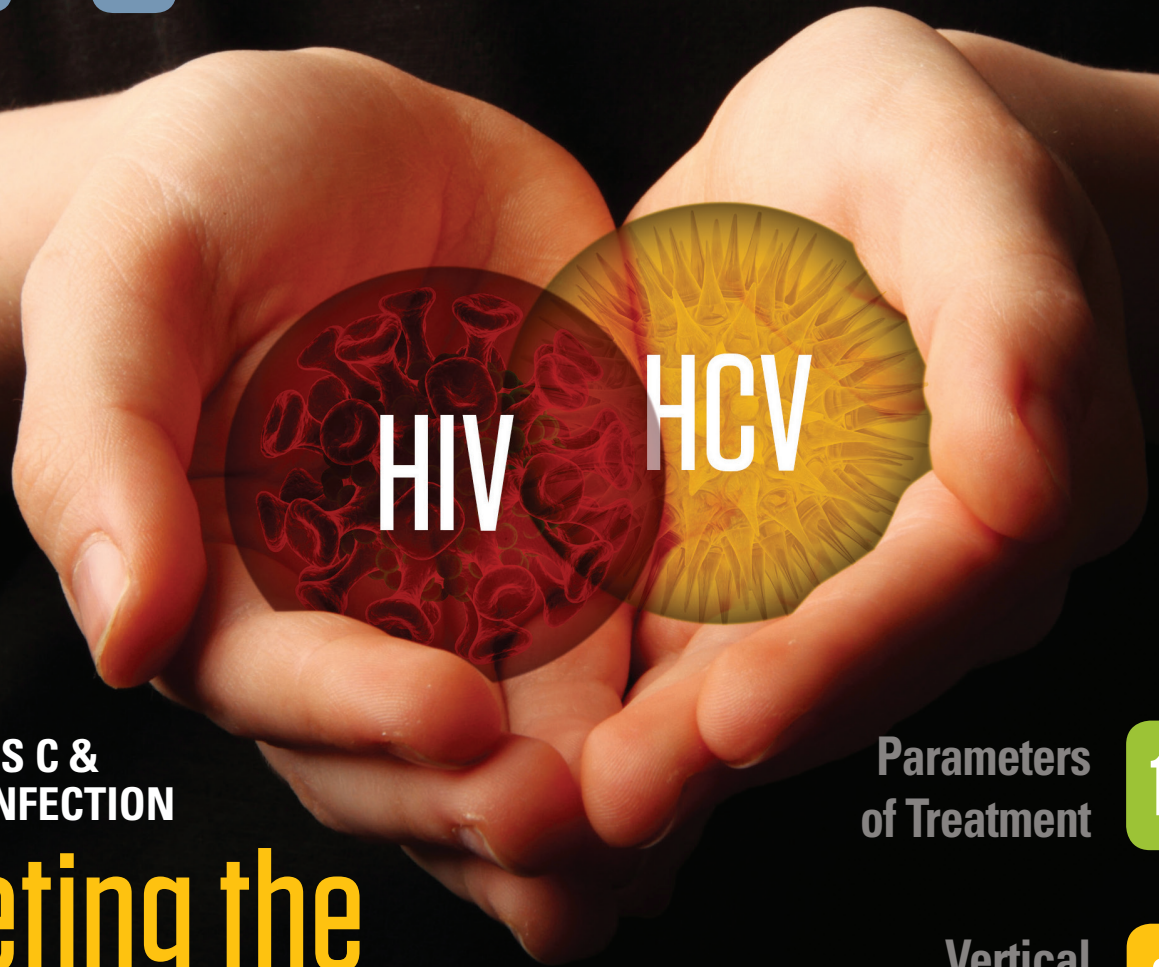


HIV Specialist



HEPATITIS C &
HIV CO-INFECTION

Meeting the Challenge

Parameters
of Treatment

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Vertical
Transmission

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Start or Switch: Consider the possibilities

For adults with no ARV treatment history and with HIV-1 RNA $\leq 100,000$ copies/mL at the start of therapy or to replace current ARV therapy in certain stably suppressed adults with no history of virologic failure and no resistance to COMPLERA



INDICATION

COMPLERA is indicated as a complete regimen for the treatment of HIV-1 infection in adults with no ARV treatment history and with HIV-1 RNA $\leq 100,000$ copies/mL at the start of therapy; and in certain virologically suppressed (HIV-1 RNA < 50 copies/mL) adults on a stable ARV regimen at the start of therapy to replace their current regimen, efficacy was established in patients who were virologically suppressed on a stable ritonavir-boosted protease inhibitor-containing regimen. Additional monitoring of HIV-1 RNA and regimen tolerability is recommended after replacing therapy to assess for potential virologic failure or rebound. COMPLERA is not recommended for patients < 18 years of age.

- **Prescribing considerations in adults with no ARV treatment history:** Virologic failure (HIV-1 RNA ≥ 50 copies/mL) was higher in subjects with baseline HIV-1 RNA $> 100,000$ copies/mL

and in subjects with baseline CD4 cell count < 200 cells/mm³ (regardless of baseline HIV-1 RNA levels). Compared to efavirenz, virologic failure in rilpivirine-treated subjects conferred a higher rate of overall resistance and cross-resistance to the NNRTI class and more subjects developed tenofovir and lamivudine/emtricitabine associated resistance

- **Prescribing considerations in virologically suppressed adults:** Patients must have no history of virologic failure, be stably suppressed (HIV-1 RNA < 50 copies/mL) for ≥ 6 months prior to switching therapy, currently be on their first or second ARV regimen prior to switching therapy, and have no current or past history of resistance to any component of COMPLERA

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including **BOXED WARNING**, on the following pages.

ARV=antiretroviral; NNRTI=non-nucleoside reverse transcriptase inhibitor.

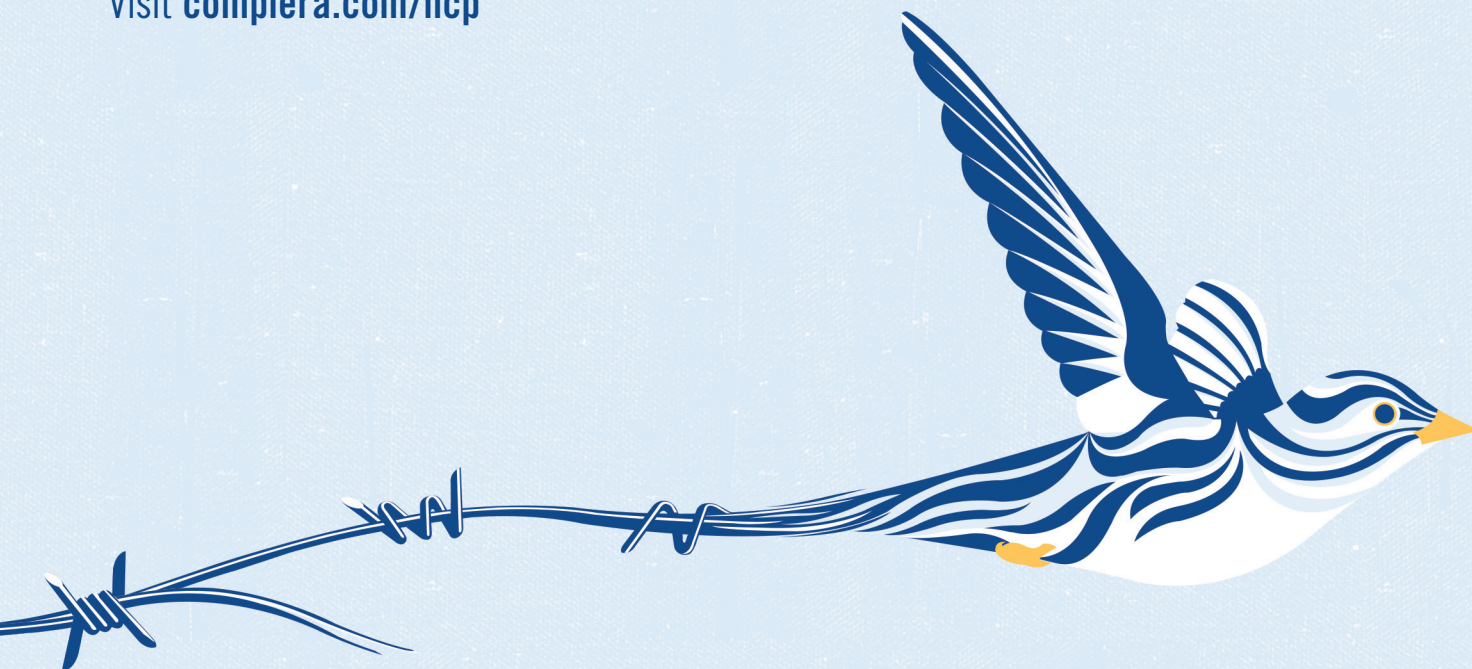
References: 1. COMPLERA Prescribing Information. Gilead Sciences, Inc; June 2014. 2. US Department of Health and Human Services, Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. <http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf>. Accessed May 5, 2014.



DHHS-Recommended

in adults with no ARV treatment history with pretreatment HIV-1 RNA <100,000 copies/mL and with CD4 count >200 cells/mm³.²

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IMPORTANT SAFETY INFORMATION

BOXED WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate (tenofovir DF), a component of COMPLERA, in combination with other antiretrovirals
- COMPLERA is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of COMPLERA have not been established in patients coinfecting with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with HBV and HIV-1 and have discontinued emtricitabine or tenofovir DF, which are components of

COMPLERA. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfecting with HIV-1 and HBV and discontinue COMPLERA. If appropriate, initiation of anti-hepatitis B therapy may be warranted

Contraindications

- **Coadministration:** COMPLERA should not be coadministered with drugs that induce CYP3A or increase gastric pH as this may lead to loss of virologic response and possible resistance to COMPLERA or the NNRTI class. Use of the following drugs with COMPLERA is contraindicated: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin, rifapentine, proton pump inhibitors (e.g., esomeprazole, lansoprazole, dexlansoprazole, omeprazole, pantoprazole, rabeprazole), systemic dexamethasone (>1 dose) and St. John's wort



COMPLERA[®]

emtricitabine 200mg/rilpivirine 25mg/
tenofovir disoproxil fumarate 300mg tablets

IMPORTANT SAFETY INFORMATION (CONT)

Warnings and Precautions

- **New onset or worsening renal impairment:** Cases of acute renal failure and Fanconi syndrome have been reported with the use of tenofovir DF. In all patients, assess estimated creatinine clearance (CrCl) prior to initiating and during therapy. In patients at risk for renal dysfunction, additionally monitor serum phosphorus, urine glucose, and urine protein. Do not administer COMPLERA in patients with CrCl <50 mL/min. Avoid concurrent or recent use with a nephrotoxic agent. Cases of acute renal failure, some requiring hospitalization and renal replacement therapy, have been reported after initiation of high dose or multiple NSAIDs in patients with risk factors for renal dysfunction; consider alternatives to NSAIDs in these patients. Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function
- **Drug interactions:** Use COMPLERA with caution when given with drugs that may reduce the exposure of rilpivirine or when coadministered with a drug with known risk of Torsades de Pointes. Supratherapeutic doses of rilpivirine have been shown to prolong the QTc interval of the electrocardiogram (ECG) in healthy subjects
- **Depressive disorders:** The incidence of depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) reported in clinical trials (N=686) was 9% (most were mild or moderate in severity); and Grades 3 and 4 depressive disorders (regardless of causality) was 1%. Suicidal ideation was reported in 4 subjects and suicide attempt was reported in 2 subjects. Patients with severe depressive symptoms should seek immediate medical evaluation and the risks of continued therapy should be determined
- **Hepatotoxicity:** Hepatic adverse events have been reported, including cases of hepatic toxicity in patients without pre-existing hepatic disease or other identifiable risk factors. Patients with underlying hepatitis B or C, or those with marked elevations in liver-associated tests may be at increased risk. Appropriate laboratory testing and monitoring before and during therapy is recommended in patients with underlying hepatic disease or in patients with marked elevations in liver-associated tests prior to treatment initiation; consider testing and monitoring in patients without pre-existing hepatic dysfunction or other risk factors
- **Bone effects:** Decreases in bone mineral density (BMD) and mineralization defects, including osteomalacia, have been seen in patients treated with tenofovir DF. Consider monitoring BMD in patients with a history of pathologic fracture or risk factors for bone loss. In patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms, hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered
- **Antiviral products:** COMPLERA is a complete regimen for the treatment of HIV-1 infection. Do not coadminister with other antiretrovirals including products containing any of the same active components (unless needed for dose adjustment); products containing lamivudine; or with adefovir dipivoxil

- **Fat redistribution** and accumulation has been observed in patients receiving ARV therapy
- **Immune reconstitution syndrome**, including the occurrence of autoimmune disorders with variable times to onset, has been reported

Adverse Reactions

- **In adults with no ARV treatment history:** Common adverse reactions reported in clinical studies (incidence $\geq 2\%$, Grades 2-4) were depressive disorders (2%), insomnia (2%) and headache (2%)
- **In virologically suppressed adults:** No new types of adverse reactions to COMPLERA were identified in stable, virologically suppressed patients switching to COMPLERA from a regimen containing a ritonavir-boosted protease inhibitor; however, the frequency of adverse reactions increased by 20% after switching to COMPLERA

Drug Interactions

- **CYP3A inducers:** Drugs that induce CYP3A may decrease rilpivirine plasma concentrations which may lead to loss of virologic response and possible resistance to COMPLERA or the NNRTI class
- **CYP3A inhibitors:** Drugs that inhibit CYP3A may increase rilpivirine plasma concentrations
- **Drugs increasing gastric pH** may significantly decrease rilpivirine plasma concentrations and lead to loss of virologic response and possible resistance to COMPLERA or the NNRTI class
 - Use of proton pump inhibitors with COMPLERA is contraindicated
 - Antacids should be administered ≥ 2 hours before or ≥ 4 hours after COMPLERA
 - H_2 receptor antagonists should be administered ≥ 12 hours before or ≥ 4 hours after COMPLERA
- **Drugs affecting renal function:** Coadministration of COMPLERA with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of emtricitabine and tenofovir
- **Prescribing information:** Consult the full Prescribing Information for COMPLERA for more information on potentially significant drug interactions, including clinical comments

Pregnancy and Breastfeeding

- **Pregnancy Category B:** There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if potential benefits justifies the potential risk. An Antiretroviral Pregnancy Registry has been established
- **Breastfeeding:** Emtricitabine and tenofovir have been detected in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed

Dosage and Administration

Adults: One tablet taken orally once daily with food.

Renal Impairment: Do not use in patients requiring dose reduction including in patients with estimated CrCl <50 mL/min.

Rifabutin coadministration: Additional rilpivirine 25 mg taken once daily with a meal is recommended.

Please see Brief Summary of full Prescribing Information, including **BOXED WARNING**, on the following pages.



COMPLERA®
emtricitabine 200mg/rilpivirine 25mg/
tenofovir disoproxil fumarate 300mg tablets

COMPLERA® (emtricitabine 200 mg, rilpivirine 25 mg, tenofovir disoproxil fumarate 300 mg) tablets, for oral use
Brief Summary of full Prescribing Information. See full Prescribing Information. Rx Only.

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate (tenofovir DF), a component of COMPLERA, in combination with other antiretrovirals [See Warnings and Precautions].

COMPLERA is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of COMPLERA have not been established in patients coinfecting with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with HBV and human immunodeficiency virus-1 (HIV-1) and have discontinued emtricitabine or tenofovir DF, which are components of COMPLERA. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfecting with HIV-1 and HBV and discontinue COMPLERA. If appropriate, initiation of anti-hepatitis B therapy may be warranted [See Warnings and Precautions].

INDICATIONS AND USAGE:

COMPLERA is indicated as a complete regimen for the treatment of HIV-1 infection in adults with no antiretroviral (ARV) treatment history and with HIV-1 RNA $\leq 100,000$ copies/mL at the start of therapy; and in certain virologically suppressed (HIV-1 RNA < 50 copies/mL) adults on a stable ARV regimen at the start of therapy to replace their current regimen, efficacy was established in patients who were virologically suppressed on a stable ritonavir-boosted protease inhibitor-containing regimen. Additional monitoring of HIV-1 RNA and regimen tolerability is recommended after replacing therapy to assess for potential virologic failure or rebound. COMPLERA is not recommended for patients < 18 years of age.

Prescribing considerations when initiating therapy with COMPLERA in adults with no ARV treatment history:

- More rilpivirine-treated subjects with HIV-1 RNA $> 100,000$ copies/mL at the start of therapy experienced virologic failure (HIV-1 RNA ≥ 50 copies/mL) compared to rilpivirine-treated subjects with HIV-1 RNA $\leq 100,000$ copies/mL.
- Regardless of HIV-1 RNA level at the start of therapy, more rilpivirine-treated subjects with CD4+ cell count < 200 cells/mm³ experienced virologic failure compared to rilpivirine-treated subjects with CD4+ cell count ≥ 200 cells/mm³.
- The observed virologic failure rate in rilpivirine-treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz.
- More subjects treated with rilpivirine developed tenofovir and lamivudine/emtricitabine associated resistance compared to efavirenz.

