The AMERICAN ACADEMY of HIV MEDICINE®

HIV SPECIALIST

PATIENT CARE, PRACTICE MANAGEMENT & PROFESSIONAL DEVELOPMENT INFORMATION for HIV CARE PROVIDERS

June 2012 Volume 4 No. 2 www.aahivm.org

HIV & Healthy Relationships

What's Ahead for HIV Providers with the Affordable Care Act, Ryan White and Medicaid

JOIN US!

WHAT

On the eve of the International AIDS Conference, the AAHIVM Policy Forum will bring together top government leaders and healthcare experts to discuss what lies ahead for US HIV providers in the coming years, including impact of health reform implementation, the future of the Ryan White program, and what HIV practitioners need to do to prepare for the coming changes.

WHO

Former Assistant Secretary for Public Affairs to Secretary Sebelius, **Richard Sorian**, will serve as moderator and will welcome the following confirmed participants:

- **Dr. Steve Cha**
  Medical Director, Medicaid and CHIP, CMS
- **Jeffrey Crowley**
  former Director of the White House Office of National AIDS Policy (ONAP)
- **Jennifer Kates**
  Vice President and Director of HIV Policy at the Kaiser Family Foundation
- **Amy Killelea, JD**
  Senior Clinical Fellow, Harvard Law School and the Treatment Access Expansion Project
- **Courtney Mulhern-Pearson**
  Director of State and Local Affairs, San Francisco AIDS Foundation
- **Dr. Deborah Parham Hopson**
  Associate Administrator for HIV/AIDS, HIV/AIDS Bureau, HRSA
- **Dr. Donna Sweet**
  Chair of the AAHIVM Board of Directors
- ****Dr. Grant Colfax**
  Director of the White House Office of National AIDS Policy (*Invited*)

WHERE

Grand Hyatt Hotel,
Constitution A Room
1000 H Street, NW
Washington, DC

WHEN

July 21, 2012
1pm-4pm

AAHIVM
American Academy of HIV Medicine

To register, go to our website at **www.aahivm.org.**

BY JAMES M. FRIEDMAN, MHA, EXECUTIVE DIRECTOR, AAHIVM

Uncertainty But Not Dread

Uncertainty Offers the Opportunity for Real Improvements

AS I CONSIDERED A TOPIC for this column, I looked back to some of my earlier columns for some guidance. Some of the topics included federal support for HIV workforce; routine testing and quality referrals; budgetary concerns; and HIV and aging. All good topics, and all had a certain underlying theme that I had not recognized before. They reflect a sense of moving forward and overcoming problems that many thought were unsolvable.

James Friedman

Looking at the current state of HIV care, uncertainty abounds around every corner.

- The changes brought on by the implementation of the Affordable Care Act (ACA) will impact patients and practitioners in a variety of ways—mostly good, but the transition period will be difficult—as change usually is.
- The Supreme Court will be handing down its decision on several aspects of the ACA later this summer. How they rule may change the infrastructure of the ACA in ways that could extend and alter the nature of the transition.
- And yes, there is a Presidential election in November—and its outcome will certainly will have an impact on the issues that affect our practices.
- Irrespective of how the three above issues are resolved, there is a giant federal debt that certainly will create downward spending pressures on discretionary federal funding. Programs we depend on, that we care for are in that discretionary category: HIV prevention in CDC, HIV care in the Ryan White Program, and HIV research in NIH.
- The FDA Advisory Committee reviewed the Truvada application for PrEP earlier this month—and the CDC PrEP guidance will be published later this year. Both will certainly create changes in HIV medical practice in the short term. In addition the FDA Blood Products Advisory Committee considered an over-the-counter HIV rapid test kit that could increase the number of HIV patients seeking care.
- HIV patients are living longer and growing older. The co-morbidities of aging will make their care more complicated.

There is plenty of uncertainty for our members and the patients we serve. And if we believe that "worse case scenarios" will occur in each of these areas of uncertainty, then we are in real trouble. But if history repeats itself, as it usually does, then we will find a way to succeed. And in each of these areas, there is the real chance to improve prevention, care and outcomes.

Now is the time for optimism. But optimism is rational only if we work hard to achieve it. Dread is easy. HIV

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p: 202-659-0699 • f: 202-659-0976
e: info@aahivm.org • w: www.aahivm.org

Primary Care Physicians to Get Medicaid Raise

PRIMARY CARE PHYSICIANS serving Medicaid patients will see their Medicaid payments rise under a proposed rule announced May 9 by Health and Human Services (HHS) Secretary Kathleen Sebelius.

Through the Affordable Care Act, the increase would bring Medicaid primary care service fees in line with those paid by Medicare. The boost would be in effect for calendar years 2013 and 2014. States would receive a total of more than $11 billion in new funds to bolster their Medicaid primary care delivery systems.

The increase, said Secretary Sebilius, is in addition to the nearly $560 million in higher Medicare payments that primary care physicians received in 2011 because of the Affordable Care Act.

The proposed rule would implement the Affordable Care Act's requirement that Medicaid reimburse family medicine, general internal medicine, pediatric medicine, and related subspecialists at Medicare levels in CY 2013 and CY 2014. The increase in payment for primary care is paid entirely by the federal government with no matching payments required of states.

Kathleen Sebelius

The health care law also includes other initiatives to bolster primary care and support the primary care workforce, including efforts to boost primary care residency slots, physician assistant and nurse practitioner training, and the National Health Service Corps.

Congress appropriated the necessary funds to cover these increases when it approved the health care law, so additional action is not required. However, the provision is among hundreds that could be nullified if the Supreme Court overturns the law in its entirety when it rules on constitutional challenges. A decision is expected late in June.

HHS Releases Adult and Adolescent Antiretroviral Treatment Guidelines

THE HHS PANEL ON ANTIRETROVIRAL GUIDELINES for Adults and Adolescents has released updated *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. Revisions to the October 14, 2011, version of the guidelines include both new sections and key updates to existing sections, including:

- New section on HIV and the older patient.
- New table on cost of antiretroviral drugs.
- Updated recommendations on initiation of antiretroviral therapy (ART) in treatment-naive individuals.
- Expanded discussion of use of hormonal contraceptives in HIV-infected women.
- Preliminary recommendations on coadministration of the newly approved hepatitis C virus (HCV) NS3/4A protease inhibitors (PIs) boceprevir and telaprevir.
- Recommendations on "when to start" ART in HIV-infected individuals diagnosed with tuberculosis but not receiving ART.
- Discussion of the role of effective ART in preventing HIV transmission.

For a complete preview of key updates to the guidelines, please visit http://aidsinfo.nih.gov.

ISTOCK, TOPNEWS.COM.SG

IN THE NEWS

FDA Panel Recommends Home HIV Test

A Food and Drug Administration advisory committee recently recommended approval by the Food and Drug Administration of the OraQuick In-Home HIV Test. The panel said the test should be made available over-the-counter (OTC), saying it is safe and effective and that the benefits far outweigh the potential risks.

If approved by the FDA, the test will be the first OTC test to be marketed for HIV or any infectious disease. FDA advisory committee recommendations are not binding, but are generally followed.

OraSure Technologies, Inc., the test manufacturer, also makes the already approved OraQuick ADVANCE Rapid HIV-1/2 Antibody Test. That test can only be used in a clinical setting and results are provided in 20 minutes. The In-home test is a modified version where the individual swabs the upper and lower gums with a test pad device. That device is then inserted into a vial of solution. Much like a pregnancy test, one line shows up if the test is negative, two lines means it's positive.

