In another study, despite efforts in outreach and testing and other initiatives, average CD4+ cell count at presentation increased among HIV-infected individuals by just 1.5/µL per year between 1991 and 2011, with an overall average of 307/µL.⁶ Thus, identifying HIV-infected individuals and engaging them in care at earlier stages of disease remains a major challenge, with considerable opportunities for improvement in testing approaches to foster earlier identification of infection, prior to disease progression.

**Linkage to and Retention in Care**

With regard to linkage to care, problems are exemplified by the findings of a 2-year study at the University of Alabama at Birmingham (UAB) 1917 Clinic. Of 522 new patients who called to establish care at the clinic between 2004 and 2006, 160 (30.7%) did not attend a clinic visit within 6 months of the initial call.⁷ The average time from initial call to scheduled visit was 28 days. This delay from call to scheduled visit was a major hurdle, as much can occur in an individual’s life in 4 weeks that might dispose the individual to miss a scheduled visit. Project CONNECT (Client-Oriented New Patient Navigation to Encourage Connection to Treatment) was developed in response to this hurdle.

In Project CONNECT, the initial hour-long social work visit was uncoupled from the initial hour-long medical visit (at 4 weeks) and scheduled for within 5 days after an individual’s initial phone call to the clinic. In essence, individuals are welcomed into the clinic, interviewed about factors such as housing, disclosure of HIV serostatus to others, substance use, and mental health, and questionnaires that screen for depression, substance use, stigma, and other issues are administered. Social workers are able to identify and address any potential barriers to care before the initial medical visit. Baseline laboratory results are also obtained at this first visit. Prophylaxis is prescribed if needed, for *Pneumocystis jiroveci* pneumonia and *Mycobacterium avium* complex, and this information is then available at the first medical visit. Project CONNECT did not increase costs to the clinic, as it represented largely a shifting of tasks and timing in linking a patient to care at the clinic.

Of the first 361 HIV-infected persons who called the UAB 1917 Clinic after implementation of Project CONNECT, 17.7%
did not attend their scheduled visit compared with 30.7% before implementation; the odds ratio (OR) for not attending was substantially reduced on unadjusted analysis (OR, 0.48; 95% CI, 0.35-0.68) and on multivariate analysis adjusted for age, race or ethnicity, sex, insurance status, location of residence, and time from call to scheduled visit (OR, 0.54; 95% CI, 0.38-0.76). Currently, the UAB 1917 Clinic achieves a linkage-to-care rate of 85% to 95% of HIV-infected persons who call to schedule a visit, and this has been sustained over time, since the implementation of Project CONNECT, which is recognized by the Centers for Disease Control and Prevention (CDC) as an evidence-informed best practice intervention.

Following an initial HIV clinic visit, missed visits during the first year of care and low CD4+ cell count at time of entry into care are better predictors of long-term mortality among persons initiating outpatient HIV care than are initial viral load or whether antiretroviral therapy is started in the first year. In a study at the UAB 1917 Clinic, hazard ratios (HRs) for mortality among 543 individuals initiating outpatient HIV care between 2000 and 2005 were 2.90 (95% CI, 1.28-6.56) for a missed visit in the first year after diagnosis, 2.70 (95% CI, 1.00-7.30) for a CD4+ count below 200/µL versus at or above this count, and 1.58 (95% CI, 1.12-2.22) for each 10-year increase in age, with initial plasma HIV RNA level and initiation of antiretroviral therapy (alone, not sustained treatment) being nonsignificant in analysis adjusted for sex, race or ethnicity, insurance status, affective mental health status, and alcohol or substance use. Similar data have been reported by others.

The effect of missed visits on mortality points to missed visits as a warning sign that factors in individuals’ lives may be interfering with their ability to remain in care. Clinicians—including pharmacists, nurses, social workers, and physicians—should reach out to a patient immediately when there is a missed visit. A missed visit is an easily measured and actionable event with profound prognostic value for untoward clinical events.

Missed visits are more likely among black than white individuals. In a study by Zinski and colleagues involving 10,000 participants at 6 US sites, black participants were more likely to have 2, 3, or 4 missed visits per year than white participants. However, when the 2 groups were stratified by number of missed visits, the proportions of participants who achieved viral suppression were similar. Similar findings have been made in other studies. Such findings indicate that increased efforts to reduce missed visits among black individuals could help to reduce the disparities in virologic suppression and mortality observed between white and black individuals in epidemiologic studies, which aligns with a principal tenet of the National HIV/AIDS Strategy to address and overcome disparities.

Current guidelines for interventions to achieve linkage to and retention in HIV care include monitoring of entry into and retention in care; use of brief, strength-based case management, focusing on the internal assets and strengths of an individual and applying these self-care engagement and adherence behaviors to linkage to care (eg, the Antiretroviral Treatment and Access to Services [ARTAS] model); intensive outreach for retention in care; and use of peer or paraprofessional navigation for retention in care. Clinics typically do not have sufficient resources to implement these interventions and often rely on and cooperate with the community and health departments to offer such services.