Prescribing considerations that should be met when replacing current ARV regimen with COMPLERA in virologically suppressed adults:

- Patients should have no history of virologic failure.
- Patients should have been stably suppressed (HIV-1 RNA < 50 copies/mL) for ≥ 6 months prior to switching therapy.
- Patients should currently be on their first or second ARV regimen prior to switching therapy.
- Patients should have no current or past history of resistance to any component of COMPLERA.

DOSAGE AND ADMINISTRATION:

See **Warnings and Precautions**, **Adverse Reactions**, and **Use in Specific Populations** for additional information.

Adult Dosage: One tablet taken orally once daily with food.

Renal Impairment: Do not use in patients with estimated creatinine clearance (CrCl) < 50 mL/min.

Rifabutin Coadministration: Additional rilpivirine 25 mg taken once daily with a meal during rifabutin coadministration.

CONTRAINDICATIONS:

Coadministration: Do not use with drugs that induce CYP3A or increase gastric pH as significant decreases in rilpivirine plasma concentrations may occur leading to loss of virologic response and possible resistance to COMPLERA or to the class of NNRTIs [See Drug Interactions].

- Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- Antimycobacterials: rifampin, rifapentine
- Proton pump inhibitors: esomeprazole, lansoprazole, dexlansoprazole, omeprazole, pantoprazole, rabeprazole
- Systemic glucocorticoid: dexamethasone (> 1 dose)
- Herbal product: St. John's wort

WARNINGS AND PRECAUTIONS:

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir DF, a component of COMPLERA, in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with

no known risk factors. Treatment with COMPLERA should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Patients Coinfected with HIV-1 and HBV: All patients with HIV-1 should be tested for chronic HBV before initiating ARV therapy. COMPLERA is not approved for the treatment of chronic HBV infection and the safety and efficacy of COMPLERA have not been established in patients coinfecting with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with HBV and HIV-1 and have discontinued emtricitabine or tenofovir DF, two of the components of COMPLERA. In some patients infected with HBV and treated with emtricitabine, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. Patients who are coinfecting with HIV-1 and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with COMPLERA. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

New Onset or Worsening Renal Impairment: Renal impairment, including acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with tenofovir DF. Assess estimated CrCl in all patients prior to initiating therapy and as clinically appropriate during therapy with COMPLERA. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving adefovir dipivoxil, it is recommended that estimated CrCl, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of COMPLERA, and periodically during COMPLERA therapy. COMPLERA should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high dose or multiple NSAIDs) [See Drug Interactions]. Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir DF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered in patients at risk for renal dysfunction. Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients. Do not use COMPLERA in patients with estimated CrCl < 50 mL/min.

Drug Interactions: Caution should be given when prescribing COMPLERA with drugs that may reduce the exposure of rilpivirine or when coadministered with a drug with a known risk of Torsade de Pointes. In healthy subjects, supratherapeutic doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram (ECG) [See Contraindications and Drug Interactions].

Depressive Disorders: Depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) have been reported with rilpivirine. Through 96 weeks in Phase 3 trials (N=686), the incidence of depressive disorders (regardless of causality, severity) was 9% (most events were mild or moderate in severity), Grades 3 and 4 depressive disorders (regardless of causality) was 1%, and discontinuation due to depressive disorders was 1%; suicidal ideation was reported in 4 subjects and suicide attempt was reported in 2 subjects. Patients with severe depressive symptoms should seek immediate medical evaluation to assess the possibility that the symptoms are related to COMPLERA, and if so, to determine whether the risks of continued therapy outweigh the benefits.

Hepatotoxicity: Hepatic adverse events have been reported with rilpivirine. Patients with underlying hepatitis B or C, or marked elevations in liver-associated tests prior to treatment may be at increased risk for worsening or development of liver-associated tests elevations with use of COMPLERA. A few cases of hepatic toxicity have been reported in patients receiving a rilpivirine containing regimen who had no pre-existing hepatic disease or other identifiable risk factors. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with COMPLERA is recommended in patients with underlying hepatic disease such as hepatitis B or C, or in patients with marked elevations in liver-associated tests prior to treatment initiation. Liver-associated test monitoring should also be considered for patients without pre-existing hepatic dysfunction or other risk factors.

Bone Effects of Tenofovir DF: Bone mineral density (BMD): In clinical trials in HIV-1 infected adults, tenofovir DF was associated with decreases in BMD and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving tenofovir DF. For more information, please consult the VIREAD (tenofovir DF) full Prescribing Information. The effects of tenofovir DF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Consider assessing BMD in patients with a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and Vitamin D was not studied, such supplementation may be beneficial. If bone abnormalities are suspected, appropriate consultation should be obtained. **Mineralization defects:** Cases of osteomalacia associated with proximal renal tubulopathy manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of tenofovir DF. Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF.

Coadministration with Other Products: COMPLERA should not be administered concurrently with other products containing any of the same active components (emtricitabine, rilpivirine or tenofovir DF) unless needed for dose adjustment; with products containing lamivudine; or with adefovir dipivoxil.

Fat Redistribution: Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving ARV therapy. The mechanism and long-term consequences of these events are unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome (IRS): IRS has been reported in patients treated with combination ARV therapy, including the components of COMPLERA. During the initial phase of combination ARV treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (e.g., *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment. Autoimmune disorders (e.g., Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

ADVERSE REACTIONS:

See **BOXED WARNING** and **Warnings and Precautions** for additional serious adverse reactions.

In HIV-1 Infected Subjects with No ARV Treatment History:

The safety assessment of rilpivirine, used in combination with other antiretrovirals, is based on the week 96 pooled data from two Phase 3 trials in ARV treatment-naïve HIV-1 infected adults. A total of 686 subjects received rilpivirine in combination with other antiretrovirals as background regimen; 550 of whom received emtricitabine/tenofovir DF. The median duration of exposure for subjects was 104 weeks.

Adverse Reactions: Treatment emergent adverse reactions (Grades 2-4) reported in ≥2% of subjects receiving rilpivirine + emtricitabine/tenofovir DF (N=550) through week 96 were: depressive disorders (2%; includes depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, and suicidal ideation), headache (2%), and insomnia (2%). Frequencies of adverse reactions are based on all Grades 2-4 treatment emergent adverse reactions assessed to be related to study drug. No new adverse reactions were identified between weeks 48 and 96. The adverse reactions observed in this subset of subjects were generally consistent with those seen for the overall patient population (for additional information, consult the Edurant [rilpivirine] full Prescribing Information). Two percent of subjects discontinued treatment with rilpivirine + emtricitabine/tenofovir DF due to adverse reactions (regardless of severity). The most common adverse reactions leading to discontinuation were psychiatric disorders (9 [1.6%] subjects); rash led to discontinuation in 1 [0.2%] subject. **Rilpivirine adverse reactions:** Treatment emergent adverse reactions (≥Grade 2) occurring in <2% of subjects receiving rilpivirine (N=686) were (grouped by Body System): vomiting, diarrhea, abdominal discomfort, abdominal pain, fatigue, cholecystitis, cholelithiasis, decreased appetite, somnolence, sleep disorders, anxiety, glomerulonephritis membranous, glomerulonephritis mesangioproliferative, and nephrolithiasis.

Laboratory Abnormalities: Treatment emergent laboratory abnormalities (Grades 1, 2, 3, and 4, respectively) occurring in subjects receiving rilpivirine + emtricitabine/tenofovir DF (N=550) through week 96 were: increased creatinine (6%, 1%, <1%, 0%), increased AST (16%, 4%, 2%, 1%), increased ALT (19%, 5%, 1%, 1%), increased total bilirubin (6%, 3%, 1%, 0%), increased fasting total cholesterol (14%, 6%, <1%, 0%), increased fasting LDL cholesterol (13%, 5%, 1%, 0%), and increased fasting triglycerides (0%, 1%, 1%, 0%).

Adrenal Function: Mean changes from baseline in basal cortisol and ACTH-stimulated cortisol at week 96 (N=686) were -19.1 nmol/L (95% CI: -30.9; -7.4) and +18.4 ± 8.36 nmol/L, respectively; both values were within normal range. Effects on adrenal function were comparable by background N(t)RTIs. No serious adverse reactions, deaths, or treatment discontinuations were attributed to adrenal insufficiency.

Serum Creatinine: Mean change from baseline in serum creatinine at week 96 (N=686) was 0.1 mg/dL (range: -0.3 mg/dL to 0.6 mg/dL); most increases occurred within the first four weeks of treatment. Observed serum creatinine increases were similar among subjects with baseline mild or moderate renal impairment and subjects with baseline normal renal function; increases were comparable by background N(t)RTIs. No changes were considered to be clinically relevant and no subject discontinued treatment due to serum creatinine increases.

Serum Lipids: Mean changes from baseline in fasting serum lipids at week 96 were: total cholesterol: +2 mg/dL (N=430; baseline 162 mg/dL); HDL-cholesterol: +4 mg/dL (N=429; baseline 42 mg/dL); LDL-cholesterol: -1 mg/dL (N=427; baseline 97 mg/dL); and triglycerides: -14 mg/dL (N=430; baseline 123 mg/dL). The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and week 96 values. Subjects receiving lipid lowering agents during treatment were excluded from these lipid analyses.

Subjects Coinfected with Hepatitis B and/or Hepatitis C Virus: In patients coinfecting with hepatitis B or C virus receiving rilpivirine, the incidence of hepatic enzyme elevation was higher than in subjects receiving rilpivirine who were not coinfecting. The pharmacokinetic exposure of rilpivirine in coinfecting subjects was comparable to that in subjects without coinfection.

In Virologically Suppressed HIV-1 Infected Subjects:

No new types of adverse reactions to COMPLERA were identified in stable, virologically suppressed subjects switching to COMPLERA from a regimen containing a ritonavir-boosted protease inhibitor; however, the frequency of adverse reactions increased by 20% after switching to COMPLERA.

Consult the respective full Prescribing Information for each individual component of COMPLERA for additional information regarding adverse reactions, including laboratory abnormalities and postmarketing events.

DRUG INTERACTIONS:

See **Contraindications** for additional serious drug interactions.

COMPLERA is a complete regimen for the treatment of HIV-1 infection and should not be administered with other antiretrovirals. Information regarding potential drug interactions with other antiretrovirals is not provided.

Drugs Inducing or Inhibiting CYP3A: Rilpivirine is primarily metabolized by CYP3A, thus drugs that induce or inhibit CYP3A may affect the clearance of rilpivirine. Coadministration of rilpivirine and drugs that induce CYP3A may result in decreased plasma concentrations of rilpivirine leading to loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs. Coadministration of rilpivirine and

drugs that inhibit CYP3A may result in increased plasma concentrations of rilpivirine. Rilpivirine at a dose of 25 mg once daily is not likely to have a clinically relevant effect on the exposure of drugs metabolized by CYP enzymes.

Drugs Increasing Gastric pH: Coadministration of rilpivirine with drugs that increase gastric pH may decrease plasma concentrations of rilpivirine leading to loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs.

Drugs Affecting Renal Function: Because emtricitabine and tenofovir are primarily eliminated by the kidneys through a combination of glomerular filtration and active tubular secretion, coadministration of COMPLERA with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and other renally eliminated drugs, which may increase the incidence of adverse reactions [See **Warnings and Precautions**].

QT Prolonging Drugs: There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and drugs that prolong the QTc interval of the ECG. In a study of healthy subjects, supratherapeutic doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the ECG. COMPLERA should be used with caution when coadministered with a drug with a known risk of Torsade de Pointes.

Established and Other Potentially Significant Drug Interactions: The drug interactions described are based on studies conducted with individual components of COMPLERA or are predicted drug interactions that may occur with COMPLERA; no drug interaction studies have been conducted using COMPLERA as a fixed-dose combination tablet. The list includes potentially significant interactions but is not all inclusive. For additional information, consult the Edurant, EMTRIVA (emtricitabine) or VIREAD full Prescribing Information. **An alteration in dose or regimen may be recommended when the following drugs are coadministered with COMPLERA:**

- Antacids: aluminum, magnesium hydroxide, calcium carbonate. Antacids should be taken ≥2 hours before or ≥4 hours after COMPLERA.
- Antimicrobials: rifabutin. Give additional rilpivirine 25 mg once daily with a meal during rifabutin coadministration.
- Azole Antifungals: fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole. No dose adjustment required; monitor for breakthrough fungal infections.
- H₂-Receptor Antagonists: cimetidine, famotidine, nizatidine, ranitidine. H₂-receptor antagonists should be taken ≥12 hours before or ≥4 hours after COMPLERA.
- Macrolide/Ketolide Antibiotics: clarithromycin, erythromycin, telithromycin. Consider alternatives (e.g., azithromycin) when possible.
- Narcotic Analgesic: methadone. No dose adjustment required at therapy initiation; monitor during treatment; methadone maintenance dose may need adjustment.

Consult the full Prescribing Information prior to and during treatment with COMPLERA for potential drug interactions; this list is not all inclusive.

USE IN SPECIFIC POPULATIONS:

Pregnancy: COMPLERA is Pregnancy Category B; however, there are no adequate and well-controlled studies in pregnant women. COMPLERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to COMPLERA, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that rilpivirine and tenofovir are secreted in milk. Emtricitabine and tenofovir have been detected in human milk; it is not known if rilpivirine is secreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions and/or drug resistance in nursing infants, **mothers should be instructed not to breastfeed if they are receiving COMPLERA.**

Pediatric Use: COMPLERA is not recommended for patients <18 years of age because not all the individual components of COMPLERA have safety, efficacy and dosing recommendations available for all pediatric age groups.

Geriatric Use: Clinical studies of emtricitabine, rilpivirine, or tenofovir DF did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patients should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Impairment: COMPLERA should not be prescribed for patients with moderate, severe or end stage renal impairment (CrCl <50 mL/min) or patients who require dialysis [See **Warnings and Precautions**].

Hepatic Impairment: No dose adjustment of COMPLERA is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. COMPLERA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

OVERDOSAGE:

If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with COMPLERA consists of general supportive measures including monitoring of vital signs and ECG (QT interval) as well as observation of the clinical status of the patient.

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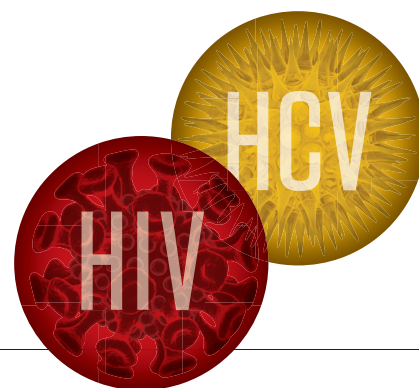
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Big News

THIS ISSUE FOCUSES ON HIV/HCV CO-INFECTION, and it comes at a good time given the attention the Academy has given to hepatitis C. As you may know, approximately one-third of HIV patients are co-infected with HCV and, according to a recent survey we conducted (see Bruce Packett's article on page 25), many of our members treat HCV as well as HIV. And now that there are more tolerable treatments that often results in a cure, more of you will be testing and treating HCV.

Approximately one-third of HIV patients are co-infected with HCV and...many of our members treat HCV as well as HIV.

Beyond the focus of this issue, for several years the Academy has put forth substantial effort into providing HCV CME for our members. We provided two years of workshops on HIV/HCV co-infection in more than a dozen cities around the country. And just this month, we are launching an e-newsletter, the *HIV/HCV Co-infection ReSource*, guided by Drs. Margaret Hoffman-Terry and Mark Sulkowski. In an article in this issue by Dr. Hoffman-Terry, she describes the newsletter as a place where busy HIV practitioners can find syntheses of major clinical and non-clinical issues related to co-infection.

As private insurers and Medicaid programs have placed barriers on HIV practitioners to provide appropriate treatment to those infected with HCV, the Academy, working with the HIV Medicine Association (HIVMA), have sent letters and published press releases to address this problem.

And just a couple of weeks ago at our National Board meeting in Chicago, the Board decided to create the AAHIVM Institute for Hepatitis C, where all of



James M. Friedman

our co-infection programs and activities will be housed.

The other big news from our Board meeting was that Dr. Donna Sweet, who has been our Chair for six years, has stepped down. Dr. Sweet's leadership has brought the Academy an expanded credentialing program, a substantial increase in membership, the creation of this magazine, and a much improved financial position. She will remain as the head of our Mountain Plains Chapter and continue to serve on

the Executive Committee as the Immediate Past Chair.

Dr. Zelalem Temesgen becomes the Chairman of the National Board. Dr. Temesgen, who practices at the Mayo Clinic in Rochester, Minnesota, has been the Vice Chair for six years and an integral part of the leadership team. Dr. Margaret Hoffman-Terry, who also chairs our Policy Committee, becomes our new Vice Chair. Other new Board Officers include Dr. William Short as Secretary, Dr. John Appelbaum as Treasurer and PA Gary Spinner as the At Large member of the Executive Committee. This new leadership team will continue the growth and influence of the Academy. 

James M. Friedman

A TIP FROM A
**FORMER
SMOKER**

**HIV alone
didn't cause the
clogged artery
in my neck.
Smoking with
HIV did.**

Brian, age 45, California

Brian had his HIV under control with medication. But smoking with HIV caused him to have serious health problems, including a stroke, a blood clot in his lungs and surgery on an artery in his neck. Smoking makes living with HIV much worse. You can quit.

CALL 1-800-QUIT-NOW.