The kit includes step-by-step instructions on when to test, how to set-up and administer the test, and how to interpret the results. The company also provides information on how to follow-up on the results through OraQuick's Answer Center for support and local medical referral is also provided. The center is staffed 24 hours a day, 7 days a week.

FDA presenters favored approval.

"Greater access to testing will potentially lead to more people knowing their HIV status." said Dr. Elliot Cowan, who spoke on behalf of the FDA. "It appears there is a benefit in increasing the number of HIV positive people who know their status. There is public health impact and personal health impact."

"We plan to work with the FDA over the coming months to refine product label enhancements," said Douglas Michaels, the company's president and CEO. "And as quickly as we can get that done will determine how quickly we can get the product to retailers."

FDA UPDATE

HIV Advocates Urge FDA Approval of PrEP

NUMEROUS HIV/AIDS AND HEALTH ORGANIZATIONS have urged Food and Drug Administration (FDA) approval of emtricitabine/ tenofovir disoproxil fumarate (TDF/FTC or Truvada®) as pre-exposure prophylaxis (PrEP) to prevent HIV infection in adult men and women.

Their comments, submitted in advance of a May 10 FDA Advisory Committee meeting, pointed to compelling evidence on the efficacy of TDF/FTC as PrEP and highlighted the unique potential of this intervention to help slow the HIV epidemic in the U.S.

With PrEP, HIV-negative individuals who are at risk for HIV take anti-HIV medications in order to reduce their chances of becoming infected if exposed to the virus. FDA's advisory panel is considering data from clinical trials showing that TDF/FTC reduced the risk of sexual transmission of HIV in populations including men who have sex with men (MSM) and heterosexual women and men.

Modeling studies have shown that widespread access to PrEP could reduce new HIV infections, and thus the scale of the global HIV epidemic, substantially around the world. The FDA's decision on TDF/FTC as PrEP could help pave the way for global health funders and developing countries to step up their planning for implementation.

FDA Panel Recommends Gilead's Quad for HIV

A FOOD AND DRUG ADMINISTRATION ADVISORY PANEL on May 11 voted 13-1 to recommend Gilead Sciences Inc.'s Quad pill for people with HIV who have never been treated.

Independent experts caution that patients taking the drug should be monitored for possible kidney problems. Additionally, the experts urged for further research to assess the safety of Quad for women, who were under-represented in clinical trials.

"There are plenty of alternatives to Quad," said Dr. Michelle Estrella of Johns Hopkins University School of Medicine, who cast the sole dissenting vote. "There's no huge hurry in approving this drug before the outstanding studies are completed."

The pill is a combination of four agents: an experimental integrase inhibitor (elvitegravir), a booster (cobicistat), and two nucleotide reverse transcriptase inhibitors (emtricitabine and tenofovir).

In clinical trials, Quad was 88 percent effective in suppressing HIV, besting Gilead HIV treatment Atripla's efficacy of 84 percent. Nonetheless, trial data suggest there were a disproportionate number of kidney problems.

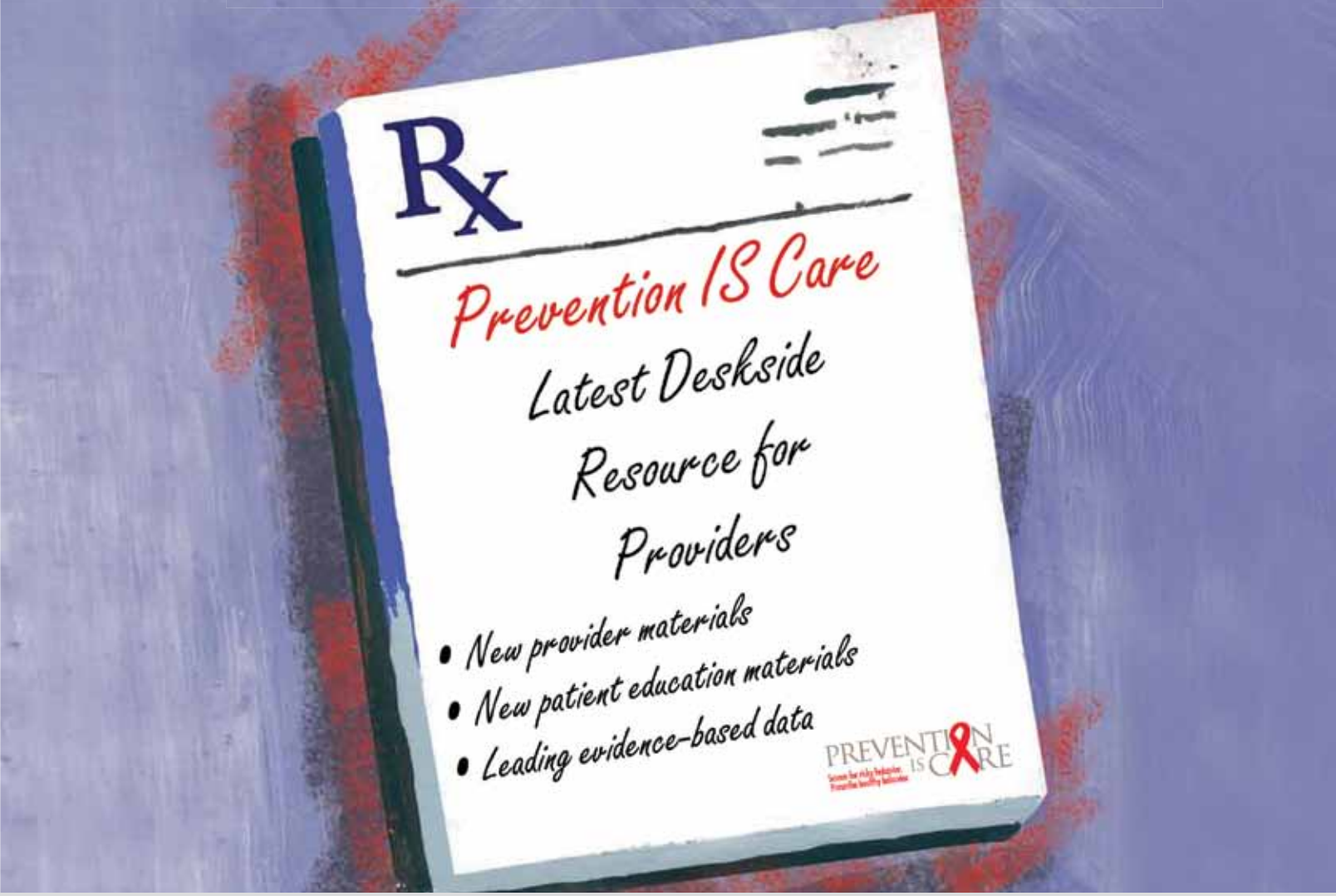
The once-daily pill schedule would help patients adhere to Quad, boosting treatment efficacy, said Gilead. The firm said it has not set a possible price for Quad. In an era of restricted public assistance for treatment, AIDS advocates worry about the cost of new AIDS drugs that offer only modest improvements in treatment.

The panel's recommendation will be considered by FDA regulators, and a decision on final approval is expected August 27.

ISTOCK, THINKSTOCK

NEW

Discussing prevention helps protect your patients and their partners.



CDC is pleased to announce a new *Prevention IS Care* Resource Kit with tools for HIV providers to use in HIV prevention discussions with patients.

To order free materials, visit www.cdc.gov/PreventionIsCare or call 1-800-CDC-INFO (232-4636).