One program for improving retention in care is highly clinic based and provides clinics with an opportunity to use low-cost interventions shown to have positive results. The UAB 1917 Clinic was 1 of 6 sites that participated in the CDC/Health Resources and Services Administration (HRSA)–cofunded Stay Connected study of this program. Phase I of the program included a clinic-wide intervention involving the use of posters and brochures in waiting and exam rooms and brief messages from all clinic staff, all with the message of staying connected, attending visits, and staying in care. Phase II of the program consisted of patient-centered behavioral interventions, including enhanced contact in the form of personal reminder phone calls (not automated) made by the same clinic staff person at 7 and 2 days before each scheduled visit and within 24 to 48 hours after a missed visit. Also in phase II, skill-building learning modules for patients, presented in 2 brief sessions, focused on problem solving, communication with health care practitioners, and organizational skills.

An evaluation that compared preintervention with postintervention results after phase I showed that there was a 3.0% improvement overall in visit adherence, with improvements of 7.6% for individuals new to or reengaged in care, 5.5% for those with detectable viral loads preintervention, and 5.5% for those with CD4+ cell counts below 350/µL preintervention. Among participants in phase II who were randomly assigned to the intervention program or standard of care, the interventions increased visit adherence.

### Figure 3. National HIV/AIDS Strategy 2020 goals. Changes from the 2015 goals are underlined. ART indicates antiretroviral therapy. Adapted from Mugavero et al and Ulett et al.
adherence from 67% to 72% overall, from 66% to 70% among black individuals, from 65% to 70% among women, from 65% to 74% among individuals with Medicare benefits, and from 66% to 71% among individuals with Medicaid benefits.16

The CDC continues to build its library of best practices to improve linkage to and retention and reengagement in care.14 HRSA, through the National Resource Center, has also created a resource for training and improving clinic-based retention interventions.17

Adherence to Antiretroviral Therapy

Adherence guidelines indicate that adherence to antiretroviral therapy should be monitored in clinical practice through self-reporting or pharmacy refills and not through measurement of drug concentrations, pill count, electronic devices, or measurement of viral load (as viral load is the biologic correlate of adherence behavior).15,18 To improve or ensure adherence, barriers must be identified before an increase in viral load is observed; viral load is the biologic correlate of the nonadherence behavior and should not be used as a screening tool for adherence to antiretroviral therapy. The goal is to identify suboptimal adherence and intervene before it reaches a level that results in viral load rebound.

What should the clinician do if an individual reports “very good” or “good” adherence on a scale ranging from “very poor” to “excellent”? Available data indicate that self-reported adherence tends to be overestimated. Thus, individuals should be questioned for more specific information if self-reported adherence is anything lower than “excellent” or “perfect.” There is a dose-response relationship between self-reported adherence and risk of virologic failure.19 A practitioner may ask a patient directly how many doses have been missed and then question further based on the patient’s answer. However, it is imperative that practitioners normalize missed doses and doses taken off schedule and avoid leading, penalizing, or pejorative comments related to nonadherence. If a framework for open discussion and trust is established, there is considerably greater likelihood of identifying specific challenges with adherence and troubleshooting with a patient to address their individual circumstances and challenges (eg, evening dose, weekend doses, travel-related nonadherence).

In current adherence guidelines,13 strategies for improving adherence include reminder devices and interactive communication technologies; education and counseling using adherence-related tools; various individual, group, and peer education and counseling; case manager services (eg, assistance obtaining food or housing); and integration of medication management into pharmacy systems.

Returning to the patient referenced above, in April 2013, he returned to the clinic with an HIV RNA level of 79 copies/mL and his CD4+ cell count increased to 253/µL. He then missed a visit and was called immediately by his nurse practitioner to find out what had happened and to encourage him to come to the clinic. In December 2013 when he returned to the clinic, prompted by the personal call, his HIV RNA level had rebounded to 525 copies/mL and his CD4+ cell count was 226/µL. Since then, he has maintained adherence to clinic visits. In March 2014, his HIV RNA level was below 20 copies/mL and his CD4+ cell count was 365/µL. He participated in a triathlon in the summer of 2014 and remains in care with sustained viral suppression through September 2016, when he was last seen in clinic.

Summary

Engagement across the continuum of HIV care is dynamic and impacts individual- and population-level health. Systematic monitoring of engagement in care and adherence to antiretroviral therapy is foundational, and the prognostic value of missed visits and the predictive value of any self-reported nonadherence must be recognized. Evidence-based interventions to improve engagement in care and adherence to antiretroviral therapy are amenable to and should be implemented in clinical settings. Ultimately, partnerships between HIV clinics and public health and community agencies are essential to improve outcomes in the continuum of HIV care, particularly at the community-clinical interface of linkage to and reengagement in care.

Presented by Dr Mugavero in December 2015. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Mugavero in October 2016.

Financial affiliations in the past 12 months: Dr Mugavero has served on advisory boards for Bristol-Myers Squibb, Gilead Sciences, Inc, and Janssen Therapeutics, and as a consultant or an advisor to Abt Associates, Gilead Sciences, Inc, and Merck & Co, Inc.

References


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