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#CDCTips



In the NEWS

Half of HIV+ gay and bisexual men received treatment in 2010

AMONG GAY AND BISEXUAL MEN IN THE UNITED STATES who have been diagnosed with HIV, only half are receiving care and treatment for their infection, according to a new analysis by the Centers for Disease Control and Prevention (CDC). Only 42 percent have achieved viral suppression.

Published September 23 in CDC's *Morbidity and Mortality Weekly Report*, the study analyzes the proportion of men who have sex with men (MSM) diagnosed with HIV who were engaged at each stage of care in the U.S. in 2010. The report also indicates that young MSM and African-American MSM were the least likely to receive care and treatment.

Jonathan Mermin, M.D., director of CDC's National Center for HIV/AIDS, Viral Hepatitis, STD, and Tuberculosis Prevention, said these latest figures are "unacceptable."

"A top prevention priority at CDC is making sure every gay man with HIV knows his status and receives ongoing medical care—otherwise, we will never tackle the HIV epidemic in the country," he said.

To help achieve the goals of the National HIV/AIDS Strategy, CDC said that since 2010 it has:

- Realigned prevention and surveillance funding to better match the burden of disease
- Restructured prevention strategies and programs to increase the focus on people living with HIV—75 percent of prevention funding to health departments must be focused on HIV testing, condom distribution,



policy initiatives, and comprehensive prevention with HIV-positive individuals

- Funded, in collaboration with the Health Resources and Services Administration, the Retention in Care Study—a randomized controlled trial of a clinic-based retention intervention showing improvements in retention.

Revised in March 2012, U.S. clinical guidelines now recommend that everyone with HIV begin therapy upon diagnosis, regardless of their CD4 immune cell count or viral load.

Overall, among MSM diagnosed with HIV, 77.5 percent were linked to care within three months of diagnosis, but only 50.9 percent were retained in care. Largely because many were not in care, only 49.5 percent of MSM diagnosed with HIV were prescribed antiretroviral therapy and only 42 percent achieved viral suppression.

While 71 percent of young (aged 13-24) MSM diagnosed with HIV were linked to care, only 45.7 percent were retained in care. Largely as a result, 30.5 percent of those aged 18-24 (the most comparable age group for which data are available) were prescribed antiretroviral therapy, and just 25.9 percent achieved viral suppression (vs. 42 percent of MSM overall).

While 72 percent of black MSM diagnosed with HIV had been linked to care, only 46 percent were retained in care. As a result, 47.1 percent of black MSM were prescribed antiretroviral therapy and just 37 percent achieved viral suppression (vs. 44 and 42 percent of white and Hispanic MSM, respectively).

CDC said the analysis highlights the need for improvements at each stage of care for men who have already been diagnosed. But it is equally important to reach the estimated 19 percent of gay and bisexual men who don't yet know they're infected, CDC added. Fully capitalizing on the benefits of antiretroviral therapy—both for individual health and for prevention—will require significant investment in closing gaps across the board, from testing to retention in care and adherence to treatment, said CDC.

Data indicate that diagnosing individuals living with HIV, engaging them in ongoing care and prevention services, and ensuring they can stay on treatment are among the most cost-effective ways to prevent new infections.

For additional resources, visit www.cdc.gov/nchhstp/newsroom.

Tybost (Cobicistat) and Vitekta (Eltivitegravir) OK'd as HIV Drugs

A next-generation boosting agent, Tybost (cobicistat) and Vitekta (eltivitegravir), an integrase inhibitor, are now approved HIV medications, the FDA announced September 24.

As a result of these approvals, each component of the single-tablet regimen Stribild (eltivitegravir/cobicistat/emtricitabine/tenofovir) is now approved for use separately in HIV treatment regimens in the U.S. FDA approved Stribild in August 2012.

Tybost is indicated specifically for use as a booster drug. FDA's approval notice restricts the indication for the drug's use, so it is recommended only to enhance the potency of two once-daily protease inhibitors: Reyataz (atazanavir) and Prezista (darunavir). (Tybost is specifically not intended for use with twice-daily dosing of these drugs.)

New CDC campaign encourages all HIV+ people to start and stay on treatment

HIV Treatment Works, a communication campaign focused exclusively on encouraging treatment and care for people living with HIV, was launched September 17 by CDC.

"Today, not only can HIV treatment save lives, it can help stop a national epidemic in its tracks," said Jonathan Mermin, M.D., M.P.H., director of CDC's National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention. "Our goal is to help everyone with HIV know the tremendous health benefits treatment offers to them and the protection it provides to their partners."

In addition to the positive impact it can have on a person's health and well-being, people who start and continue treatment are 96 percent less likely to transmit HIV to others, said CDC. Developed with the input of more than 100 HIV-positive men and women, *HIV Treatment Works* reflects the diversity of people living with HIV and shows how treatment and care empowers people to lead full and healthier lives, and stops the spread of HIV. The campaign includes personal stories about how the participants overcame barriers to care and treatment and provides advice for others living with HIV.

Components of the campaign include online, print, TV, and outdoor ads. Additionally, the campaign includes social media outreach and a dedicated website with information and resources for people living with HIV. The campaign will initially be promoted at upcoming community events in Atlanta, Miami, and Washington, DC.

HIV Treatment Works is the latest component of CDC's Act Against AIDS initiative, a national communication campaign to combat complacency about HIV in the United States. The campaign also advances the National HIV/AIDS Strategy, which includes decreasing the number of new infections, reducing stigma and discrimination against people living with HIV, and educating Americans about the threat of HIV and how to prevent it. Other Act Against AIDS efforts include *Start Talking Stop HIV* for gay and bisexual men of all races, *Reasons/Razones* targeting Latino gay and bisexual men, and *Take Charge. Take the Test.* for African American women.

For more information about HIV Treatment Works, please visit <http://www.cdc.gov/actagainstaids/campaigns/HIVTreatmentWorks/index.html>.

Gay and bisexual men see HIV as key health concern, but most aren't worried and don't get tested

At a time when HIV infections among gay and bisexual men are on the rise, a new national study by the Kaiser Family Foundation (KFF) finds that although HIV/AIDS is named as their top concern, 56 percent are not personally concerned and few report having been tested recently.

Only 30 percent said they were tested during the past year, and those under age 35 are twice as likely as their older peers to report never having been tested—44 percent vs. 21 percent. The study said 26 percent know about PrEP and its ability to lower the

risk of HIV-negative people getting infected, but 80 percent said they have heard "only a little" or "nothing at all" about the new prevention option.

Moreover, the study said that only 46 percent of gay and bisexual men are aware that current guidelines are for people with HIV to start ARV treatment as soon as they are diagnosed, and only 25 percent know about treatment as prevention. Fifty-six percent said a doctor has never recommended they get tested for HIV, and 61 percent said they rarely or never discuss HIV when they visit a doctor.

GUIDELINES:

HIV patients with kidney disease should avoid Tenofovir

HIV-POSITIVE PATIENTS WITH REDUCED KIDNEY FUNCTION should avoid HIV antiretroviral therapy regimens that contain tenofovir (Viread), according to the latest treatment guidelines issued by the HIV Medicine Association (HIVMA).

The updated guidelines provide recommendations on the management of the 5 to 10 percent of HIV patients with chronic kidney disease (CKD), according to HIVMA. The recommendations include ways to monitor kidney function and kidney damage, in particular, by measuring glomerular filtration rate (GFR).

When treating HIV-positive patients with CKD, the recommendations state:

"In patients infected with HIV who have a GFR < 60 mL/minute/1.73 m², we recommend avoiding tenofovir and other potential nephrotoxic drugs (e.g., nonsteroidal anti-inflammatory drugs) when feasible."

Additionally, the guidelines recommend kidney transplantation for patients living with HIV whose kidneys are failing, along with HIV treatment dose adjustment and close monitoring of drug interactions.

HRSA awards \$9.9 million for HIV services in community health centers

Health Resources and Services Administration (HRSA) Administrator Mary K. Wakefield, PhD, RN, announced \$9.9 million in funding through the Affordable Care Act and the Secretary's Minority AIDS Initiative Fund, to 22 health centers in Florida, Massachusetts, Maryland and New York.

The awards will support the integration of high-quality HIV services into primary care through partnerships between the health centers and state health departments. The funding, announced September 18, supports workforce development, infrastructure development, HIV service delivery, partnership building, and quality improvement activities in health centers. The four states are participants in a new HRSA-CDC partnership.

The funding will help an estimated 8,000 patients living with HIV receive access to expanded HIV care and treatment services. Care will be provided through 36 newly established HIV Care Teams made up of one primary care provider trained in HIV care and at least two other service providers.

These awards are part of a new three-year, multi-agency project called Partnerships for Care: Health Departments and Health Centers Collaborating to Improve HIV Health Outcomes. Run by the Centers for Disease Control and Prevention and HRSA, the project will enable HRSA-funded health centers to work with CDC-funded state health departments to expand the provision of HIV prevention, testing, care, and treatment services, especially among racial/ethnic minorities.

HCV & HIV CO INFECTION OVERVIEW

THE HEPATITIS C VIRUS (HCV), a member of the *Flaviviridae* family, has long been a problem for our HIV-infected patients, causing significant morbidity and mortality. Many of us have wrestled with the challenge of whether to treat, and when to treat, the HCV in our co-infected patients.

Both patients and providers understandably have had fears about interferon. And yet, despite its side effects, interferon is a potent agent that, along with ribavirin and now newer agents, has helped cure an increasing number of patients over the years.

Unlike HIV, HCV RNA is not reverse transcribed or integrated into the DNA, so is inherently curable. New direct-acting antivirals (DAAs) already are revolutionizing the treatment and cure rates for those with chronic HCV. This article will briefly review the epidemiology of HCV in patients with HIV, and then discuss the work-up and newest treatment guidelines for chronic HCV infection in this population.

Epidemiology

Approximately 3.9 million Americans have chronic hepatitis C, and 2.7 million of these have chronic infection.¹ Estimates are that approximately one-quarter of HIV-infected patients are co-infected with hepatitis C.² Rates of HCV co-infection of 50-90 percent have been reported in populations of HIV-infected drugs users.³ There have been increasing reports of outbreaks of acute hepatitis C among men who have sex with men (MSM).

A study from New York City reported 74 new infections among MSM in the five years leading up to 2010, with a greater risk associated with receptive anal intercourse, sex while using methamphetamines, and participation in group sex.⁴ Additionally, rates of progression to cirrhosis are increased among people with HIV infection, up to three times that seen in those with HCV mono-infection.⁵ In 2012, the CDC recommended one-time screening for all baby boomers, those born between 1945 and 1965, as this is where 75 percent of the cases of HCV have occurred.⁶

Diagnosis and work-up

Hepatitis C is diagnosed with a positive enzyme immunoassay (EIA) for HCV antibody, and chronic infection should be confirmed by an HCV-RNA level in all patients who test antibody positive for HCV. If

the HCV RNA is negative, then chronic disease has been excluded. The only times when the HCV antibody may be negative, and the patient still could have hepatitis C, is during acute infection before antibody has developed, and in advanced HIV infection with very low CD4 cell counts, where the only way to make

the diagnosis is through RNA testing. In one study, seronegative, chronic HCV infection was more likely among patients with sexual rather than parenteral transmission of their HIV infection.⁷

Once the diagnosis of chronic HCV infection has been established, evaluation for possible treatment should be undertaken. This work-up includes HCV subtyping, also referred to as genotyping, in addition to a standard complete blood count and chemistry profile. Testing for thyroid stimulating hormone (TSH) should be done at baseline, if interferon is to be used as a part of therapy. Many experts perform baseline ANA testing to exclude concomitant autoimmune hepatitis.

Urine pregnancy should be performed at baseline for females, or female partners of a male, who will be on ribavirin, with precautions taken to use two forms of birth control during and for six months after completion of ribavirin therapy.

Depression screening is also important, particularly if interferon is planned as part of the therapy. An alcohol screen also should be done prior to therapy, in addition to screening for other substances. These evaluations should be individualized, and need not necessarily exclude patients from consideration of treatment.

Some experts also perform IL28b genotyping, which helps determine the likelihood of a treatment response. While this was done in most HCV therapeutic trials, it is not required to treat patients. The CC genotype has been associated with the best treatment response rates with interferon-based therapy, and TT the worst, with CT somewhere in between. In addition, the CC genotype is associated with a greater likelihood of spontaneous clearance of HCV after acute infection, and is less common among those of African descent.⁸

Unlike HIV, HCV RNA is not reverse transcribed or integrated into the DNA, so is inherently curable. New direct-acting antivirals (DAAs) already are revolutionizing the treatment and cure rates for those with chronic HCV.

PARAMETERS *of* TREATMENT

BY DOUGLAS G. FISH, MD, AAHIVS



ISTOCK/ SHUTTERSTOCK/ THINKSTOCK

The next step in the evaluation of chronic HCV is some determination of the degree of liver fibrosis. Historically, this has been done via a liver biopsy. Increasingly, non-invasive makers of fibrosis have been utilized, compiled from an array of laboratory-based markers. In 2013, the Fibroscan was FDA-approved as a measure of liver elastography, done via an ultrasound technique. This may gain more utilization over time, and is already being used in some liver centers in the U.S.

Finally, if the patient has more advanced fibrosis, meaning a Metavir score of F3 or F4, then screening for hepatocellular carcinoma (HCC) with alpha fetoprotein and imaging such as ultrasound or CT scan should be done as part of pre-treatment work-up. If a mass is identified, this needs to be worked up as it may significantly affect management. An additional and important point about screening for HCC is that this surveillance should continue, even if the patient has experienced a sustained virologic response (SVR) after treatment, as cirrhosis does not disappear with successful therapy.

Therapy

The treatment of HCV/HIV co-infection is confounded by the potential drug interactions with antiretroviral therapy. This has been more of an issue with the HCV protease inhibitors, with fewer interactions seen with the available polymerase inhibitor, sofosbuvir.

Besides pegylated interferon (PegIFN) with ribavirin (RBV), three HCV protease inhibitors have been FDA-approved: boceprevir, telaprevir, and more recently, simeprevir. The American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) no longer recommends the first two, boceprevir and telaprevir, for use in HCV treatment due to their dosing complexity and side effect profiles.⁹

Some patients are unwilling to take interferon, so they become candidates for interferon-sparing regimens. Medical contraindications to interferon include prior intolerance to interferon or allergy to any of its components, autoimmune hepatitis, decompensated cirrhosis, uncontrolled depression, pre-existing cardiac disease, uncontrolled thyroid or lung disease, or baseline neutrophil count < 1500 cells/mcL, platelets below 90,000 mcL, or hemoglobin < 10 g/dL.

Simeprevir (Olysio), a once-daily NS3/4A second generation HCV protease inhibitor, has been FDA approved to be used with PegIFN and RBV in a response-guided fashion in patients with genotype 1, chronic hepatitis C. Baseline screening of HCV genotype 1a patients for the Q80K polymorphism is recommended in the simeprevir package insert, due to poorer treatment responses seen with simeprevir in some genotype 1a patients harboring this mutation.¹⁰ This is not a concern for patients with genotype 1b.

Simeprevir should only be used with the antiretroviral therapies with which it has been studied, which include abacavir,

emtricitabine, enfuvirtide, lamivudine, maraviroc, raltegravir, rilpivirine, and tenofovir.

Sofosbuvir (Sovaldi) is a once-daily NS5B polymerase inhibitor FDA-approved to be used with PegIFN and RBV for patients with genotype 1 or 4 chronic hepatitis C, or with ribavirin only (without interferon), for patients with HCV genotype 2 or 3.¹¹ Treatment courses of 12-24 weeks are pre-defined based on genotype, and are not response-guided.

As noted, boceprevir and telaprevir are no longer recommended to be used in patients with chronic hepatitis C. In addition, PegIFN with RBV for 48 weeks is no longer recommended. Similarly, no drug should be used as mono-therapy. Finally, patients with decompensated cirrhosis should not be treated with interferon or simeprevir. Treatment of any patient with decompensated cirrhosis requires the expertise of a liver transplantation center.

Following is a summary of the recommendations for treatment of HCV based on the August 2014 updated AASLD/IDSA HCV treatment guidelines, which include a section for patients with HCV/HIV co-infection.⁹ The newer DAAs appear to work as well in co-infected patients as they do in the HCV- mono-infected patients.

The guidelines include recommendations for treatment-naïve and relapsed patients, as well as for those treatment-experienced patients who were previous partial or null responders. They include primary recommendations, and in some instances, alternative recommendations.

Genotype 1 is the most complicated, and will be addressed last. Ribavirin dosing is always weight-based when used with the DAAs, meaning patients whose weight is < 75 kg should receive 1000 mg/day of ribavirin split in twice daily fashion, such as 400 mg in the AM and 600 mg in the PM, and those weighing > 75 kg should be prescribed 600 mg twice daily. Ribavirin doses should be decreased further for patients whose glomerular filtration rate (gfr) is < 50 mL/minute, based on the dosing guidelines.

HCV Genotype 2 or 3

For patients with HCV genotype 2, the guidelines recommend sofosbuvir plus weight-based ribavirin for 12 weeks, and for those with genotype 3, sofosbuvir and weight-based ribavirin for 24 weeks. These recommendations come, in part, from the PHOTON-1 trial, where 182 treatment-naïve HCV/HIV co-infected subjects received the combination of sofosbuvir with RBV for 12-24 weeks, depending on genotype.^{12,13} Subjects with genotype 1 received 24 weeks of the combination therapy, and those with genotypes 2 or 3 received 12 weeks. Ninety percent of individuals completed therapy, with a 12-week SVR of 76 percent seen in these treatment-naïve subjects with genotype 1, 88 percent for genotype 2, and 67 percent for genotype 3.