CDC

PREVENTION IS CARE
Screen for risky behavior. Prescribe healthy behavior.

A Single Tablet Regimen That Reaches Many Treatment-Naïve Adults[1]

Indication[1]

COMPLERA is indicated for use as a complete regimen for the treatment of HIV-1 infection in antiretroviral treatment-naïve adults.

This indication is based on Week 48 safety and efficacy analyses from 2 randomized, double-blind, active controlled, Phase 3 trials in treatment-naïve subjects comparing rilpivirine to efavirenz.

The following points should be considered when initiating therapy with COMPLERA:

- More rilpivirine-treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure compared to subjects with HIV-1 RNA less than 100,000 copies/mL at the start of therapy
- 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 lamivudine/emtricitabine associated resistance compared to efavirenz

COMPLERA is not recommended for patients less than 18 years of age.

Please see additional Important Safety Information for COMPLERA on following pages.

Patient models. Pill shown is not actual size.

GILEAD

Important Safety Information[1]

BOXED WARNINGS: 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, 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 coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued EMTRIVA® (emtricitabine) or VIREAD® (tenofovir disoproxil fumarate), 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 coinfected with HIV-1 and HBV and discontinue COMPLERA. If appropriate, initiation of anti-hepatitis B therapy may be warranted**

References: 1. COMPLERA Prescribing Information. Gilead Sciences, Inc; August 2011. **2.** Molina J-M, Cahn P, Grinsztejn B, et al; for ECHO Study Group. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. *Lancet.* 2011;378(9787):238-246. **3.** Cohen CJ, Andrade-Villanueva J, Clotet B, et al; for THRIVE Study Group. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. *Lancet.* 2011;378(9787):229-237.

Put These Benefits Within Reach for Your Patients

Proven viral suppression through 48 weeks (HIV-1 RNA <50 copies/mL)[1-3]*

- Proven non-inferior viral suppression to efavirenz: 83% with rilpivirine + emtricitabine/tenofovir disoproxil fumarate (N=550) versus 81% with efavirenz + emtricitabine/tenofovir disoproxil fumarate (N=546)[1-3]
- Incidence of virologic failure: 13% with rilpivirine + emtricitabine/tenofovir disoproxil fumarate (N=550) versus 8% with efavirenz + emtricitabine/tenofovir disoproxil fumarate (N=546)[1]
- More rilpivirine-treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure compared to subjects with HIV-1 RNA less than 100,000 copies/mL at the start of therapy[1]
- 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[1]
- More subjects treated with rilpivirine developed lamivudine/emtricitabine associated resistance compared to efavirenz[1]

Demonstrated safety through 48 weeks[1]

- The most common adverse drug reactions (Grades 2-4, ≥2%) were insomnia and headache[1]
- Low rate of discontinuation due to adverse reactions (2% with rilpivirine + emtricitabine/tenofovir disoproxil fumarate versus 5% with efavirenz + emtricitabine/tenofovir disoproxil fumarate)[1]
- Smaller mean changes in fasting lipid levels (rilpivirine + emtricitabine/tenofovir disoproxil fumarate versus efavirenz + emtricitabine/tenofovir disoproxil fumarate)[1]
  - Total cholesterol (0 mg/dL versus 25 mg/dL), HDL cholesterol (3 mg/dL versus 9 mg/dL), LDL cholesterol (–2 mg/dL versus 13 mg/dL), triglycerides (–11 mg/dL versus 8 mg/dL)[1]

Additional information: Pregnancy Category B[1]

- There are no adequate and well-controlled studies in pregnant women[1]
- COMPLERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus[1]
- To monitor fetal outcomes of pregnant women exposed to COMPLERA, an Antiretroviral Pregnancy Registry has been established and healthcare providers are encouraged to register patients by calling 1-800-258-4263[1]

A complete once-daily, single tablet regimen[1]

- The recommended dose of COMPLERA is one tablet taken orally once daily with a meal[1]
- Because COMPLERA is a fixed-dose combination, it should not be prescribed for patients requiring dose adjustment such as those with moderate or severe renal impairment (creatinine clearance below 50 mL/min)[1]

For more information, please visit

www.complera.com

Safety and efficacy have not been established in patients less than 18 years old.[1]

*Study designs: The efficacy of COMPLERA is based on the analyses of 48-week data from 2 randomized, double-blind, controlled studies C209 (ECHO) and C215 (THRIVE) in treatment-naïve, HIV-1–infected subjects (N=1368). The studies were identical in design with the exception of the BR. Subjects were randomized in a 1:1 ratio to receive either rilpivirine 25 mg (N=686) once daily or efavirenz 600 mg (N=682) once daily in addition to a BR. In the ECHO study (N=690), the BR was emtricitabine/tenofovir disoproxil fumarate. In the THRIVE study (N=678), the BR consisted of 2 NRTIs: emtricitabine/tenofovir disoproxil fumarate (60%, n=406), lamivudine/zidovudine (30%, n=204), or abacavir + lamivudine (10%, n=68). The median baseline plasma HIV-1 RNA was 5 $\log_{10}$ copies/mL (range 2-7).[1] The primary endpoint was non-inferior viral suppression to efavirenz through 48 weeks (HIV-1 RNA <50 copies/mL).[2,3]

BR=background regimen; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor.

COMPLERA®

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

ONE COMPLETE SINGLE TABLET

Important Safety Information for COMPLERA *(cont)*

Please see previous page for **Boxed WARNINGS** about **lactic acidosis, severe hepatomegaly with steatosis,** and **exacerbations of hepatitis B upon discontinuation of therapy**.

CONTRAINDICATIONS

COMPLERA should not be coadministered with the following drugs, as significant decreases in rilpivirine plasma concentrations may occur due to CYP3A enzyme induction or gastric pH increase, which may result in loss of virologic response and possible resistance to COMPLERA or to the class of NNRTIs

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the antimycobacterials rifabutin, rifampin, rifapentine
- proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
- the glucocorticoid systemic dexamethasone (more than a single dose)
- St. John's wort (*Hypericum perforatum*)

WARNINGS AND PRECAUTIONS

New onset or worsening renal impairment

- Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir disoproxil fumarate. Assess creatinine clearance (CrCl) before initiating treatment with COMPLERA. Monitor CrCl and serum phosphorus in patients at risk for renal impairment, including patients who have previously experienced renal events while receiving HEPSERA® (adefovir dipivoxil). Avoid administering COMPLERA with concurrent or recent use of nephrotoxic drugs. Patients with CrCl below 50 mL per minute should not receive COMPLERA

Drug interactions

- COMPLERA should be used with caution when given with drugs that may reduce the exposure of rilpivirine
- COMPLERA should be used with caution when coadministered with a drug with a known risk of Torsade de Pointes

Depressive disorders

- The adverse reaction depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) has been reported with rilpivirine. During the Phase 3 trials (N=1368), the incidence of depressive disorders (regardless of causality, severity) reported among rilpivirine (N=686) or efavirenz (N=682) was 8% and 6%, respectively. Most events were mild or moderate in severity. The incidence of Grade 3 and 4 depressive disorders (regardless of causality) was 1% for both rilpivirine and efavirenz. The incidence of discontinuation due to depressive disorders among rilpivirine or efavirenz was 1% in each arm. Suicide attempt was reported in 2 subjects in the rilpivirine arm while suicide ideation was reported in 1 subject in the rilpivirine arm and in 3 subjects in the efavirenz arm. 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

Decreases in bone mineral density

- Bone mineral density (BMD) monitoring should be considered for patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of VIREAD® (tenofovir disoproxil fumarate)

Coadministration with other products

- COMPLERA should not be administered concurrently with other medicinal products containing any of the same active components, emtricitabine, rilpivirine, or tenofovir disoproxil fumarate (EMTRIVA® [emtricitabine], EDURANT™ [rilpivirine], VIREAD, TRUVADA® [emtricitabine/tenofovir disoproxil fumarate], ATRIPLA® [efavirenz/emtricitabine/tenofovir disoproxil fumarate]), with medicinal products containing lamivudine (EPIVIR® or EPIVIR-HBV® [lamivudine], EPZICOM® [abacavir sulfate/lamivudine], COMBIVIR® [zidovudine/lamivudine], TRIZIVIR® [abacavir sulfate/lamivudine/zidovudine]), or with adefovir dipivoxil (HEPSERA)

Fat redistribution

- Redistribution/accumulation of body fat has been observed in patients receiving antiretroviral therapy

Immune reconstitution syndrome

- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including the components of COMPLERA. Further evaluation and treatment may be necessary

ADVERSE REACTIONS

- The most common adverse drug reactions to rilpivirine (incidence greater than or equal to 2%, Grades 2-4) were insomnia and headache
- The most common adverse drug reactions to emtricitabine and tenofovir disoproxil fumarate (incidence ≥10%) were diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash

DRUG INTERACTIONS

- COMPLERA should not be used with drugs where significant decreases in rilpivirine plasma concentrations may occur **(See CONTRAINDICATIONS)**
- COMPLERA is a complete regimen for the treatment of HIV-1 infection; therefore, COMPLERA should not be administered with other antiretroviral medications
- **Drugs inducing or inhibiting CYP3A enzymes**: Rilpivirine is primarily metabolized by cytochrome P450 (CYP) 3A, and drugs that induce or inhibit CYP3A may thus affect the clearance of rilpivirine. Coadministration of rilpivirine and drugs that induce CYP3A may result in decreased plasma concentrations of rilpivirine and 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
- **Drugs increasing gastric pH**: Coadministration of rilpivirine with drugs that increase gastric pH may decrease plasma concentrations of rilpivirine and 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, coadministration of COMPLERA with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated drugs. Some examples include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, and valganciclovir
- **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 electrocardiogram. 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 electrocardiogram. COMPLERA should be used with caution when coadministered with a drug with a known risk of Torsade de Pointes

DOSAGE AND ADMINISTRATION

Adults: The recommended dose of COMPLERA is one tablet taken orally once daily with a meal.

Renal Impairment: Because COMPLERA is a fixed-dose combination, it should not be prescribed for patients requiring dose adjustment such as those with moderate or severe renal impairment (creatinine clearance below 50 mL per minute).

Please see brief summary of Full Prescribing Information for COMPLERA on following pages, including **Boxed WARNINGS** about **lactic acidosis, severe hepatomegaly with steatosis,** and **exacerbations of hepatitis B upon discontinuation of therapy**.

GILEAD

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

COMPLERA® (emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg) tablets Brief Summary of full prescribing information. See full prescribing information. Rx Only.

WARNINGS: 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, 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 coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued EMTRIVA or VIREAD, 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 coinfected 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 (emtricitabine/rilpivirine/tenofovir disoproxil fumarate) is indicated for use as a complete regimen for the treatment of HIV-1 infection in antiretroviral treatment-naive adults.

This indication is based on Week 48 safety and efficacy analyses from 2 randomized, double-blind, active controlled, Phase 3 trials in treatment-naive subjects comparing rilpivirine to efavirenz *[See Clinical Studies in Full Prescribing Information]*.

The following points should be considered when initiating therapy with COMPLERA:

- More rilpivirine-treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure compared to subjects with HIV-1 RNA less than 100,000 copies/mL at the start of therapy *[See Clinical Studies in Full Prescribing Information]*.
- 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 *[See Microbiology in Full Prescribing Information]*.
- More subjects treated with rilpivirine developed lamivudine/emtricitabine associated resistance compared to efavirenz *[See Microbiology in Full Prescribing Information]*.

COMPLERA is not recommended for patients less than 18 years of age *[See Use in Specific Populations]*.

DOSAGE AND ADMINISTRATION

Adults: The recommended dose of COMPLERA is one tablet taken orally once daily with a meal *[See Clinical Pharmacology in Full Prescribing Information]*.

Renal Impairment: Because COMPLERA is a fixed-dose combination, it should not be prescribed for patients requiring dose adjustment such as those with moderate or severe renal impairment (creatinine clearance below 50 mL per minute).

DOSAGE FORMS AND STRENGTHS

COMPLERA is available as tablets. Each tablet contains 200 mg of emtricitabine (FTC), 27.5 mg of rilpivirine hydrochloride (equivalent to 25 mg of rilpivirine) and 300 mg of tenofovir disoproxil fumarate (TDF, equivalent to 245 mg of tenofovir disoproxil).

The tablets are purplish-pink, capsule-shaped, film-coated, debossed with "GSI" on one side and plain-faced on the other side.

CONTRAINDICATIONS

COMPLERA should not be coadministered with the following drugs, as significant decreases in rilpivirine plasma concentrations may occur due to CYP3A enzyme induction or gastric pH increase, which may result in loss of virologic response and possible resistance to COMPLERA or to the class of NNRTIs *[See Drug Interactions and Clinical Pharmacology in Full Prescribing Information]*:

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the antimycobacterials rifabutin, rifampin, rifapentine
- proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
- the glucocorticoid systemic dexamethasone (more than a single dose)
- St. John's wort (*Hypericum perforatum*)

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 disoproxil fumarate, 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: It is recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B virus before initiating antiretroviral 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 coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued emtricitabine or tenofovir disoproxil fumarate, two of the components of COMPLERA. In some patients infected with HBV and treated with EMTRIVA, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. Patients who are coinfected 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 cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir disoproxil fumarate *[See Adverse Reactions]*.

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with COMPLERA. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment, including patients who have previously experienced renal events while receiving HEPSERA.

COMPLERA should be avoided with concurrent or recent use of a nephrotoxic agent.

Emtricitabine and tenofovir are principally eliminated by the kidney; however, rilpivirine is not. Since COMPLERA is a combination product and the dose of the individual components cannot be altered, patients with creatinine clearance below 50 mL per minute should not receive COMPLERA.

Drug Interactions: Caution should be given to prescribing COMPLERA with drugs that may reduce the exposure of rilpivirine *[See Contraindications, Drug Interactions, and Clinical Pharmacology in Full Prescribing Information]*.

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 *[See Drug Interactions and Clinical Pharmacology in Full Prescribing Information]*. COMPLERA should be used with caution when coadministered with a drug with a known risk of Torsade de Pointes.

Depressive Disorders: The adverse reaction depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) has been reported with rilpivirine. During the Phase 3 trials (N = 1368), the incidence of depressive disorders (regardless of causality, severity) reported among rilpivirine (N = 686) or efavirenz (N = 682) was 8% and 6%, respectively. Most events were mild or moderate in severity. The incidence of Grade 3 and 4 depressive disorders (regardless of causality) was 1% for both rilpivirine and efavirenz. The incidence of discontinuation due to depressive disorders among rilpivirine or efavirenz was 1% in each arm. Suicide attempt was reported in 2 subjects in the rilpivirine arm while suicide ideation was reported in 1 subject in the rilpivirine arm and in 3 subjects in the efavirenz arm. 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.