In the PHOTON-2 trial presented this summer in Melbourne, Australia, genotype 3 subjects received 24 weeks of sofosbuvir



HCV/HIV co-infection is confounded by the potential drug interactions with antiretroviral therapy. This has been more of an issue with the HCV protease inhibitors, with fewer interactions seen with the available polymerase inhibitor, sofosbuvir.

with RBV instead of 12 weeks, and the SVR 12 rate was 91-92 percent in those **without** cirrhosis, and 78-100 percent in those **with** cirrhosis, depending on prior treatment history.¹⁴ In some categories the number of participating subjects was low, however. In summary, those with genotype 2 can be treated with 12 weeks of combination sofosbuvir plus RBV, and those with genotype 3 with 24 weeks of this 2-drug combination.

The guidelines also state that those genotype 2 subjects with cirrhosis who were prior non-responders, may be considered for 16 weeks of combination therapy instead of 12 weeks, based on data from the FUSION trial.¹⁵ In this study, treatment-experienced subjects with genotype 2 who had cirrhosis did better with 16 weeks of sofosbuvir plus RBV, with a SVR of 78 percent compared to those subjects who received only 12 weeks, with an overall SVR of 60 percent. The VALENCE study demonstrated an 88 percent SVR 12 rate among HCV GT2 patients with cirrhosis, with a 78 percent SVR-12 among those who were treatment-experienced.¹⁶

An alternative regimen for those genotype two or three patients who can take interferon is the same regimen used to treat those with genotype 1 infection, PegIFN with RBV plus sofosbuvir for 12 weeks. This is similar to the recommendation for those with HCV mono-infection.

Genotypes 4, 5 or 6

HCV/HIV co-infected patients with genotypes 4, 5 and 6 should be treated the same as those with HCV mono-infection, based largely on the experience from the mono-infection trials. The primary recommendation for this group of individuals is similar to those with genotype 1 HCV, which is 12 weeks of PegIFN plus RBV plus sofosbuvir. An alternative recommendation for genotype 4, treatment-naïve patients is 12 weeks of simeprevir with RBV plus 24 to 48 weeks of PegIFN. An alternative regimen for genotype 5 or 6, treatment-naïve patients is 48 weeks of weight-based RBV and PegIFN, without a DAA.

Genotype 1

Genotype 1 is the most complicated, is harder to treat, and has subtypes 1a and 1b, with 1a being the most common in the United States. Genotype 1a is the only one where the Q80K polymorphism test should be done before simeprevir is used, with alternative regimens considered if the Q80K is present, due to the increased potential for lower treatment responses.¹⁰ This will likely become a preferred regimen for genotype 1 patients in the next HCV treatment guidelines update.

The primary recommendation for treatment-naïve or relapsed patients with genotype 1 HCV/HIV co-infection, regardless of subtype, has been 12 weeks of PegIFN plus RBV plus sofosbuvir. This is not response-guided therapy. The NEUTRINO study evaluated this regimen in 291 GT1 HCV mono-infected patients, with an SVR12 of 89 percent.¹⁷ The smaller Rodriguez-Torres study evaluated 23 HCV/HIV co-infected patients with HCV

HCV/HIV
co-infected
patients
should be
monitored
carefully
when
undergoing
HCV therapy.
A nurse
to help
with prior
authorizations,
adherence
monitoring,
and tracking
of labs,
visits,
and other
activities is
extremely
helpful.

GT 1-4, using the same regimen of sofosbuvir plus PegIFN plus RBV for 12 weeks, and 19 of these patients had genotype 1.¹⁸ The SVR 12 was identical at 89 percent. If patients cannot tolerate or are unwilling to take PegIFN, then either sofosbuvir plus RBV for 24 weeks or simeprevir plus sofosbuvir, with or without RBV for 12 weeks is recommended.

The primary recommendation for treatment-experienced patients who did not respond to previous PegIFN plus RBV therapy is sofosbuvir plus simeprevir, with or without RBV, for 12 weeks. If the patient also had prior HCV protease inhibitor therapy exposure, the recommendation is similar to those with HCV mono-infection: sofosbuvir plus RBV for 12 weeks, with 12-24 weeks of PegIFN, regardless of HCV GT1 subtype.

Therapy with simeprevir plus sofosbuvir, with or without ribavirin, for 12-24 weeks was informed by the COSMOS trial, where two cohorts of HCV mono-infected patients were enrolled.¹⁹ Cohort 1 included 80 prior null responders with Metavir scores of F0-F2, and Cohort 2 included 87 treatment-naïve and prior null responders with Metavir scores of F3-F4. Patients were randomized to receive simeprevir plus sofosbuvir, either with or without RBV, for 12 versus 24 weeks. Overall response rates demonstrated that 90 percent of those in Cohort 1 and 94 percent of patients in Cohort 2 had a SVR at 12 weeks post-therapy. Extending the treatment to 24 weeks did not improve SVRs in most patients.

Though this combination is not a FDA-approved therapy, it is a recommended regimen for those treatment-naïve or relapsed patients who are interferon-ineligible, and for those treatment-experienced GT1 patients who have not had prior HCV protease inhibitor exposure.

A new combination, anti-HCV therapy was FDA-approved on October 10, the fixed dose combination of sofosbuvir, the NS5B polymerase inhibitor, with ledipasvir, an NS5A inhibitor, for the treatment of HCV genotype 1 in adults. For HCV treatment-naïve patients and treatment-experienced patients who do not have cirrhosis, 12 weeks of therapy is recommended, and for treatment-experienced patients with cirrhosis, 24 weeks of therapy is recommended. Phase 3 trials have consistently demonstrated greater than 90 percent SVR12 rates. The most common side effects, those occurring in more than 10 percent of subjects who took the therapy, were fatigue and headache. While this therapy is not specifically approved for HCV-HIV co-infected patients, it can and should be used in this patient population. This therapy will be a significant addition to our currently available therapies, and will be the first FDA-approved, interferon-free regimen for patients with HCV genotype 1. This will likely become a preferred regimen for genotype 1 patients in the next HCV treatment guidelines update.

Monitoring and Side Effects

HCV/HIV co-infected patients should be monitored carefully when undergoing HCV therapy. A nurse to help with prior authorizations, adherence monitoring, and tracking of labs, visits,



and other activities is extremely helpful. Most practitioners see patients back at one-to-two weeks after the start of therapy, with safety labs of a complete blood count and chemistry profile done at 2 weeks, and then at two-to-four week intervals, depending on the previous results and patients' comorbidities.

Simeprevir was studied with PegIFN and RBV and approved with stopping rules.¹⁰ If the HCV RNA is > 25 IU/mL at any time-point of four, 12 or 24 weeks, the patient has failed HCV therapy and the treatment should be stopped. Sofosbuvir therapy is not response-guided and does not require a four-week viral load, though this often is done to ensure adherence, and for positive reinforcement for both the patient the provider. A viral load always is done at the end of treatment, and again at 12 and 24 weeks after the completion of therapy, to ensure a sustained treatment response, or cure.

Fatigue, nausea, headache and insomnia may be seen with the DAAs, in addition to the hematologic side effects which can occur from PegIFN and ribavirin. Side effect management includes the reduction of ribavirin dosing for anemia. If this is not sufficient, practitioners have successfully used erythropoietin for anemia, and granulocyte-macrophage colony stimulating factor for neutropenia. Mood alterations are common with interferon-based regimens as well; hence the need to pre-screen for depression. Rash can occur with simeprevir, and sun-protective measures should be recommended when this therapy is prescribed. Monitoring for worsening rash should continue, and the drug should be discontinued if mucosal signs or systemic symptoms develop.¹⁰

Insurance and Cost

The advent of the DAAs has come a significant price tag. This has resulted in the DAAs all requiring prior authorization and being available largely through specialty pharmacies. A common practice for these pharmacies

is to make contact with the patient prior to shipping the next month of medication. However, some patients use phone cards that run out of minutes, or do not answer calls from 800 numbers, as examples. To get around this, many practices, after obtaining the prior authorization, have the pharmacy ship the drug to the office, where it is available for patient so there is not a lapse in treatment. Patient assistance programs are also available to help get insurance coverage, or to get the drugs themselves.

Newer Agents

Additional DAAs soon will be available, and several currently are pending with the FDA. These are largely interferon-free regimens, with once or twice daily dosing, and fixed dose combinations. So the pipeline is rich, and the prognosis for our patients with HCV is excellent.

Summary

The newer direct-acting antiviral agents are revolutionizing HCV treatment responses. For decades we have looked for reasons not to treat HCV in our HIV-infected patients, due to the rigors of treatment, but now we should be looking to see how best we can treat them. Not everyone can be treated at once, but nothing beats a motivated patient. Patients with more advanced fibrosis with Metavir scores of F3-F4 have the most to gain, and may be considered a priority for treatment.

HIV



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References

- Centers for Disease Control and Prevention. Viral hepatitis and injection drug users. Sept. 2002 at: http://www.cdc.gov/odp/hepatitis/viral_hep_drug_use.pdf
- Sherman KE, Rouster SD, Chung RT et al. Hepatitis C Virus prevalence among patients infected with Human Immunodeficiency Virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. *Clin Infect Dis* 2002;34:831-837.
- Hagan H and Des Jarlais DC. HIV and HCV infection among injecting drug users. *Mt Sinai J Med*. 2000 Oct-Nov;67(5-6):423-8.
- Centers for Disease Control and Prevention. Sexual transmission of hepatitis C virus among HIV-infected men who have sex with men--New York City, 2005-2010. *Morb Mortal Wkly Rep* 2011;60(28):945-950.
- Graham CS, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis*. 2001;33(4):562-569.
- Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *Morb Mortal Wkly Rep* 2012;61(RR04):1-18.
- George SL, Gebhardt J, Klinzman D et al. Hepatitis C virus viremia in HIV-infected individuals with negative HCV antibody tests. *J Acquir Immune Defic Syndr*. 2002 Oct 1;31(2):154-62.
- Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature*. 2009 Oct 8;461(7265):798-801.
- AASLD/IDSA Recommendations for Testing, Managing, and Treating Hepatitis C, revised 8/11/14 at www.hcvguidelines.org
- Janssen Therapeutics. Simeprevir [package insert]. 2013. Titusville, NJ, Janssen Therapeutics.
- Gilead Sciences Inc. Sofosbuvir [package insert]. 2013. Foster City, CA, Gilead Sciences, Inc.
- Sulkowski M, Rodriguez-Torres M, Lalezari JP, et al. All-Oral Therapy with Sofosbuvir Plus Ribavirin for the treatment of HCV genotype 1, 2 and 3 infection in patients co-infected with HIV (PHOTON-1). AASLD Annual Meeting 2013. Nov 1-5, 2013, 2013; Washington, DC.
- Naggie S, Sulkowski M, Lalezari J, et al. Sofosbuvir plus ribavirin for HCV genotype 1-3 infection in HIV coinfecting patients (PHOTON-1). CROI 2014. Conference on Retroviruses and Opportunistic Infections. March 3-6, 2014. Boston. Abstract 26.
- Molina JM, Orkin C, Iser DM, et al. All-oral therapy with sofosbuvir plus ribavirin for the treatment of HCV genotypes 1, 2, 3 and 4 infection in patients co-infected with HIV (PHOTON-2). AIDS 2014. 20th International AIDS Conference. July 20-25, 2014. Melbourne. Abstract MOAB0105LB.
- Jacobson IM¹, Gordon SC, Kowdley KV et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med*. 2013; 368(20):1867-1877.
- Zeuzem S, Dusheiko DM, Salopere R et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med*. 2014; 370(21):1993-2001.
- Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis infection. *N Engl J Med*. 2013;368(20):1878-1887.
- Rodriguez-Torres M, Rodriguez-Orengo J, Gaggara A et al. ID Week, October 2-6, 2013; San Francisco. Abstract 714.
- Jacobson IM, Ghalib RM, Rodriguez-Torres M et al. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naïve and prior null responder patients: the COSMOS study. 64th Annual Meeting of the American Association for the Study of Liver Diseases, Washington DC, abstract LB-3, 2013

HCV & HIV MEETING THE CHALLENGE

BY JASON J. SCHAFER,
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What's in a NAME?

WITH SEEMINGLY COUNTLESS NEW DIRECT ACTING ANTIVIRALS (DAAs) becoming available for the treatment of hepatitis C infection, it is easy to feel overwhelmed when trying to stay current. There are more than 20 agents that are either currently in use in the United States or in the various stages of development. This excludes the number of new fixed-dosed combination products that will allow for hepatitis C treatment with a single tablet similar to the contemporary management of HIV.

Not only is the number of new agents for hepatitis C infection overwhelming, but trying to identify agents by name, sorting them into their respective classes and recalling their unique characteristics seems even more daunting. Fortunately, like many other classes of medications, the names of the new DAAs are designed to help clinicians. Each new DAA has within its name clues that can be used to identify the class of the agent and how it works. Once the class has been identified, the clinician can assign certain characteristics that are common to all agents within the class.

Using the nomenclature clues to reliably identify DAAs requires an understanding of the hepatitis C life cycle and the targets of therapy. After viral entry and uncoating, hepatitis C RNA migrates to the endoplasmic reticulum where translation occurs and a large polypeptide structure is developed. The polypeptide contains proteins bound together so that when they are released they will either perform RNA replication (non-structural, or NS proteins) or provide structure for the new virus. Protease enzymes, including the NS3/NS4A protease cleave the polypeptide structure to release the other NS proteins including NS5A and NS5B. The

Drug Class	Nomenclature	Genotype Coverage	Resistance Barrier	Potential for Drug Interactions	Potential for Side Effects
NS3/4A Protease Inhibitors	"previr"	1st generation agents have limited coverage	Moderate-high	High, occurring through CYP pathways	High, rash can occur with all available agents
NS5A Inhibitors	"asvir"	Moderate	Low-moderate	Low	Low
NS5B Nucleoside Polymerase Inhibitors	"buvir"	Broad	High	Low	Low
NS5B Non-Nucleoside Polymerase Inhibitors	"buvir"	Limited	Low	Low	Low

NS5A protein will help to form the RNA replication complex, while the NS5B protein will perform RNA replication as a polymerase enzyme.

Each of the NS proteins serves as a target for DAAs, and treatment regimens often combine agents to achieve highly potent antiviral activity. Importantly, the classes of DAAs may differ considerably in several key areas including genotype coverage, barrier to viral resistance, potential for drug-drug interactions, and tolerability. Below is a brief description of each DAA class that highlights these key areas and provides the nomenclature clues that can be used to sort agents into their respective classes.

NS3/NS4A Protease Inhibitors

The protease inhibitors, telaprevir and boceprevir, were the first DAAs to become available. The newest agent in the class is simeprevir. The names of the current agents and those in development all share the suffix "previr."

The current protease inhibitors have limited genotypic coverage, and are approved for use in genotype 1 infections. Future agents in this class are likely to have broader coverage. Protease inhibitors tend to have a moderate-high barrier to resistance. The q80k polymorphism is common in genotype 1a infection and can confer resistance to simeprevir.

Telaprevir and boceprevir have many side effects, while simeprevir is better tolerated. Common among all three agents is the possibility of patients having a rash or skin reaction during therapy. This side effect is most commonly seen with telaprevir and can be severe. Simeprevir is associated with a photosensitivity skin reaction for which patients should take protective measures.

Drug interactions appear to be most common within this class of DAAs. All three agents have many cytochrome P450 interactions, making them very difficult to use in patients on other medications, particularly antiretroviral agents used to treat HIV.

NS5A Inhibitors

Ledipasvir is the first agent available in this class. It was recently approved as part of a single tablet HCV regimen also containing the NS5B inhibitor, sofosbuvir. Ledipasvir and all other NS5A

inhibitors in development such as daclatasvir and ombitasvir all share the suffix "asvir."

Agents from this class generally have antiviral activity limited to genotype 1, although daclatasvir may be an exception demonstrating broad genotypic coverage.

Unlike protease inhibitors, NS5A inhibitors have a low-intermediate barrier to resistance. They also appear to be well tolerated and are unlikely to have many drug interactions as they are not substrates, inducers or inhibitors of cytochrome P450 enzymes. Ledipasvir is a substrate and inhibitor of p-glycoprotein which may result in drug interactions with other agents using this pathway.

NS5B Polymerase Inhibitors

NS5B inhibitors can be divided into two subclasses: nucleoside analogues (i.e. sofosbuvir) and non-nucleoside analogues (i.e. dasabuvir). Agents in these subclasses all share the suffix "buvir."

Nucleoside analogues have very broad genotypic coverage while non-nucleoside agents have limited coverage. The subclasses also differ in regards to their resistance barriers. Nucleoside analogues have a high resistance barrier, while non-nucleoside agents tend to have a lower barrier to resistance.