Decreases in Bone Mineral Density: Bone mineral density (BMD) monitoring should be considered for HIV-1 infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and Vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Tenofovir Disoproxil Fumarate: In a 144 week study of HIV-1 infected treatment-naive adult subjects treated with tenofovir disoproxil fumarate (Study 903), decreases in BMD were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving tenofovir disoproxil fumarate + lamivudine + efavirenz (-2.2% ± 3.9) compared with subjects receiving stavudine + lamivudine + efavirenz (-1.0% ± 4.6). Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the tenofovir disoproxil fumarate group vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through 144 weeks. Twenty-eight percent of tenofovir disoproxil fumarate treated subjects vs. 21% of the comparator subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the tenofovir disoproxil fumarate group and 6 subjects in the comparator group. Tenofovir disoproxil fumarate was associated with significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N telopeptide), suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving tenofovir disoproxil fumarate.

The effects of tenofovir disoproxil fumarate-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. For additional information, please consult the VIREAD prescribing information.

Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of VIREAD *[See Adverse Reactions]*.

Coadministration with Other Products: COMPLERA should not be administered concurrently with other medicinal products containing any of the same active components, emtricitabine, rilpivirine, or tenofovir disoproxil fumarate (EMTRIVA, EDURANT, VIREAD, TRUVADA, ATRIPLA), with medicinal products containing lamivudine (EPIVIR, EPIVIR-HBV, EPZICOM, COMBIVIR, TRIZIVIR), or with adefovir dipivoxil (HEPSERA).

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 antiretroviral therapy. The mechanism and long-term consequences of these events are unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including the components of COMPLERA. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

ADVERSE REACTIONS

The following adverse drug reactions are discussed in other sections of the labeling:

- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[See Boxed Warning, Warnings and Precautions]*.
- Severe Acute Exacerbations of Hepatitis B *[See Boxed Warning, Warnings and Precautions]*.
- New Onset or Worsening Renal Impairment *[See Warnings and Precautions]*.
- Depressive Disorders *[See Warnings and Precautions]*.
- Decreases in Bone Mineral Density *[See Warnings and Precautions]*.
- Immune Reconstitution Syndrome *[See Warnings and Precautions]*.

Adverse Reactions from Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Studies C209 and C215 – Treatment-Emergent Adverse Drug Reactions: The safety assessment of rilpivirine, used in combination with other antiretroviral drugs, is based on pooled data from 1368 patients in the Phase 3 trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) in antiretroviral treatment-naive HIV-1 infected adult patients. A total of 686 patients received rilpivirine in combination with other antiretroviral drugs as background regimen; most (N= 550) received emtricitabine + tenofovir disoproxil fumarate as background regimen. The number of subjects randomized to the control arm efavirenz was 682, of which 546 received emtricitabine + tenofovir disoproxil fumarate as background regimen *[See Clinical Studies in Full Prescribing Information]*. The median duration of exposure for subjects in either treatment arm was 56 weeks.

Adverse drug reactions (ADR) observed in patients who received rilpivirine or efavirenz plus emtricitabine + tenofovir disoproxil fumarate as background regimen are shown in Table 1. The adverse drug reactions observed in this subset of patients were generally consistent with those seen for the overall patient population participating in these studies (refer to the prescribing information for EDURANT).

The proportion of subjects who discontinued treatment with rilpivirine or efavirenz + emtricitabine/tenofovir disoproxil fumarate due to ADR, regardless of severity, was 2% and 5%, respectively. The most common ADRs leading to discontinuation were psychiatric disorders: 8 (1.5%) subjects in the rilpivirine + emtricitabine/tenofovir disoproxil fumarate arm and 12 (2.2%) subjects in the efavirenz + emtricitabine/tenofovir disoproxil fumarate arm. Rash led to discontinuation in 1 (0.2%) subjects in the rilpivirine + emtricitabine/tenofovir disoproxil fumarate arm and 10 (1.8%) subjects in the efavirenz + emtricitabine/tenofovir disoproxil fumarate arm.

Common Adverse Drug Reactions

Clinical ADRs to rilpivirine or efavirenz of at least moderate intensity (≥ Grade 2) reported in at least 2% of adult subjects are shown in Table 1.

Table 1 Selected Treatment-Emergent Adverse Reactions[a] (Grades 2–4) Reported in ≥2% of Subjects Receiving Rilpivirine or Efavirenz in Combination with Emtricitabine/Tenofovir Disoproxil Fumarate in Studies C209 and C215 (Week 48 analysis)

	Rilpivirine + FTC/TDF N=550	Efavirenz + FTC/TDF N=546
Gastrointestinal Disorder		
Nausea	1%	2%
Nervous System Disorders		
Headache	2%	2%
Dizziness	1%	7%
Psychiatric Disorders		
Depressive disorders[b]	1%	2%
Insomnia	2%	2%
Abnormal dreams	1%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	1%	5%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, assessed to be related to study drug.

b. Includes adverse drug reactions reported as depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicide ideation.

Rilpivirine: Treatment-emergent adverse drug reactions of at least moderate intensity (≥ Grade 2) that occurred in less than 2% of subjects treated with rilpivirine plus any of the allowed background regimen (N=686) in clinical studies C209 and C215 include (grouped by Body System): vomiting, diarrhea, abdominal discomfort, abdominal pain, fatigue, cholecystitis, cholelithiasis, decreased appetite, somnolence, sleep disorders, anxiety, glomerulonephritis membranous and glomerulonephritis mesangioproliferative.

Emtricitabine and Tenofovir Disoproxil Fumarate: The following adverse reactions were observed in clinical trials of emtricitabine or tenofovir disoproxil fumarate in combination with other antiretroviral agents:

The most common adverse drug reactions occurred in at least 10% of treatment-naive subjects in a phase 3 clinical trial of emtricitabine and tenofovir disoproxil fumarate in combination with another antiretroviral agent are diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. In addition, adverse drug reactions that occurred in at least 5% of treatment-experienced or treatment-naive subjects receiving emtricitabine or tenofovir disoproxil fumarate with other antiretroviral agents in clinical trials include abdominal pain, dyspepsia, vomiting, fever, pain, nasopharyngitis, pneumonia, sinusitis, upper respiratory tract infection, arthralgia, back pain, myalgia, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), anxiety, increased cough, and rhinitis.

Skin discoloration has been reported with higher frequency among emtricitabine-treated subjects; it was manifested by hyperpigmentation on the palms and/or soles and was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

Laboratory Abnormalities: The percentage of subjects treated with rilpivirine + emtricitabine/tenofovir disoproxil fumarate or efavirenz + emtricitabine/tenofovir disoproxil fumarate in studies C209 and C215 with selected treatment-emergent laboratory abnormalities (Grade 1 to 4), representing worst grade toxicity are presented in Table 2.

Table 2 Selected Laboratory Abnormalities (Grades 1-4) Reported in Subjects Who Received Rilpivirine or Efavirenz in Combination with Emtricitabine/Tenofovir Disoproxil Fumarate in Studies C209 and C215 (Week 48 Analysis)

Laboratory Parameter Abnormality, (%)	DAIDS Toxicity Range	Rilpivirine + FTC/TDF N=550	Efavirenz + FTC/TDF N=546
BIOCHEMISTRY			
Increased Creatinine			
Grade 1	≥1.1-≤1.3 x ULN[a]	5%	<1%
Grade 2	>1.3-≤1.8 x ULN	<1%	1%
Increased AST			
Grade 1	≥1.25-≤2.5 x ULN	13%	16%
Grade 2	> 2.5-≤5.0 x ULN	3%	7%
Grade 3	>5.0-≤10.0 x ULN	2%	2%
Grade 4	>10.0 x ULN	<1%	1%
Increased ALT			
Grade 1	≥1.25-≤2.5 x ULN	16%	19%
Grade 2	>2.5-≤5.0 x ULN	4%	6%
Grade 3	>5.0-≤10.0 x ULN	1%	2%
Grade 4	>10.0 x ULN	1%	1%
Increased Total Bilirubin			
Grade 1	≥1.1-≤1.5 x ULN	5%	<1%
Grade 2	>1.5-≤2.5 x ULN	2%	<1%
Grade 3	>2.5-≤5.0 x ULN	<1%	<1%
Increased Total Cholesterol (fasted)			
Grade 1	5.18-6.19 mmol/L 200-239 mg/dL	13%	29%
Grade 2	6.20-7.77 mmol/L 240-300 mg/dL	4%	15%
Grade 3	>7.77 mmol/L >300 mg/dL	<1%	2%
Increased LDL Cholesterol (fasted)			
Grade 1	3.37-4.12 mmol/L 130-159 mg/dL	11%	25%
Grade 2	4.13-4.90 mmol/L 160-190 mg/dL	5%	11%
Grade 3	>4.91 mmol/L >191 mg/dL	1%	2%
Increased Triglycerides (fasted)			
Grade 2	5.65-8.48 mmol/L 500-750 mg/dL	1%	1%
Grade 3	8.49-13.56 mmol/L 751-1,200 mg/dL	<1%	1%

N = number of subjects per treatment group

a. ULN = Upper limit of normal value.

Note: Percentages were calculated versus the number of subjects in ITT population with emtricitabine + tenofovir disoproxil fumarate as background regimen.

Emtricitabine or Tenofovir Disoproxil Fumarate: The following laboratory abnormalities have been previously reported in subjects treated with emtricitabine or tenofovir disoproxil fumarate with other antiretroviral agents in other clinical trials: Grade 3 or 4 laboratory abnormalities of increased pancreatic amylase (>2.0 x ULN), increased serum amylase (>175 U/L), increased lipase (>3.0 x ULN), increased alkaline phosphatase (>550 U/L), increased or decreased serum glucose (<40 or >250 mg/dL), increased glycosuria (≥3+), increased creatine kinase (M: >990 U/L; F: >845 U/L), decreased neutrophils (<750/mm³) and increased hematuria (>75 RBC/HPF) occurred.

Adrenal Function: In the pooled Phase 3 trials of C209 and C215, in subjects treated with rilpivirine plus any of the allowed background regimen (N=686), at Week 48, the overall mean change from baseline in basal cortisol showed a decrease of -13.1 nmol/L in the rilpivirine group, and an increase of +9.0 nmol/L in the efavirenz group. At Week 48, the mean change from baseline in ACTH-stimulated cortisol levels was lower in the rilpivirine group (+16.5 ± 6.14 nmol/L) than in the efavirenz group (+58.1 ± 6.66 nmol/L). Mean values for both basal and ACTH-stimulated cortisol values at Week 48 were within the normal range. Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency. Effects on adrenal function were comparable by background N(t)RTIs.

Serum Creatinine: In the pooled Phase 3 trials of C209 and C215 trials in subjects treated with rilpivirine plus any of the allowed background regimen (N=686), increases in serum creatinine occurred within the first four weeks of treatment and remained stable through 48 weeks. A mean change of 0.09 mg/dL (range: -0.20 mg/dL to 0.62 mg/dL) was observed after 48 weeks of treatment. In subjects who entered the trial with mild or moderate renal impairment, the serum creatinine increase observed was similar to that seen in subjects with normal renal function. These changes are not considered to be clinically relevant and no subject discontinued treatment due to increases in serum creatinine. Creatinine increases were comparable by background N(t)RTIs.

Serum Lipids: Changes from baseline in total cholesterol, LDL-cholesterol and triglycerides are presented in Table 3.

Table 3 Lipid Values Reported in Subjects Receiving Rilpivirine or Efavirenz in Combination with Emtricitabine/ Tenofovir Disoproxil Fumarate in Studies C209 and C215[a]

	Pooled Data from the C209 and C215 Trials							
	Rilpivirine + FTC/TDF N=550				Efavirenz + FTC/TDF N=546			
		Baseline	Week 48			Baseline	Week 48	
Mean	N	Mean (mg/dL)	Mean (mg/dL)	Mean Change[b] (mg/dL)	N	Mean (mg/dL)	Mean (mg/dL)	Mean Change[b] (mg/dL)
Total Cholesterol (fasted)	460	162	162	0	438	160	185	25
HDL-cholesterol (fasted)	459	42	45	3	437	40	49	9
LDL-cholesterol (fasted)	457	97	95	-2	436	95	109	13
Triglycerides (fasted)	460	122	111	-11	438	129	138	8

N = number of subjects per treatment group

a. Excludes subjects who received lipid lowering agents during the treatment period.

b. The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 values.

Subjects Coinfected with Hepatitis B and/or Hepatitis C Virus: In patients coinfected with hepatitis B or C virus receiving rilpivirine in studies C209 and C215, the incidence of hepatic enzyme elevation was higher than in subjects receiving rilpivirine who were not coinfected. The same increase was also observed in the efavirenz arm. The pharmacokinetic exposure of rilpivirine in coinfected subjects was comparable to that in subjects without coinfection.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of emtricitabine or tenofovir disoproxil fumarate. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Emtricitabine: No postmarketing adverse reactions have been identified for inclusion in this section.

Tenofovir Disoproxil Fumarate:

Immune System Disorders: allergic reaction, including angioedema

Metabolism and Nutrition Disorders: lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, and Mediastinal Disorders: dyspnea

Gastrointestinal Disorders: pancreatitis, increased amylase, abdominal pain

Hepatobiliary Disorders: hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)

Skin and Subcutaneous Tissue Disorders: rash

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

Renal and Urinary Disorders: acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria

General Disorders and Administration Site Conditions: asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

DRUG INTERACTIONS

COMPLERA is a complete regimen for the treatment of HIV-1 infection; therefore, COMPLERA should not be administered with other antiretroviral medications. Information regarding potential drug-drug interactions with other antiretroviral medications is not provided. Please refer to the EDURANT, VIREAD and EMTRIVA prescribing information as needed.

There were no drug-drug interaction trials conducted with the fixed-dose combination tablet. Drug interaction studies were conducted with emtricitabine, rilpivirine, or tenofovir disoproxil fumarate, the components of COMPLERA. This section describes clinically relevant drug interactions with COMPLERA *[See Contraindications and Clinical Pharmacology in Full Prescribing Information]*.

Drugs Inducing or Inhibiting CYP3A Enzymes

Rilpivirine is primarily metabolized by cytochrome P450 (CYP) 3A, and drugs that induce or inhibit CYP3A may thus affect the clearance of rilpivirine *[See Clinical Pharmacology in Full Prescribing Information, Contraindications]*. Coadministration of rilpivirine and drugs that induce CYP3A may result in decreased plasma concentrations of rilpivirine and 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 and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs *[see Table 4]*.

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/or other renally eliminated drugs. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, and valganciclovir.