Both classes of agents appear to have good tolerability. They are also unlikely to have many drug interactions. For example, similar to the nucleoside analogues used for the treatment of HIV and hepatitis B, hepatitis C nucleoside analogues are not metabolized by cytochrome P450 enzymes. Like ledipasvir, however, sofosbuvir is a p-glycoprotein substrate and may be subject to interactions with strong inhibitors or inducers of this pathway. **HIV**



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Drug-Drug Interactions Between HIV ARVs and HCV Treatment



IN APRIL OF 2011, a new era of hepatitis C treatment was revealed: the direct acting antivirals (DAAs). These groundbreaking advancements gave hope to many people infected with hepatitis C, as the previous standard of care was subpar in terms of success and side effects.

Although the first round of DAAs (telaprevir and boceprevir) came on the market with a boom, they were not without their own problems. For the HIV community, which comprises roughly 10 percent of all HCV cases in the USA, one of the major hurdles was drug interactions with antiretrovirals (ARVs). With more than 11 DAAs set to be on the market within the next year, information on drug interactions is critical to plan for patients' treatment options.

The first class of DAAs to be approved, first generation protease inhibitors, came with considerable interactions to ARVs among other drugs. Both telaprevir and boceprevir were contraindicated with half of the preferred ARVs at the time of their launch.^{1,2} Although never approved for the use of HCV treatment in co-infection, there was a significant demand, and many HIV providers dove into the uncharted waters of co-infection treatment with new agents. Now, providers have been advised by Vertex that telaprevir will be discontinued from



production in October as newer agents have contributed to a significant decline in its use.

With the second round of DAA approvals in late 2013, the discussion of drug interactions with ARVs became much easier. Sofosbuvir, an NS5B polymerase inhibitor, is the first of its class to be approved. Sofosbuvir is unique in its mechanism of action, as it is a prodrug that is metabolized into the active form, which is then able to enter the infected cell. Its metabolism is extensively in the liver. Because of this, plasma concentrations are not necessary.

Furthermore, with no metabolism involving CYP450, sofosbuvir has minimal drug interactions. Per the package insert, the only antiretroviral that is contraindicated is tipranavir, due to a P-glycoprotein transport induction that could lower sofosbuvir levels.³ Not only does sofosbuvir have a fairly clean interaction profile, it is the first DAA to be approved specifically for the co-infected population.

Simeprevir, the second line HCV protease inhibitor DAA, was also approved in late 2013. Drug interaction studies were completed for a number of ARVs. As was seen with the first generation HCV PIs, drug interactions are common as simeprevir is a CYP3A4 substrate. Once again, antiretroviral protease inhibitors, as well as efavirenz and the single tablet regimen Stribild, are contraindicated with simeprevir.⁴ Drug interaction studies with rilpivirine, raltegravir, and tenofovir showed no significant interactions.⁴ Although there is no evidence of interactions with dolutegravir, abacavir, lamivudine and emtricitabine, there are no expected interactions based on drug metabolic mechanisms.

With the recent approval of ledipasvir/sofosbuvir fixed dose tablet (marketed as Harvoni) on October 10th 2014, more options have been added to the field for the HIV/HCV coinfecting patient. Ledipasvir is a substrate of the drug transporters p-gp, as well as being an inhibitor of p-gp. Because of this, there are few interactions with HIV treatment. One specific interaction, which can affect many patients on HIV treatment, is the increased plasma concentration of tenofovir when given in combination with ledipasvir. Based on this interaction, caution is advised when given with the fixed dose combinations of Complera and Atripla.⁵ Additionally, as tenofovir concentrations are increased when used with a boosted protease inhibitor, the recommendation is to consider alternative ART or HCV treatment to avoid the increased tenofovir exposure, however if no other options are available, close monitoring of renal toxicity is highly recommended.⁵ Lastly, due to the boosting effect of cobicistat in the fixed dose combination STRIBILD, the coadministration of Harvoni is not recommended.⁵

Looking ahead to HCV treatment still in clinical trial, pharmaceutical companies are becoming increasingly aware of the need for HCV treatment in the co-infected population and trials specifically for co-infected patients are being conducted. Some companies have included co-infected patients into the pivotal trials, showing HIV is no longer a unique or special population.⁵

Because trials are currently ongoing, data on drug interactions with ARVs are limited; however, below are tables of HCV treatment in phase 3 trials and any known information on drug interactions with ARVs. With this information, planning for HCV treatment for a co-infected patient can begin.

HIV

References for article

- 1 Incivek Prescribing Information, Vertex Pharmaceuticals Inc, October 2013.
- 2 Victrelis Prescribing Information, Merck & Co Inc, September 2013
- 3 Sovaldi US Prescribing Information, Gilead Sciences, December 2013.
- 4 Olysio US Prescribing Information, Janssen, December 2013
- 5 Harvoni US Prescribing Information, Gilead Sciences, October 2014.
- 6 *A Study of the Combination Regimen MK-5172 and MK-8742 ± Ribavirin in Participants With Chronic Hepatitis C (MK-5172-035) (C-WORTHy)*. information from clinicaltrials.gov

References for Table 1

- 1 A. Khatri, et.al. Drug-Drug Interactions of the Direct Acting Antiviral Regimen of ABT-450/r, Ombitasvir and Dasabuvir with HIV Protease Inhibitors. ICAAC 2014 poster V-484
- 2 A. Khatri, et.al. Drug-Drug Interactions of the Direct Acting Antiviral Regimen of ABT-450/r, Ombitasvir and Dasabuvir with Emtricitabine + Tenofovir, Raltegravir, Rilpivirine and Efavirenz. ICAAC 2014 poster V-483
- 3 Yeh.W, et al. No Meaningful PK Interaction Between HCV Protease Inhibitor MK-5172 and Tenofovir or Raltegravir. [CROI Abstract 500]. In Speical Issue. Abstracts From the 2014 Conference on Retroviruses and Opportunistic Infections. Top Antivir Med. 2014;22(e-1):34.

References for Table 2

- 1 A. Khatri, et.al. Drug-Drug Interactions of the Direct Acting Antiviral Regimen of ABT-450/r, Ombitasvir and Dasabuvir with HIV Protease Inhibitors. ICAAC 2014 poster V-484
- 2 A. Khatri, et.al. Drug-Drug Interactions of the Direct Acting Antiviral Regimen of ABT-450/r, Ombitasvir and Dasabuvir with Emtricitabine + Tenofovir, Raltegravir, Rilpivirine and Efavirenz. ICAAC 2014 poster V-483
- 3 Bifano M, Hwang C, Oosterhuis B, et al. Assessment of HIV ARV drug interactions with the HCV NS5A replication complex inhibitor BMS-790052 demonstrates a pharmacokinetic profile which supports co-administration with tenofovir disoproxil fumarate, efavirenz, and atazanavir/ritonavir [abstract 618]. CROI2012, Seattle, WA.
- 4 Yeh.W, et al. TDF, EFV, or RAL and MK-8742. [CROI Abstract 498]. In Speical Issue. Abstracts From the 2014 Conference on Retroviruses and Opportunistic Infections. Top Antivir Med. 2014;22(e-1):34.
- 5 Yeh.W, et al. Ritonavir-Boosted Atazanavir, Lopinavir, & Darunavir Increase HCV NS5A Inhibitor MK-8742 Levels. CROI2014 poster 638

References for Table 3

- 1 A. Khatri, et.al. Drug-Drug Interactions of the Direct Acting Antiviral Regimen of ABT-450/r, Ombitasvir and Dasabuvir with HIV Protease Inhibitors. ICAAC 2014 poster V-484
- 2 A. Khatri, et.al. Drug-Drug Interactions of the Direct Acting Antiviral Regimen of ABT-450/r, Ombitasvir and Dasabuvir with Emtricitabine + Tenofovir, Raltegravir, Rilpivirine and Efavirenz. ICAAC 2014 poster V-483



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Table 1: Drug-Drug Interactions between First-Line ART and Investigational HCV Protease Inhibitors

	EFV	RPV	RAL	DTG	EVG/COBI/FTC/TDF	ATV/r	DRV/r	FTC/TDF	ABC/3TC
ABT 450/r									
MK5712									

Table 2. Drug-Drug interactions Between First-Line ART and Investigational HCV NS5A Inhibitors

	EFV	RPV	RAL	DTG	EVG/COBI/FTC/TDF	ATV/r	DRV/r	FTC/TDF	ABC/3TC
DCV 60mg	Need 90mg					Need 30mg			
ABT-267									
MK8742									

Table 3. Drug-Drug Interactions between First-Line ART and Investigational HCV Polymerase Inhibitors

	EFV	RPV	RAL	DTG	EVG/COBI/FTC/TDF	ATV/r	DRV/r	FTC/TDF	ABC/3TC
ABT 333									



COLOR-CODING:

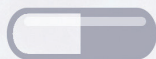
- No clinical meaningful interactions noted and/or based on metabolism no expected interactions
- Interactions noted, caution and/or more information needed
- Significant interactions noted
- No Data Available to date



MEETING THE
CHALLENGE

BY CARL SCHMID

HELP



MEDICAL

HEALTHCARE

Health Care Reform Brings Increased Opportunities TESTING HEPATITIS C

HALF TO THREE-QUARTERS of the estimated 3 million people with the hepatitis C virus (HCV) in the United States do not know they are infected. Members of the “baby boomer” cohort, born between 1945 and 1965, are infected at a significantly higher rate than other age groups. There is also a high incidence—around 25 percent—of co-infection in people living with HIV.

While federal resources to combat HCV are scarce, significant strides have been made in a strategy to find people with HCV, through increased testing—the first step in linking people with HCV into treatment and hopefully, curing their infection.

Under health care reform, several policy improvements have the potential to open up access to HCV screening as a fully covered preventive service. Turning these policies into widespread practice is a challenge for all, including providers who must bill for these covered services.

Evidence-based Guidelines

In 2012, the Centers for Disease Control and Prevention (CDC) began recommending a one-time test for baby-boomers “without prior ascertainment of HCV risk.” The CDC also identified specific high-risk groups for routine testing, including people with HIV and intravenous drug users.

As the CDC has renewed an emphasis on testing, so too have recent health care reforms opened new sources of financing, as more preventive services are covered by nearly all payers.

First, action was needed by the U.S. Preventive Services Task Force (USPSTF), the leading independent panel of private-sector experts in prevention and primary care. Based on “rigorous, impartial assessments” of the evidence, this body grades the overall effectiveness of clinical preventive services. A grade of “A” or “B” means that the preventive service under review should be provided in primary care settings. (The USPSTF also can recommend against providing a service, if it applies a lower “C” or “D” grade or finds insufficient evidence).

In June 2013, the USPSTF took the next step, which widely expanded insurance coverage for HCV screening. As a result of great advocacy by patient and provider groups, it upgraded its assessment of HCV as a preventive service, giving a “B” grade to one-time testing of baby boomers—those born between 1945 and 1965 screening—as well as periodic testing among high-risk individuals.

Health Care Reform

The major insurance provisions of the Affordable Care Act of 2010 (ACA) went into effect this year, extending coverage to millions of families and individuals through new private insurance exchanges and optional expanded Medicaid. Other provisions of the ACA provide preventive services as standard benefits at no charge to patients. The general effect is to require or promote coverage of preventive services that have been graded “A” or “B” by the USPSTF.

The impact of policy changes and the current state of coverage for HCV testing are outlined below.

- **Private Insurance Plans.** With limited exception, private insurance must cover “A” and “B” graded services without

cost-sharing. As a result, enrollees in any plan effective June 2014 (one year after the USPSTF recommendation) have access to HCV screening as recommended—periodically for those “at risk” and one-time for “baby-boomers.”

- **Traditional Medicaid.** In federal policy, a medically-necessary HCV test is covered in traditional Medicaid, as are other laboratory tests. If the test is offered routinely, a state’s individual coverage rules apply. Routine screening coverage currently is not common across the states. However, the ACA offers extra federal matching funds to states that expand coverage of HCV testing, and all other USPSTF-graded “A” and “B” services. States that have done so as of July 2014 are California, Colorado, Delaware, Hawaii, Kentucky, New Hampshire, New Jersey, Nevada, New York, Ohio, and Wisconsin. In these states and in a handful of others that have decided to cover HCV screening, traditional Medicaid covers one-time screening of “baby boomer” enrollees as well as routine risk-based testing.

- **Expanded Medicaid.** Enrollees of the newly expanded Medicaid programs have the same access to preventive services as those in the new private plans, consistent with USPSTF recommendations. Accordingly, those “at risk” and “baby-boomer” enrollees in the new Medicaid will have coverage for HCV testing, as recommended. To take advantage of this coverage, the state obviously must agree to expand Medicaid.

- **Medicare.** Under a 2008 law, Medicare is authorized to cover “A” & “B” graded preventive services provided in primary care settings, after a separate coverage determination process. The ACA took this reform a step further and removed beneficiary cost-sharing for Medicare preventive services. In June 2014, CMS issued a National Coverage Determination, establishing national coverage for one-time HCV testing for “baby boomers,” and annual testing for those “at risk.”

As described above and in The AIDS Institute’s *HCV Testing Coverage Guide*, great progress has been made. Clinical guidelines, preventive services evidence, and financing policies are now largely aligned, with large-scale potential to identify people with HCV and engage them in treatment. Additional advocacy is needed in some states to ensure traditional Medicaid covers HCV screening and Medicaid expansion occurs in all states, but now the biggest challenge is that providers need to offer the test to patients and bill payers, as appropriate.

HIV



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Vertical Transmission of Hepatitis C

TREATING PREGNANT WOMEN

PROVIDERS encounter many issues when caring for patients with chronic hepatitis C virus infection. Preventing hepatitis C vertical transmission is a daunting challenge because there are presently no vaccines available or approved therapies that can be administered safely during pregnancy, as is the case with women infected with human immunodeficiency virus (HIV).

Natural history of Hepatitis C in Pregnancy

The immune system has evolved a complex set of mechanisms, which are beyond the scope of this review, to discriminate “self” and “nonself.” When the immune system recognizes something as foreign, a series of events leads to destruction. This not only involves microorganisms, but also transplanted tissues/organs and tumor cells. A unique phenomenon occurs with pregnancy in which the maternal immune system tolerates the presence of paternal alloantigens (nonself) and does not cause rejection.¹

Due to changes in the immune system during pregnancy, it has been noted that the hepatitis C viral load may increase during the second and third trimester and decrease in the post partum period. Some studies have also shown a decrease in serum alanine transferase levels (ALT) in the second and third trimester, which corresponds to the increase in viral load seen.²

There are also studies that have shown an increase in hepatitis C specific T-cell responses in the third trimester and post partum period, corresponding to the drop in hepatitis C

viral load. In a study from Japan, 22 pregnant women and 120 non-pregnant women with chronic hepatitis C virus infection with positive hepatitis C RNA (indicating chronic infection) were studied. Significantly more pregnant patients lost HCV RNA after delivery than did non-pregnant controls. These findings suggest that pregnancy and parturition appear to influence the clinical course of HCV infection.³

Timing of Transmission and Incidence

Vertical transmission can occur through several routes from an infected mother to her newborn, including intrauterine, intrapartum, and postpartum. The mechanisms underlying these are poorly understood.

The estimates on the incidence of hepatitis C vertical transmission vary significantly. A systematic review looked at 77 studies published from 1992 to 2000, which identified an overall adjusted rate of vertical hepatitis C transmission of 1.7 percent. Many variables influenced this rate and HIV was most strongly associated with an increased rate of transmission (19 percent).⁴



Treatment during pregnancy

Currently, there is no safe treatment for Hepatitis C infection during pregnancy. In the past, treatment with pegylated interferon alfa-2a (Pegasys) and ribavirin (Rebetol) could not be used because of the teratogenic effects of ribavirin.⁵ There is a paucity of data on the use of the newer potent direct-acting agents during pregnancy, and further studies are needed to assess their safety and efficacy in pregnant women.

Mode of delivery

There is not an association between the mode of delivery and the risk of vertical transmission of hepatitis C.⁶ The European Pediatric Hepatitis C Network concluded in a study carried out on 1,758 mother-infant pairs that there was no significant difference in vertical transmission between elective C-section vaginal delivery, or emergent C-section.⁷

Diagnosis in the newborn

Diagnosis of vertically transmitted infection is difficult because maternal hepatitis C antibodies (IgG) cross the placenta and can persist for a prolonged period of time. By the time the infant is one year of age, approximately 95 percent of the maternal antibodies are cleared.⁸ According to a National Institutes of Health consensus statement, infants should be tested for hepatitis C RNA on two occasions between the ages of two and six months and/or be tested for antibody to hepatitis C virus after 15 months of age.⁹

Breast Feeding

Hepatitis C virus has been detected in both breast milk and colostrum.¹⁰ Most of the studies have shown that the viral load in breast milk is extremely low and likely becomes inactivated in the digestive tract of infants.^{4,11}

The American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, and the Centers for Disease Control and Prevention all support breast feeding among women infected with hepatitis C. However, they should avoid breast feeding if their nipples are cracked or bleeding.^{12,13,14} In the United States, mothers who are coinfectd with HIV are recommended to follow the guidelines to prevent HIV transmission, which includes the avoidance of breastfeeding.