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 electrocardiogram. 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 electrocardiogram *[See Clinical Pharmacology in Full Prescribing Information]*. 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

Important drug interaction information for COMPLERA is summarized in Table 4. The drug interactions described are based on studies conducted with emtricitabine, rilpivirine, or tenofovir disoproxil fumarate as individual medications that may occur with COMPLERA or are potential drug interactions; no drug interaction studies have been conducted using COMPLERA [for pharmacokinetic data see *Clinical Pharmacology,* Tables 6-7 *in Full Prescribing Information]*. The tables include potentially significant interactions, but are not all inclusive.

Table 4 Established and Other Potentially Significant[a] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antacids: antacids (e.g., aluminium, magnesium hydroxide, or calcium carbonate)	↔ rilpivirine (antacids taken at least 2 hours before or at least 4 hours after rilpivirine) ↓ rilpivirine (concomitant intake)	The combination of COMPLERA and antacids should be used with caution as coadministration may cause significant decreases in rilpivirine plasma concentrations (increase in gastric pH). Antacids should only be administered either at least 2 hours before or at least 4 hours after COMPLERA.
Azole Antifungal Agents: fluconazole itraconazole ketoconazole posaconazole voriconazole	↑ rilpivirine[c,d] ↓ ketoconazole[c,d]	Concomitant use of COMPLERA with azole antifungal agents may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when COMPLERA is coadministered with azole antifungal agents. Clinically monitor for breakthrough fungal infections when azole antifungals are coadministered with COMPLERA.
H_2-Receptor Antagonists: cimetidine famotidine nizatidine ranitidine	↔ rilpivirine[c,d] (famotidine taken 12 hours before rilpivirine or 4 hours after rilpivirine) ↓ rilpivirine[c,d] (famotidine taken 2 hours before rilpivirine)	The combination of COMPLERA and H_2-receptor antagonists should be used with caution as coadministration may cause significant decreases in rilpivirine plasma concentrations (increase in gastric pH). H_2-receptor antagonists should only be administered at least 12 hours before or at least 4 hours after COMPLERA.
Macrolide antibiotics: clarithromycin erythromycin troleandomycin	↑rilpivirine ↔ clarithromycin ↔ erythromycin ↔ troleandomycin	Concomitant use of COMPLERA with clarithromycin, erythromycin and troleandomycin may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). Where possible, alternatives such as azithromycin should be considered.
Narcotic Analgesics: methadone	↓ R(–) methadone[c] ↓ S(+) methadone[c] ↔ rilpivirine[c] ↔ methadone[c] (when used with tenofovir)	No dose adjustments are required when initiating coadministration of methadone with COMPLERA. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.

a. This table is not all inclusive.

b. Increase = ↑; Decrease = ↓; No Effect = ↔

c. The interaction was evaluated in a clinical study. All other drug-drug interactions shown are predicted.

d. This interaction study has been performed with a dose higher than the recommended dose for rilpivirine. The dosing recommendation is applicable to the recommended dose of rilpivirine 25 mg once daily.

Drugs with No Observed or Predicted Interactions with COMPLERA

No clinically significant drug interactions have been observed between emtricitabine and famciclovir or tenofovir disoproxil fumarate. Similarly, no clinically significant drug interactions have been observed between tenofovir disoproxil fumarate and entecavir, methadone, oral contraceptives, ribavirin, or tacrolimus in studies conducted in healthy subjects.

No clinically significant drug interactions have been observed between rilpivirine and acetaminophen, atorvastatin, chlorzoxazone, ethinylestradiol, norethindrone, sildenafil, and tenofovir disoproxil fumarate. No clinically relevant drug-drug interaction is expected when rilpivirine is coadministered with ribavirin.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

Emtricitabine: The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60 times higher and in rabbits at approximately 120 times higher than human exposures at the recommended daily dose.

Rilpivirine: Studies in animals have shown no evidence of embryonic or fetal toxicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with rilpivirine during pregnancy and lactation, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo-fetal No Observed Adverse Effects Levels in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg once daily.

Tenofovir Disoproxil Fumarate: Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, 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 tenofovir is secreted in milk. Studies in lactating rats and their offspring indicate that rilpivirine was present in rat milk. It is not known whether emtricitabine, rilpivirine, or tenofovir is excreted 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 if they are receiving COMPLERA.**

Pediatric Use

COMPLERA is not recommended for patients less than 18 years of age because not all the individual components of the COMPLERA have safety, efficacy and dosing recommendations available for all pediatric age groups *[See Clinical Pharmacology in Full Prescribing Information]*.

Geriatric Use

Clinical studies of emtricitabine, rilpivirine, or tenofovir disoproxil fumarate 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 *[See Clinical Pharmacology in Full Prescribing Information]*.

Renal Impairment

Because COMPLERA is a fixed-dose combination, it should not be prescribed for patients requiring dosage adjustment such as those with moderate, severe or end stage renal impairment (creatinine clearance below 50 mL per minute) or that require dialysis *[See Warnings and Precautions, Clinical Pharmacology in Full Prescribing Information]*.

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) *[See Clinical Pharmacology in Full Prescribing Information]*.

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.

Emtricitabine: Limited clinical experience is available at doses higher than the therapeutic dose of EMTRIVA. In one clinical pharmacology study, single doses of emtricitabine 1200 mg were administered to 11 subjects. No severe adverse reactions were reported. The effects of higher doses are not known.

Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL per minute and a dialysate flow rate of 600 mL per minute). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Rilpivirine: There is no specific antidote for overdose with rilpivirine. Human experience of overdose with rilpivirine is limited. Since rilpivirine is highly bound to plasma protein, dialysis is unlikely to result in significant removal of rilpivirine.

If indicated, elimination of unabsorbed active substance may be achieved by gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance.

Tenofovir Disoproxil Fumarate: Limited clinical experience at doses higher than the therapeutic dose of VIREAD 300 mg is available. In one study, 600 mg tenofovir disoproxil fumarate was administered to 8 subjects orally for 28 days, and no severe adverse reactions were reported. The effects of higher doses are not known.

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of VIREAD, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information)

A statement to patients and healthcare providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with COMPLERA from your healthcare provider.** A Patient Package Insert for COMPLERA is available for patient information.

Information for Patients

Patients should be advised that:

- Patients should remain under the care of a healthcare provider when using COMPLERA.
- Patients should be informed that COMPLERA is not a cure for HIV infection. Patients should stay on continuous HIV therapy to control HIV infection and decrease HIV-related illnesses. Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death.
- Patients should be advised to continue to practice safer sex and to use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Patients should be advised never to re-use or share needles.
- It is important to take COMPLERA on a regular dosing schedule with a meal and to avoid missing doses. A protein drink does not constitute a meal. If the patient misses a dose of COMPLERA within 12 hours of the time it is usually taken, the patient should take COMPLERA with a meal as soon as possible and then take the next dose of COMPLERA at the regularly scheduled time. If a patient misses a dose of COMPLERA by more than 12 hours, the patient should not take the missed dose, but resume the usual dosing schedule. Inform the patient that he or she should not take more or less than the prescribed dose of COMPLERA at any one time.
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with COMPLERA should be suspended in any patients who develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) *[See Warnings and Precautions]*.
- Patients with HIV-1 should be tested for hepatitis B virus (HBV) before initiating antiretroviral therapy. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued EMTRIVA or VIREAD *[See Warnings and Precautions]*. COMPLERA should not be discontinued without first informing their healthcare provider.
- Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported in association with the use of VIREAD. COMPLERA should be avoided with concurrent or recent use of a nephrotoxic agent *[See Warnings and Precautions]*.
- COMPLERA may interact with many drugs; therefore, patients should be advised to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort *[See Warnings and Precautions]*.
- COMPLERA should not be coadministered with the following drugs, as significant decreases in rilpivirine plasma concentrations may occur due to CYP3A enzyme induction or gastric pH increase, which may result in loss of virologic response and possible resistance to COMPLERA or to the class of NNRTIs: the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin; the antimycobacterials rifabutin, rifampin, rifapentine; proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole; the glucocorticoid systemic dexamethasone (more than a single dose); or St. John's wort (*Hypericum perforatum*) *[See Contraindications]*.
- Patients should be informed that depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) have been reported with COMPLERA. If they experience depressive symptoms, they should seek immediate medical evaluation *[See Warnings and Precautions]*.
- Decreases in bone mineral density have been observed with the use of VIREAD. Bone monitoring should be considered in patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss *[See Warnings and Precautions]*.
- COMPLERA should not be coadministered with ATRIPLA, TRUVADA, EMTRIVA, VIREAD or EDURANT; or with drugs containing lamivudine, including COMBIVIR, EPIVIR or EPIVIR-HBV, EPZICOM, or TRIZIVIR; or with HEPSERA *[See Warnings and Precautions]*.
- Redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known *[See Warnings and Precautions]*.
- In some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Patients should be advised to inform their healthcare provider immediately of any symptoms of infection *[See Warnings and Precautions]*.