Summary

The overall incidence of hepatitis C vertical transmission is low; however, the risk of transmission with maternal HIV infection is increased. There is no standard treatment for hepatitis C during pregnancy, and pregnant women are not advised to have a cesarean delivery, unless indicated for other reasons. Preconceptional counseling is the key is to identify

women who are at risk for hepatitis C infection and screen and potentially treat prior to conception. **HIV**



ABOUT THE AUTHOR:

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References

1. Bainbridge, DR. (2000) Evolution of mammalian pregnancy in the presence of the maternal immune system. *Rev Reprod*, Vol 5, No. 2, pp.67-74.
2. Gervais A, Bacq Y, Bernuau J, et al. Decease in serum HCV RNA during pregnancy in women with chronic hepatitis C. *J Hepatology* 2000; 32(2): 293-299.
3. Hatori Y, Orito E, Ohno T, et al. Loss of hepatitis C virus RNA after parturition in female patients with chronic HCV infection. *J Med Virol* 2003; 71(2): 205-211.
4. Yeung LT, King SM, Roberts EA. Mother-to-infant transmission of hepatitis C virus. *Hepatology* 2001; 34: 223.
5. Kilham L, Ferm VH. Congenital anomalies induced in hamster embryos with ribavirin. *Science*. 1977; 195 (4276): 413-414.
6. Cottrell EB, Chou R, Wason N, et al. Reducing risk for mother-to-infant transmission of hepatitis C virus: A systematic review for the U.S. Preventive Services Task force. *Ann Internal Medicine* 2012.
7. European Pediatric Hepatitis C Virus Network. A significant sex-but not elective cesarean section-effect on mother to child transmission of hepatitis C virus infection. *Blood* 2000;96(6): 1872-1879.
8. England K, Pembrey L, Tovo PA, Newell ML. European Pediatric HCV Network. Excluding hepatitis C virus (HCV) infection by serology in young infants of HCV-infected mothers. *Acta Paediatr*. 2005;94(4):444-450.
9. National Institutes of Health. Management of hepatitis C: 2002. National Institutes of Health consensus statement. June 10-12, 2002. <http://consensus.nih.gov/2002/2002HepatitisC2002116pdf.pdf>. Accessed October 1, 2014.
10. Kumar RM, Shahul S. Role of breastfeeding in transmission of hepatitis C virus to infants of HCV infected others. *J Hepatol* 1998; 29(2):191-197.
11. Lin HH, Kao JH, Hsu HY, Ni YH, et al. Absence of infection in breast-fed infants born to hepatitis C virus-infected mothers. *J Pediatr* 1995; 126(4):589-591.
12. ACOG committee opinion. Breastfeeding and the risk of hepatitis C virus transmission. Number 220, August 1999. Committee on Obstetric Practice. American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet* 199;66:307.
13. American Academy of Pediatrics. Hepatitis C. In: red Book: 2012 Report of the Committee on Infectious Disease, 29, Pickering, LK (Eds), American Academy of Pediatrics, Elk Grove Village, IL 2012.p.391.
14. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention. *MMWR recomm Rep* 1998;47:1.

BY BRUCE PACKETT,
AAHIVM Director of
Professional Development

AAHIVM to Launch Institute for Hepatitis C

WE STAND ON THE THRESHOLD of revolutionizing the treatment of hepatitis C. With many of the 1.2 million HIV-infected Americans already in care for their HIV, HIV care providers are in a unique position to treat and likely cure hepatitis C in the approximately one quarter who are co-infected.

Research in hepatitis C has benefited greatly from the framework of HIV research laid down in the past 30 years, rocketing along at breakneck speed and condensing into years what previously would have taken decades. HIV providers, with their understanding of virology, resistance, drug-to-drug interactions, and the psychosocial needs of this population, stand in unique stead to expertly treat hepatitis C.

A new survey of AAHIVM HIV-treating members and specialists in community health and Ryan White clinics, private practices, and academic and/or hospital settings (N=114) showed that HIV practitioners are caring for significant numbers of patients with Hepatitis C. Some of the key statistics include:

- Respondents reported that patients with Hepatitis C infection represent 23 percent of the average respondent's patient pool, or Almost one in four of patients currently being seen by an AAHIVM member or specialist.

- Additionally, 81 percent of clinician respondents felt that they have the proper clinical knowledge and education to expertly treat HCV infection. Ninety-two percent of the respondents agreed that AAHIVM should be doing more to support member providers treating Hepatitis C.
- On the payer/access side of the issue, about 60 percent of survey respondents expected (or have experienced) insurance or cost access barriers to prescribing Hepatitis C treatments to their patients, representing a complicated but key public policy/advocacy portfolio on which to focus as an organization.

With these statistics in mind, the Board of Directors of the Academy recently voted unanimously to create the **AAHIVM Institute for Hepatitis C** to house our current and future hepatitis C education and advocacy programs and activities.

While AAHIVM has already conducted a number of HCV policy and educational initiatives (such as the clinical workshops on co-infection),

the Institute will provide a greater focus on HCV for the Academy, and expand our programmatic activities in the future.

The Institute will be visually accessible via an online portal from the AAHIVM website and will include the latest AAHIVM educational initiatives, prevention and testing information, relevant research and policy activities. As part of the Institute, we also will launch a monthly e-newsletter on co-infection (see Dr. Margaret Terry-Hoffman's adjacent article).

The Academy hopes this new Institute will improve the prevention, testing, care and outcomes for patients at heightened risk for, or infected with, Hepatitis C throughout the country. **HIV**



ABOUT THE AUTHOR:

Bruce Packett is the deputy director of the American Academy of HIV Medicine and also serves as the AAHIVM director of professional development.

HIV-HCV Co-Infection ReSource

BY MARGARET HOFFMAN-TERRY, MD, AAHIVS

AAHIVM IS PROUD TO ANNOUNCE A NEW RESOURCE

for the busy HIV practitioner called the HIV/HCV Co-infection ReSource e-newsletter.

Guided by myself and Dr. Mark Sulkowski from John Hopkins University School of Medicine, this newsletter will be sent electronically to Academy members and credentialed providers and posted within the AAHIVM Institute for Hepatitis C portal of the Academy website.

The newsletter will contain a synthesis of the most relevant recent clinical studies in co-infection presented and published throughout the world in an attempt to keep our members current in this rapidly changing arena. Case studies will be presented and used to illustrate crucial points. Each issue will also feature an article by Jules Levin highlighting the many

non-clinical issues surrounding HCV and its treatment, such as drug costs, insurance coverage, public policy, etc. "Ask the Experts" questions will be welcomed as will guest case studies.

Let AAHIVM help keep you current on the most crucial clinical and non-clinical information in this important and ever changing field by combing through the huge and ever changing body of hepatitis C literature, condensing it into an easy to read newsletter coming to you via email every two months.



ABOUT THE AUTHOR:

Dr. Margaret Hoffman-Terry is Vice-Chair of the AAHIVM Board of Directors and Chair of the AAHIVM Public Policy Committee. She is an infectious disease specialist at Leigh Valley Hospital in Allentown, Pennsylvania.

Donna E. Sweet,

MD, MACP, AAHIVS

University of Kansas, School of Medicine
Wichita, Kansas

AFTER COMPLETING HER MEDICAL SCHOOLING at the University of Kansas, School of Medicine in Wichita, Sweet went on to practice medicine at the very same place. She has been treating people living with HIV since 1983 and has spent the entirety of her medical career in practice at the University of Kansas, School of Medicine in Wichita.

Today, her medical practice association, which specializes in General Internal Medicine and HIV care, is comprised of two physicians, three advanced practice registered nurses, and one physician assistant. On any given day, Dr. Sweet sees 20 outpatient visits with a combination of HIV-infected patients and internal medical primary care. She notes that the percentage of HIV-infected patients she sees over the age of 50 has increased steadily over the years and the internal medicine practice has seen an increase in patients over the age of 70.

"This was an underserved, stigmatized population with a fascinating disease that needed care," says Dr. Sweet when asked what motivated her to pursue specializing in HIV care. Getting into HIV care, education, and advocacy early in the epidemic has given Dr. Sweet unique and valuable insights and perspectives that she has graciously shared with AAHIVM for years.

Dr. Sweet motivates her patients to adhere to their treatment regimens by providing ample information about the importance of adherence and great praise when they do well, particularly when their virus becomes undetectable because of strong adherence to treatment.

Says Dr. Sweet, "The most rewarding part is seeing patients with HIV do well over long periods of time."

Dr. Sweet and her team have implemented several unique and successful practices to improve retention rates and access to care. For instance, they have a staff person who focuses completely on patients who are lost to care, meaning they have not been seen for one year or more.

This staffer has been very successful in locating these patients through a variety of resources and has decreased



significantly the rate of patients lost to care.

Additionally, Dr. Sweet and her team travel every six to eight weeks to three sites in rural Kansas to see patients living in those areas. They are "hosted" by a variety of health care settings, but manage these patients' care from their home site in Wichita with the assistance of local area HIV case managers in these rural locations.

Dr. Sweet says financial barriers constitute the greatest obstacle she faces as an HIV care provider in keeping patients in care. To that end, she is an ardent supporter of the Ryan White Care Act and hopes to continue to see it reauthorized and appropriated.

Looking to the future, Dr. Sweet envisions HIV care will be much more integrated into primary care settings.

When asked why she is an AAHIVM Member, which she has been since the organization's inception in 2001, Dr. Sweet says, "Scott Hitt, the founder of AAHIVM, wouldn't leave me alone until I joined! He wanted me to build and chair the Mountain Plains Chapter of AAHIVM, which I have done for over a decade now."

In addition to serving as Chair of AAHIVM's Mountain Plains Chapter, Dr. Sweet has spent several years as the Chair of AAHIVM's National Board of Directors. "Her unwavering commitment to AAHIVM and its mission has been key in AAHIVM's ever-growing reach and influence," says James M. Friedman, AAHIVM executive director.

Much of AAHIVM's current ability to provide cutting-edge HIV educational content and to shape public policy to benefit HIV care providers can be credited to Sweet's excellent leadership of the organization, Friedman says. **HIV**



EDITOR'S NOTE:
This editorial
originally appeared
on www.HIV-Age.org
in recognition of
HIV/AIDS and Aging
Awareness Day.

New Horizons for HIV/AIDS

BY GREG LOUGANIS

WHEN I WAS DIAGNOSED IN 1988 WITH HIV, I thought it was a death sentence. The Olympic Games were only six months away and I had to make the decision whether to train or lock myself away and wait to die. The choice to train for the Olympics was a decision I didn't come to lightly. Once that decision was made, I listened to my doctors and religiously took my AZT. Thank God I did. My decision paid off. I won two Olympic Gold medals and was able to reclaim my championships from the previous Olympic Games. But even while celebrating my success at the Olympics at 28 years old, I honestly didn't expect to see my 30th birthday.

Now at 54, I am still here! I am healthy, both physically and emotionally. I have benefited tremendously from the extraordinary medical advances over the years. But in addition to the growing treatment options, I think another secret to my surviving and thriving is that I didn't allow my HIV/AIDS to take over as an obsession in my life. It was and still is only a mere part of me. It does not define me.

But the road has not been easy. To support myself, I had to sell my life insurance policies and ran thru my savings. By my 40's, I realized that I was going to be around a lot longer than I had expected. In other words, I said to myself, "Heck, I need to get a job!"

I had to reinvent myself. I eventually returned to diving. I began my new venture, after a near 20-year absence, as a coach for an eight to 14-year-old developmental team. It felt great to be giving back to the sport that I learned to love. I was soon recruited to become "Athlete Mentor" for USA Diving, all of which is chronicled in my Documentary "Back on Board." It is a poignant film, informative and inspiring on many levels (visit www.louganisdoc.com to learn more!).

I was recently talking with a fellow 50-something friend about the challenges facing our population of long-term HIV/AIDS survivors. We agreed that while remaining so grateful to be living longer, we are also constantly reassessing the financial burden of aging. For instance, I sold my home because the mortgage was weighing me down. My income now is modest and I have to budget for a much longer life than I had anticipated.

I find this is a struggle with many older people living with HIV/AIDS. We worry about housing and living expenses, insurance, and medical maintenance. This is not unlike the worries of the majority of older Americans. The difference is they were expecting to live to a ripe old age.

For my healthcare, I subscribe to both Eastern and Western treatment for living with my constant companion, HIV/AIDS. I take my cocktail of meds in the morning and in the evening,

along with supplements and Chinese herbs. I go to acupuncture once a week, which helps my immune support, as well as pain management of old sports injuries. I also exercise, staying active with cardio, and Yoga practices. My exercise program is just as important to me as my morning and evening meds regimen.

I will also soon be celebrating my first anniversary of being married to my soul mate. We are a "sero-different" couple, me being POZ and he negative.

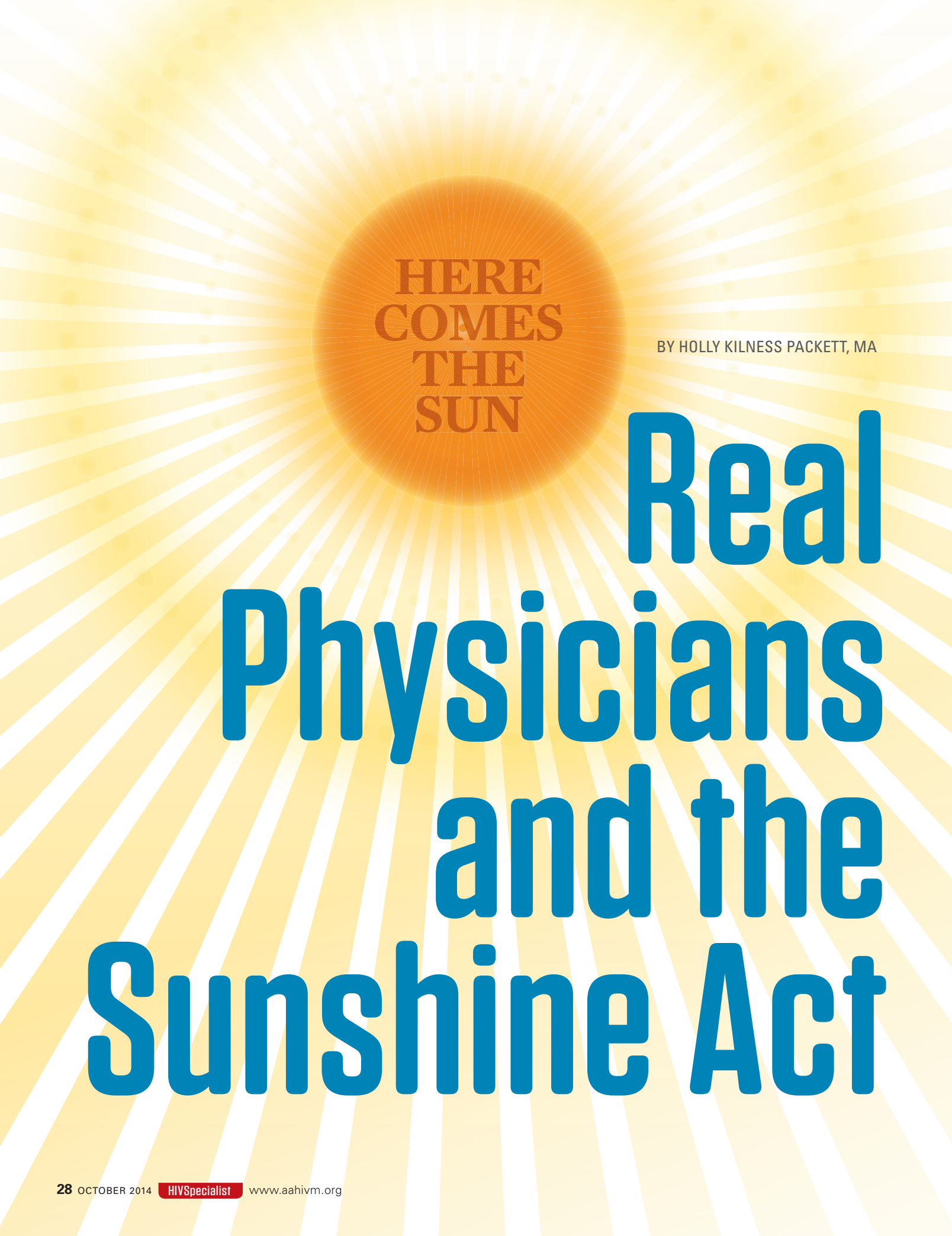
We are looking forward to growing old together and simplifying our lives. But at the moment we are looking at our finances to get a grasp on our future, determining what to do until we reach 65 or 67 when we can take advantage of our IRAs and Pensions. It's a scary proposition. But I see this as an opportunity to not give into the fears of change, but invest my energy into once again reinventing myself.

I have also found a new spiritual path of reinvention. I am finding answers in the stillness of my meditations, putting my faith in inspiration rather than "hope" and "wishful thinking." The key is action. It might not be at the pace I would have hoped for, but I ask myself everyday if my daily actions are moving me forward to my goals. If I answer "yes," then I am moving at the pace I need to be moving. This patient, steady mentality is a new skill set for me and I am still learning! I remind myself it took years to perfect a single dive, and that is what I am doing now. I am honing new skills and the learning curve might mean I have to repeat an action over and over to learn.

I guess my most valued lesson is forgiveness, mostly of myself, and living life on life's terms. I am grateful I have a husband who understands and is on that same journey with me in his own way. Forgiveness and gratitude!



Namaste, Greg Louganis



HERE
COMES
THE
SUN

BY HOLLY KILNESS PACKETT, MA

Real Physicians and the Sunshine Act

**The Sunshine Act,
a law intended
to increase
trust between
physicians,
patients, and
the general
population took
public effect
last month.**

ON SEPTEMBER, 30, 2014, the names and ID numbers of thousands of physicians across the United States were published along with information about monetary payments, research funding, ownership and investments, and other compensation they received from pharmaceutical and medical device manufacturing companies in 2013.

To implement the law, included in the Affordable Care Act, the Centers for Medicare and Medicaid Services (CMS) created a public database called the “Open Payments System,” where physicians and medical entities are listed, along with information about monetary relationships or payments. Prior to publication of the information, stakeholders—including physicians and organizations such as AAHIVM—expressed concern to CMS over the potential for confusion and misinterpretation of the data.

There was reason for this concern. When CMS released Medicare Part B data earlier this year, only names and numbers were made public, with little context explaining the data. Press coverage was filled with misinterpretations before the data could effectively be explained.

The Sunshine Act proposed to address this problem by instructing CMS to provide contextual information along with the payment data. However, the extent of the contextual information, and the manner in which it would be presented was never made clear. In addition, anecdotal reports from physician groups indicated that many physicians were unaware of the details of the law, and what it covered or did not. Even fewer seemed to be aware of the opportunity for physicians to preview the data from June 1 until the mid-September 2014 deadline, and dispute any inaccuracies.

A final alarm bell was raised when CMS said this summer that approximately one-third of the payment information would be withheld from publication due to “data inconsistencies” and “intermingled data.” CMS said some of the records linked physicians to incorrect medical license numbers or national provider identification numbers. The agency said that the withheld records would be published in the next reporting cycle in 2015. However, no information was released on exactly which data records were withheld, or who was included.

AAHIVM signed a letter with 25 other physician organizations in July expressing to CMS administrators our concern about these actions. That letter can be seen here: <http://freepdfhosting.com/8dcf424b5f.pdf>

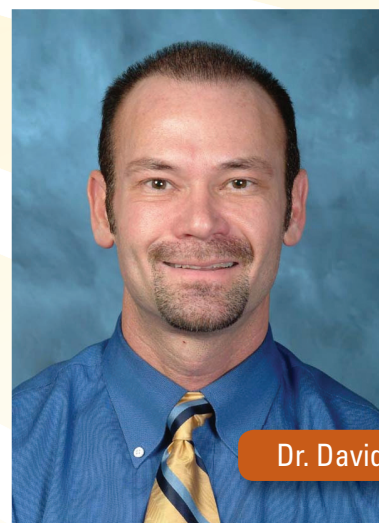
Meanwhile, physicians who have been navigating through this process have very different stories about their experiences leading up to the publication, and their positions now that the data has been published. Here are three such examples from AAHIVM members:

Dr. Hardy’s Story

Dr. David Hardy is Clinical Professor of Medicine at the David Geffen School of Medicine at UCLA. From 2002 to 2013 he was Director of the Division of Infectious Diseases at Cedars-Sinai Medical Center and oversaw academic, research and administrative activities. Dr. Hardy received his medical degree from Baylor College of Medicine, completed his residency in internal medicine at Harbor-UCLA Medical Center, and a clinical fellowship in infectious diseases/immunology and clinical AIDS research at the UCLA School of Medicine.

Dr. Hardy has been caring for persons with HIV infection since 1982, and has conducted research in HIV since 1984, including treatment and prevention of opportunistic infections, antiretroviral agents, immunotherapies and hepatitis treatments as well as retroviral vector research and gene therapy. He currently serves as a medical consultant for a small biotechnical company studying gene-modified T-cells and stem cells as a potential cure for HIV infection.

Due to these positions, and others, Dr. Hardy has received various forms of compensation for speaking engagements, participation on advisory panels, traveling to meetings and conferences, and hundreds of hours leading research efforts



Dr. David Hardy

or reviewing their results during the Sunshine Act reporting period of 2013.

Dr. Hardy was particularly interested in the Sunshine Act database leading up to its publication on September 30. He expected that he would be listed in the database, along with information about the various types of compensation he has received from his work in these projects.

He is proud of the work he has done to advance research and educate providers in the field.

“At the end of the day, I have no problem with having my financial interactions with the biotech/pharmaceutical industry detailed in writing on a government website,” stated Dr. Hardy. “I know that the relationships which I have developed, often over many years, with colleagues in this industry are carefully considered, healthy, non-reciprocal, honest and beneficial to others than myself and the industry member.”

However, Dr. Hardy was concerned about the way in which the information would appear. He was keenly aware of the possibility that the database could portray this information in a confusing and even damaging light.

For example, last year, Dr. Hardy was principle investigator of the first clinical trial of the new medication sofosbuvir (Sofvaldi), used to treat chronic hepatitis C in persons co-infected with both HIV and HCV. This study was particularly important because it was the first trial to offer these patients an all-oral treatment regimen without the use of the poorly tolerated, injectable drug pegylated interferon-alpha.

The study’s results were remarkable as they demonstrated that approximately 80 percent of study participants were CURED of their HCV infection with minimal side effects after only 12 to 24 weeks of oral treatment.

These data were used by the study sponsor, Gilead Sciences, to apply for FDA approval of this formerly experimental drug for use in the U.S. Approval was granted in late 2013.

The trial was funded by Gilead Sciences. Dr. Hardy worked on it for over two years, and was paid about \$72,000 by the company. These funds were used to cover part of the salaries and benefits of his research nurse/study coordinator, managerial assistant and for weekly stipends for the study participants. Of note, Dr. Hardy received none of these funds directly as the contract was between his medical center and the study sponsor. Moreover, none of these funds were used to pay for Dr. Hardy’s salary or benefits.

That trial was overseen by FDA, an independent data and safety monitoring board (DSMB) and by the local Institutional

Review Board at Dr. Hardy’s medical center.

Now, in large part due to the remarkable results of the study, persons co-infected with HIV and HCV have a highly effective all-oral, well-tolerated, 12 to 24 week treatment option to CURE their HCV infection. It is safe to be taken with their HIV medications.

It was difficult to know in advance whether most of this information would be included in the database. Dr. Hardy expected that it would list some version of: *Dr. Hardy received approximately \$72,000 over 2 years from Gilead Sciences, for a study related to Solvaldi*. Taken alone and without explanation, that information has the potential for confusion and misunderstanding by patients and the public. The law only requires information on payments to physicians to be recorded, not non-physician staff members. Would their payments be indicated? Would the database indicate that none of the funds went directly to pay Dr. Hardy’s salary or benefits?

CMS had stated that in the case of research payments, the database would include the study name, the name of the covered product, and the National Drug Code, if applicable. Would the database indicate this study had contributed to making the first-ever cure for HCV available and on the market?

Educational speaking engagements are another issue. Due to his experience as an HIV-treating physician, researcher, and policy expert, Dr. Hardy is often asked to participate in conferences, symposiums, panels, and roundtables.

One of these opportunities last year, was held just before the 2013 International AIDS Society Conference in Kuala Lumpur, Malaysia. Dr. Hardy spoke on the subject of “Diagnosing and Treating HIV Infection among an Aging Patient Population” to a group of HIV health care providers from medical facilities throughout the Pacific Rim shared both his long-term clinical experience as well as evidence-based treatment guidelines with symposium attendees.

Of note, Dr. Hardy created and developed all of his own material for the presentation, for which he traveled 22 hours to Kuala Lumpur, Malaysia, using his own funds.

The program was funded by ViiV Health Care/GlaxoSmithKline, which provided Dr. Hardy with an honorarium of approximately \$1,500 for his time and effort in preparing the presentation, traveling, and giving a public speech.

Dr. Hardy expected the database to list the information that he had received \$1,500 payment from ViiV Health Care/GSK. Would it explain the rest of the story?

When the database went live September 30, Dr. Hardy received an almost shocking outcome to these questions. Almost no payment information was listed for him in the database. There has been no explanation available to Dr. Hardy as to why this is the case. It is possible that his records are part of the data withheld by CMS due to “data inconsistencies.” But at the moment, there is no way to confirm through the database site if that is the case. So it only remains for Dr. Hardy to be surprised by the outcome.

Now that data has been published, physicians have until December 31, 2014 to inform CMS of any discrepancies with the information. However, that information has already been made public, so anything that is incorrect is still out there for all to see.

Dr. Sweet's Story

Dr. Donna Sweet, professor of internal medicine and a clinician at the KU School of Medicine-Wichita, focuses on treating patients with HIV and AIDS and runs one of the most lauded Ryan White clinics in the nation.

Before attending medical school at KU, Dr. Sweet had a background in microbiology research. She joined the KU faculty in 1982 and has over 25 years of experience working in HIV medicine. In addition to her role as a clinician, Dr. Sweet is president of the Medical Society of Sedgwick County and past Chair of the Board of AAHIVM. She works extensively with the Health Resources and Services Administration (HRSA), and is director of the Kansas AIDS Education and Training Center. She also serves as national co-chair for the CDC HRSA HIV/AIDS Advisory Council (CHAC).

Dr. Sweet lectures throughout the United States and the world to educate other health care providers about HIV and AIDS. For example, she participated in the Eurasian Medical Education Program, traveling to Russia 16 times to educate physicians on HIV and tuberculosis. She spends hundreds of days each year fulfilling requests for her participation on advisory panels and in speaking engagements at various trainings, meetings and conferences.

For many of these events, Dr. Sweet books her own travel, develops her own materials, slides, or talking points, and contributes an incredible amount of time. She travels on week days and weekends, and participates in events during the day and at night, and then rushes home to see patients in her clinic, which, incidentally, continues its work in part due to significant fundraising efforts. Recently, Dr. Sweet auctioned off a night of home cooking at her house, in which she will prepare a several course meal for the guests along with wine parings and dessert. The clinic could not operate without regular fundraising efforts such as these.

Many of the professional efforts in which Dr. Sweet participates are sponsored by one pharmaceutical company or another. Sometimes directly or through a third party organization, Dr. Sweet receives compensation for some of this travel and for participating in some of these events, though not all. Therefore, Dr. Sweet expected to have an amount of information published about these engagements in the Open Payments database.

In June of 2014, CMS made an early view of the gathered data available to physicians and urged them to log on to check them for accuracy. Dr. Sweet was one of many physicians who attempted to do so and found the process excessively cumbersome.

Physicians were first required to complete the CMS e-verification process via the CMS Enterprise Portal. The second step was registration with the CMS' Open Payments system. Only then, could physicians request their individual report containing payment data attributed to them. If any of the information was incorrect, physicians could dispute it and ask for a correction.

However, to Dr. Sweet's surprise no information was listed for her in the preliminary database. There was nothing there for her to validate or dispute, and no way to contact CMS to inquire as to why.

When CMS issued announced that some of the payment data would be withheld until the next reporting cycle, it was natural to conclude that perhaps Dr. Sweet's information was part of that set. But on September 30, an even bigger surprise awaited Dr. Sweet. She

was listed in the database after all. In fact, she was listed several times. But unlike the other physicians listed, she never had the opportunity to review her information for accuracy prior to its public release.

Now that data has been published, physicians have until December 31, 2014 to inform CMS of any discrepancies with the information. However, that information has already been made public, so anything that is incorrect is still out there for all to see.



Dr. Donna Sweet

Dr. Brown's Story

Kathy Brown is the HIV Program Chief of Group Health Cooperative in Seattle, WA. She was previously a practicing internal medicine physician and HIV Specialist in Washington state and HIV Medical Director at Country Doctor Community Health Center in Seattle. She also previously served as a physician with Pike Street Medical Clinic, and worked with a community health center in Texas that provided primary care to approximately 2,000 HIV patients.

Dr. Brown received her Doctorate of Medicine Oregon Health and Sciences University Medical School and served as Adjunct Assistant Professor with the Department of Medicine at the University of Texas Medical Branch. She serves on the AAHIVM Northwest Chapter Chair and on the AAHIVM National Board, as well as on the Health HIV Board of Directors. She has nearly 20 years of experience in research, academia, and medical treatment and care.

As a practicing physician, Dr. Brown has made a standard practice of not accepting money from drug companies, both before and after the Sunshine Act. She has been fastidious in maintaining this practice, even paying for her own dinner at events sponsored by companies.

Last summer, Dr. Brown paid \$97.00 out of her own pocket for a meal at a drug company-sponsored presentation, so she wouldn't be recorded as taking money from the company. The event sponsors divided the total cost of the meal

We encourage our members to take an active role in working to ensure that the data published about them is accurate, and to open a real dialogue with your patients to address any of concerns about their interactions with companies and what it means for their care and treatment.

for all of the attendees by the number of people present and charged her for “her portion” despite the lackluster meal it represented. She was put off by the experience, concerned that it might be mistakenly reported in the database.

So this summer when the initial data was made available for physician review, she decided to check the Sunshine Act database. What she encountered was more trouble than she had ever expected. Dr. Brown said it took her two hours to complete Phase 1 of the registration process and to apply for access to the Open Payments. However, after registering and attaining access to the database, she logged onto her report, and found herself listed several times.

The database reported that Dr. Brown had received payments for consulting from a company other than the one that sponsored the dinner, and that the entries showed that she had received travel money from them. In fact, last year Dr. Brown was hired by HealthHIV, a non-profit association based in Washington DC, to participate in mentoring programs for HIV providers. She did not know that a drug company was the sole funder for that work, through a grant given to HealthHIV.

The Sunshine Act applies to payments or other transfers of value between applicable manufacturers group purchasing organizations (third party organizations), and physicians, whether they were “direct” or “indirect” in nature. So these payments were reported to CMS by the pharmaceutical company, and included in the database. However, Dr. Brown was never notified of that fact prior to checking for herself. She was as surprised as anyone to learn she had taken money from that company.

The preliminary database allowed physicians to dispute any entries they believed to be incorrect. So, Dr. Brown marked “dispute” for each of those payments on her Open Payments report. In Dr. Brown’s own words, she, “had no actual professional relationship with the company that had funded the project.”

Shortly thereafter, she was contacted by the funding company about the dispute. They informed her that their lawyers interpreted the Sunshine Act as saying the payments had to be reported, and asked that she remove her “dispute” claim, implying that it looked bad for them. Dr. Brown expressed her frustration and her concern that the payments could be



Dr. Kathy Brown

interpreted as gifts of travel and food that might appear to be compromising her standards.

The company assured her that when the payments were listed publicly, there would be contextual language along with the data entry stating that the payments were for mentoring services and associated travel on behalf of HealthHIV. The company continued to contact Dr. Brown until she officially “withdrew” all the

disputes indications on the website. However, she remained worried about what the data publication would hold.

When the database went live on September 30th, the payments were listed, along with the explanations and contextual information about the nature of the payments and program with HealthHIV.

However, she noted that the contextual information was not immediately apparent amidst the listed data. Any single entry is relatively hard to access, and the full contents of it are difficult to digest at first glance.

Ultimately, said Dr. Brown, “I’m not sure who the site is intended to serve.”

The Sunshine Aftereffect

Ultimately, AAHIVM supports efforts to increase transparency and the sharing of information about the collaborations with biopharmaceutical and medical technology companies and physicians on research, education, and improvements to prevention, care and treatment. This is why the Sunshine Act was created.

While the intent of the Sunshine Act is positive, it is important to keep in mind that this data also has potentially significant ramifications for the reputations of physicians around the country. Now that data has been published, physicians have until December 31, 2014 to inform CMS of any discrepancies.

We encourage our members to take an active role in working to ensure that the data published about them is accurate, and to open a real dialogue with your patients to address any of concerns about their interactions with companies and what it means for their care and treatment.

Hopefully, the Sunshine Act ultimately will increase awareness and dialogue on this important issue, and not create more problems than it hopes to solve in the process. **HIV**



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Preexposure Prophylaxis 101

A Practical Guide to Delivering PrEP for the HIV Care Provider

IN MAY 2014, the Centers for Disease Control and Prevention (CDC) published the first comprehensive clinical practice guideline for the use of daily oral antiretroviral preexposure prophylaxis (PrEP) for the prevention of HIV infection¹, along with a clinical providers' supplement.² If targeted to persons at substantial risk for acquiring HIV infection and taken with high adherence to daily dosing, the scale-up of PrEP use can have a significant impact and contribute to reducing the approximately 50,000 new HIV infections occurring annually in the US.

Despite increases in HIV testing, delivery of effective antiretroviral treatment to persons with diagnosed HIV infection, continued community education, and condom promotion, there has been no significant change in the estimated incidence of HIV infection in more than a decade.³ Expanded treatment has not yet achieved high enough coverage and rates of suppressed viral load to alter the course of the US epidemic.

In some subpopulations, HIV infection is actually increasing. For example, among men having sex with men (MSM), who comprise the majority of newly diagnosed HIV infections,⁴ the number of new cases reported each year is rising, and the rate of reported condom use is decreasing.⁴ Racial/ethnic disparities in rates of HIV infection are increasing for MSM, and are most marked among young African American MSM, 13-29 years old.^{3,5} These facts make it clear that additional effective prevention methods are required to meet the National HIV/AIDS Strategy goal to reduce the number of new infections.

What HIV Providers Should Know about PrEP Safety and Efficacy

The efficacy and safety of PrEP to prevent sexual HIV acquisition among MSM⁶ and heterosexuals^{7,8} have been demonstrated in several clinical trials of daily oral tenofovir (TDF) coformulated with emtricitabine (FTC) [Truvada] or TDF alone [Viread]. Based on these trials, FDA approved a Truvada indication for prevention of sexual acquisition of HIV infection in July, 2012. In 2013, a trial of daily oral TDF in injection drug users (IDU) demonstrated safe and efficacious use of PrEP for this population.¹⁰

In these trials, the level of protection was highly correlated with medication adherence. Among persons with detectable blood levels of TFV (tenofovir), effectiveness against sexual acquisition was 86-92 percent; in the IDU trial specifically it was 74 percent. Two clinical trials of PrEP among heterosexual women did not demonstrate efficacy^{9,10}; in these trials, medication adherence was very low.

Across all the PrEP trials, no clinically significant renal or bone toxicity was seen. Side effects were few (less than 5

Expanded treatment has not yet achieved high enough coverage and rates of suppressed viral load to alter the course of the US epidemic.

percent), mild, and transient, and resolved over the first one to two months of PrEP use. The most commonly reported side-effects were headache, abdominal pain, or nausea/vomiting. Among persons who acquired HIV infection in the PrEP trials, infection with virus containing mutations associated with TDF resistance (measured by standard genotyping) was seen only among those who were randomized to drug and started PrEP with unrecognized acute HIV infection.

In addition to the evidence of PrEP effectiveness for individual patients, particularly those with high medication adherence, on a population level, modeling suggests that PrEP can have significant impact if targeted to high incidence subpopulations, if high coverage in targeted populations or high levels of medication adherence are achieved.^{11,12}

Principles of Providing PrEP

HIV care clinicians who provide PrEP periodically should take brief sexual and drug use histories to screen for possible PrEP indications (See table, page 34).

When a potential PrEP candidate is identified, it will be critical to document the patient's HIV-negative status and exclude acute infection, determine that his or her estimated creatinine clearance is >60 mL/min, document hepatitis B immunity or the presence of active infection, screen for bacterial STIs, and perform a pregnancy test for women. It also will be important to determine the HIV status of a patient's usual sex partner/spouse and, if HIV-positive, their antiretroviral treatment status. For an HIV-discordant couple, where the positive partner is not being treated or is not virally suppressed, PrEP may well be indicated for the negative partner.

Table: Summary of Guidance for PrEP Use

	Men Who Have Sex with Men	Heterosexual Women and Men	Injection Drug Users
Detecting substantial risk of acquiring HIV infection	• HIV-positive sexual partner • Recent bacterial STI • High number of sex partners • History of inconsistent or no condom use • Commercial sex work	• HIV-positive sexual partner • Recent bacterial STI • High number of sex partners • History of inconsistent or no condom use • Commercial sex work • In a high-prevalence area or network	• HIV-positive injecting partner • Sharing injection equipment • Recent drug treatment (but currently injecting)
Clinically eligible	• Documented negative HIV test result before prescribing PrEP • No signs/symptoms of acute HIV infection • Normal renal function; no contraindicated medications • Documented hepatitis B virus infection and vaccination status		
Prescription	Daily, continuing, oral doses of TDF/FTC (Truvada), ≤90-day supply		
Other services	• Follow-up visits at least every 3 months to provide the following: • HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment • At 3 months and every 6 months thereafter, assess renal function • Every 6 months, test for bacterial STIs		
	Do oral/rectal STI testing	• Assess pregnancy intent • Pregnancy test every 3 months	Access to clean needles/syringes and drug treatment services

For those with indications for and no contraindications to PrEP (e.g., HIV infection or poor renal function), education should be provided about the requirements of PrEP, and patients should understand clearly that prevention effectiveness depends on high adherence to daily dosing. Patients who agree to start PrEP should then be prescribed no more than a 90-day supply of Truvada at a dose of one pill daily. During follow-up visits every three months, clinicians should document the patient's continued HIV-negative status before refilling the prescription, and perform a pregnancy test for women with pregnancy potential. Clinicians should also determine estimated creatinine clearance and screen for bacterial STIs—including syphilis testing, and pharyngeal and rectal NAAT testing for gonorrhea and chlamydia among MSM, every six months and whenever patients are symptomatic. At every visit, providers should assess medication adherence, and for risk behaviors requiring supportive counseling.

What HIV Providers Can Do

All HIV care providers should regularly ask HIV-infected patients about the HIV status of their usual partner/spouse to identify discordant relationships, and make periodic HIV testing available to partners/spouses of unknown or negative status. When partners/spouses are known to be HIV-negative, HIV care providers should offer to discuss PrEP and non-occupational postexposure prophylaxis with negative partners, and assess reproductive desires

and intent (including among MSM couples).¹⁶ Safer conception options (including PrEP) should be offered to couples in discordant relationships who desire pregnancy.¹⁷

Clinicians who only see HIV-infected patients should identify PrEP providers to whom they can refer negative partners interested in PrEP. HIV-experienced clinicians also can consult with primary care providers who have limited experience prescribing antiretroviral medications. Providers who see both HIV-infected and HIV-uninfected patients should screen for indications and prescribe PrEP when indicated for their HIV-negative patients (See figure, page 36).

Using procedures familiar to HIV care providers, clinicians providing PrEP to their HIV-uninfected patients should also inquire about insurance coverage, and help patients apply for medication or co-pay assistance programs if needed. They should also provide peer support, share lessons learned, and educate new PrEP providers who may not yet be comfortable prescribing antiretroviral medication.

Implementation Issues

Adoption of new clinical interventions is often a slow process.^{13,14} In the case of PrEP, delivery should be adapted to different practice settings (e.g., STD clinics, medication-assisted drug treatment services, community health centers) where HIV-uninfected persons seek health care for other conditions. Critical next steps for making PrEP available to those who

would benefit most from its use include: 1) expanding provider awareness of PrEP and knowledge of the science supporting its use; 2) increasing awareness of PrEP among potential users; 3) identifying sources of PrEP care for persons at substantial risk for HIV acquisition; 4) developing brief behavioral screening methods to aid busy clinicians in identifying the subset of patients with whom they should discuss PrEP; 5) creating “user-friendly” patient education materials; and 6) providing brief messages and support services (e.g., reminder devices, “apps”) to elicit high rates of PrEP medication adherence. In addition, monitoring patients for long-term clinical safety and potential increases in HIV exposure risk behaviors will be required to inform our understanding of the potential risks of PrEP.

Conclusion

Integrating PrEP into HIV prevention may significantly reduce new HIV infections in the US. To achieve the intended

impact, PrEP should be made available to high-incidence populations while encouraging high medication adherence and discouraging HIV exposure risk behaviors. Our current challenges are to increase awareness among potential users, increase provider knowledge of recommended delivery practices, and make early adopter activity observable to the majority of providers.¹⁹

HIV

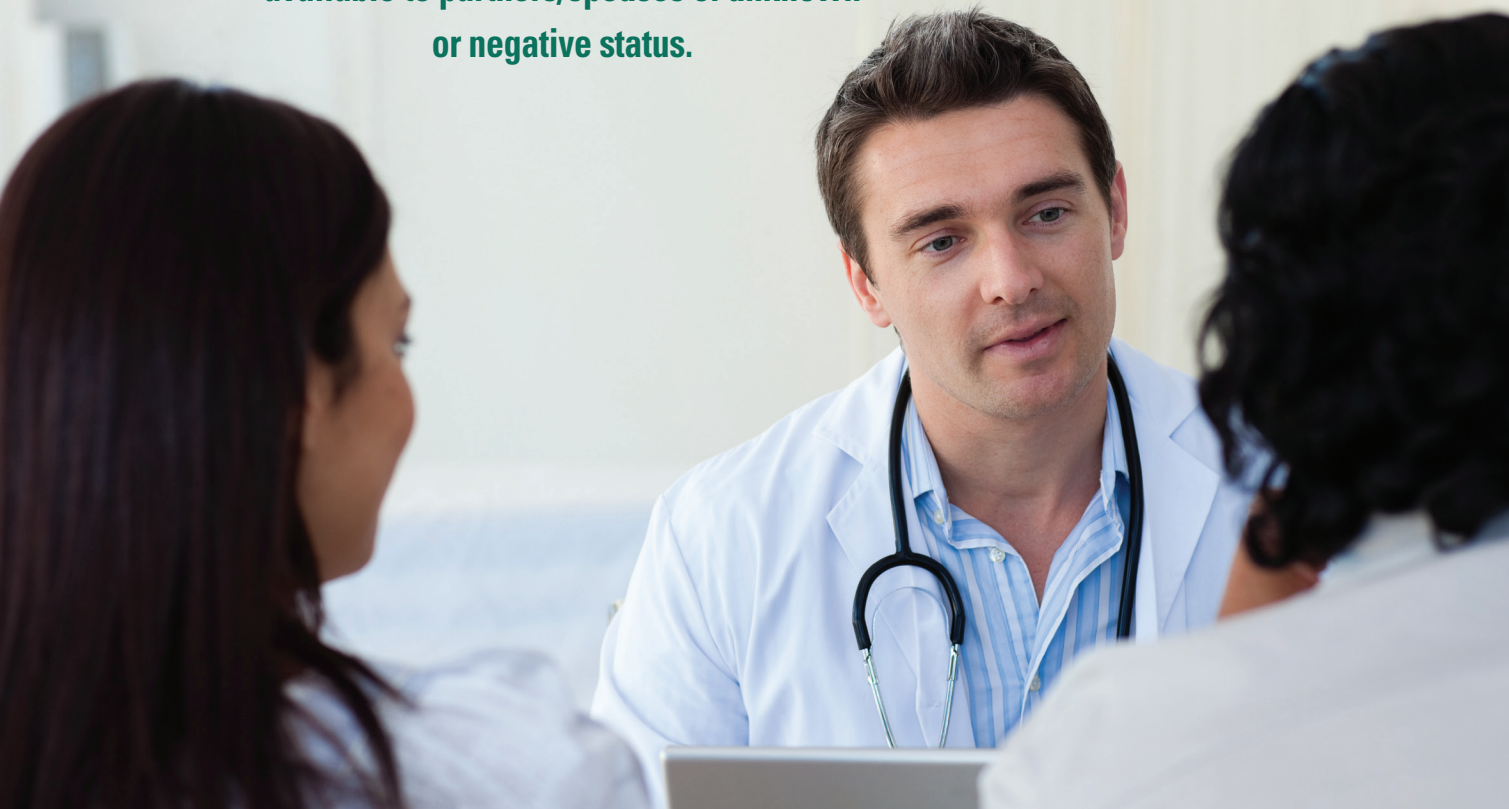


ABOUT THE AUTHOR:

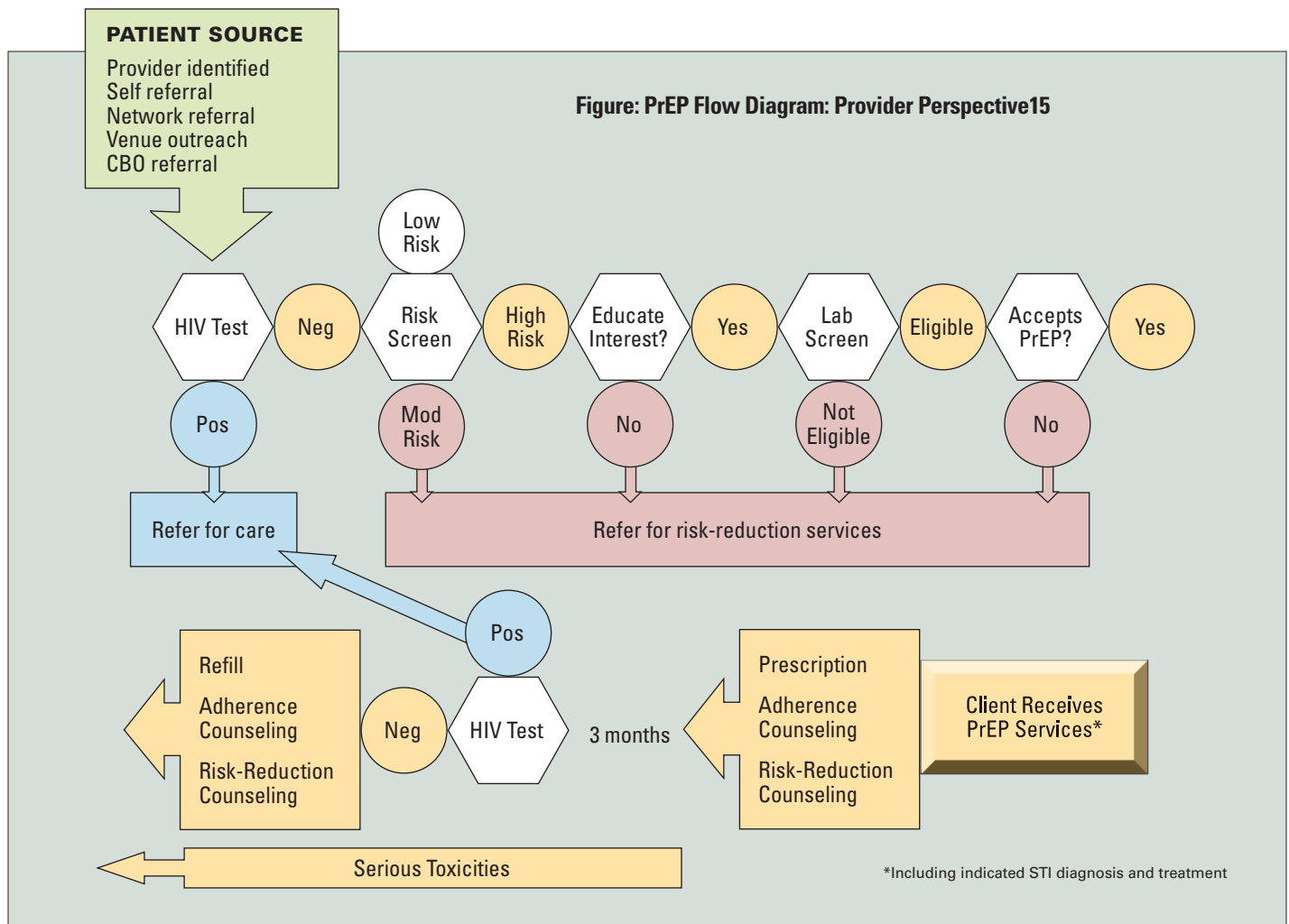
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All HIV care providers should regularly ask HIV-infected patients about the HIV status of their usual partner/spouse to identify discordant relationships, and make periodic HIV testing available to partners/spouses of unknown or negative status.

Clinicians seeking consultation about providing PrEP should call 855-HIV-PREP (855-448-7737).



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References

- Centers for Disease Control and Prevention; US Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States - 2014: a clinical practice guideline. 2014:1-67. <http://www.cdc.gov/hiv/pdf/guidelines/PrEPguidelines2014.pdf>. Accessed 28 May 2014.
- Centers for Disease Control and Prevention; US Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States—2014: clinical providers' supplement. 2014:1-43. <http://www.cdc.gov/hiv/pdf/guidelines/preprovidersupplement2014.pdf>. Accessed 28 May 2014.
- Centers for Disease Control and Prevention. Estimated HIV incidence in the United States, 2007-2010. *HIV Surveillance Supplemental Report*. 2012;17(4). http://www.cdc.gov/hiv/surveillance/resources/reports/2010supp_vol17no4/index.htm. Accessed 20 April 2013.
- Paz-Bailey G HH, Wolitski RJ, Prejean J, Van Handel MV, Le B, LaFlam M, Koenig LJ, Mendoza MCB, Rose C, Valleroy LA. HIV Testing and Risk Behaviors Among Gay, Bisexual, and Other Men Who Have Sex with Men—United States. *MMWR*. 2013;62(47):958-962.
- Prejean J, Song R, Hernandez A, et al. Estimated HIV incidence in the United States, 2006-2009. *PLoS one*. 2011;6(8):e17502.
- Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. Dec 30 2010;363(27):2587-2599.
- Baeten JM, Donnell D, Ndase P, et al. Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. *New England Journal of Medicine*. 2012;367(5):399-410.
- Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana. *New England Journal of Medicine*. 2012;367(5):423-434.
- Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *New England Journal of Medicine*. 2012;367(5):411-422.
- Jeanne Marrazzo, Gita Ramjee, Gonasagrie Nair, et al. Pre-exposure Prophylaxis for HIV in Women: Daily Oral Tenofovir, Oral Tenofovir/Emtricitabine, or Vaginal Tenofovir Gel in the VOICE Study (MTN 003). Paper presented at: 20th Conference on Retroviruses and Opportunistic Infections; 20 April 2013, 2013; Atlanta, GA.
- Buchbinder SP, Glidden DV, Liu AY, et al. HIV pre-exposure prophylaxis in men who have sex with men and transgender women: a secondary analysis of a phase 3 randomised controlled efficacy trial. *The Lancet Infectious Diseases*. 6/ 2014;14(6):468-475.
- Gomez GB, Borquez A, Case KK, Wheelock A, Vassall A, Hankins C. The Cost and Impact of Scaling Up Pre-exposure Prophylaxis for HIV Prevention: A Systematic Review of Cost-Effectiveness Modelling Studies. *PLoS Med*. 2013;10(3):e1001401.
- Balas EA BS. Managing clinical knowledge for health care improvement. *Yearbook of Medical Informatics*. 2000;Patient-centered Systems: 65-70.
- Berwick DM. Disseminating innovations in health care. *Jama*. 2003;289(15):1969-1975.

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