GILEAD

IN THE NEWS

African Americans Less Likely to Adhere to ART, Study Says

AFRICAN-AMERICANS WITH HIV are much less likely to adhere to drug therapy than others with the disease, according to a University of Michigan study.

Moreover, untreated depression may greatly hinder adherence to antiretroviral therapy (ART) for all low-income, HIV-infected patients, regardless of race.

The study is the first known to indicate a true racial disparity in antiretroviral therapy adherence, says Rajesh Balkrishnan, associate professor at the University of Michigan School of Public Health and the College of Pharmacy. Less than 30 percent of African-American HIV patients in the one-year study sustained optimal adherence to ART, compared to 40 percent of other HIV patients.

"Our results show an alarming disparity in the quality of pharmaceutical care provided to African-American Medicaid enrollees with HIV," Balkrishnan said. "These enrollees have much lower adherence rates to ARTs and a 10 percent higher incidence of depression."

More than 66 percent of the 7,034 HIV-infected patients in the study were African-American and nearly half of them reported depression.

The good news is that antidepressant treatment nearly doubled the odds of optimal ART adherence among patients of all races who reported depression, Balkrishnan says. Anything greater than 90 percent adherence to therapy was considered optimal for purposes of the study. For antiretroviral drugs to be effective, patients should sustain 90-95 percent adherence to treatment.

Balkrishnan's research group set out to examine the possible link between race and ART adherence in low income HIV-infected populations, and whether any racial differences in therapy adherence was further enhanced by depression. Racial disparities exist in many aspects of HIV/AIDS, but until now not much was known about race and ART adherence, or depression and adherence.

Though depression was high among all HIV patients regardless of race, depression did not further enhance the already-existing racial disparity in adhering to drug therapy. However, Balkrishnan pointed out that this should be interpreted with caution, since evidence has shown that African-Americans are less likely to be diagnosed and treated for depression than whites.

Balkrishnan says it's unclear exactly why African-American ART adherence is lower, but past research shows that African-Americans have less access to care, have less trust in the health care providers and are more likely to postpone care than white patients.

"The fact that many African-American patients with compromised mental health states have poorer access and use of essential ART therapy points out to significant disparities in our health care system, and we need to take proactive steps to address these gaps," he said.

The study, "Association between race, depression, and antiretroviral therapy adherence in a low-income population with HIV infection," appears in an advanced online publication of the *Journal of General Internal Medicine*.

CDC Proposes All Baby Boomers Be Tested for Hepatitis C

THE CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC) recently issued draft guidelines proposing that all U.S. baby boomers get a one-time test for the hepatitis C virus.

According to the CDC, one in 30 baby boomers - the generation born from 1945 through 1965 - has been infected with Hep C, and most are unaware. The proposed guidelines will help to address the largely preventable consequences of this disease, especially in light of newly available therapies that can cure up to 75 percent of infections.

More than 15,000 Americans, most of them baby boomers, die each year from hepatitis C-related illness, such as cirrhosis and liver cancer. Deaths have been increasing steadily for over a decade and are projected to grow significantly in coming years, according to CDC.

Current CDC guidelines call for testing only individuals with certain known risk factors for hepatitis C infection. But studies find that many baby boomers do not perceive themselves to be at risk and are not being tested.

CDC estimates one-time hepatitis C testing of baby boomers could identify more than 800,000 additional people with hepatitis C, prevent the costly consequences of liver cancer and other chronic liver diseases and save more than 120,000 lives.

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Boceprevir Improves Outcomes for HIV/HCV Coinfection, Researchers Report

ADDING BOCEPREVIR (VICTRELIS) to pegylated interferon and ribavirin for treatment of chronic hepatitis C in patients with HIV substantially increased end-of-treatment response and sustained response 12 weeks after completing therapy, according to researchers at the 47th International Liver Congress (EASL 2012) in April in Barcelona.

Recent drug-drug interaction studies showed that boceprevir can lower levels of some boosted HIV protease inhibitors, and vice versa, and the Food and Drug Administration (FDA) recently updated the Victrelis product label to reflect this new information.

In this Phase 2 trial reported at EASL, coinfected participants taking boceprevir did not show a higher rate of HIV or hepatitis C virus (HCV) breakthrough—a potential consequence of inadequate drug concentrations—than those taking pegylated interferon/ribavirin with placebo.

Josep Mallolas

Josep Mallolas from the University of Barcelona presented data from an ongoing Phase 2 trial that included 100 previously untreated HIV/HCV coinfected participants with HCV genotype 1. Co-investigator Mark Sulkowski presented 12-week sustained virological response (SVR12) findings from this study at CROI 2012 in March.

Participants started with a 4-week lead-in period taking 1.5 mcg/kg/week pegylated interferon alfa-2b (PegIntron) plus weight-adjusted ribavirin, then were randomly assigned to add 800 mg 3-times-daily boceprevir or placebo for 44 more weeks. Although many hepatitis C monoinfected patients are eligible for shorter treatment using response-guide therapy, all HIV positive people in this trial were assigned to 48 weeks of therapy; 2 people dropped out before receiving study drugs.

About 70 percent of the participants were men, about 80 percent white, with a median age of 43 years. About two-thirds had HCV genotype 1a, the rest 1b; most had high baseline HCV RNA and about 5 percent had cirrhosis. The group overall had well-controlled HIV disease with a median CD4 T-cell count of nearly 600 cells/mm3 and stable undetectable HIV viral load.

Participants were also on combination ART. Based on pharmacokinetic data, they were limited to regimens containing a ritonavir- boosted HIV protease inhibitor plus two selected nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs).

The results:

- At the end of treatment at 48 weeks, 64 percent of those in the boceprevir triple therapy arm had suppressed HCV viral load, compared with 29 percent in the placebo arm.
- Twelve months after completion of treatment, 61 of those in the boceprevir arm achieved SVR12, or continued HCV suppression, compared with 27 percent in the placebo arm.
- Nine percent of boceprevir recipients and 53 percent of placebo recipients experienced treatment failure while on HCV therapy.
- Two people taking boceprevir and three taking placebo experienced HIV viral load rebound by the end of treatment, and an additional one person did so in each arm by post-treatment week 12.
- Approximately one-fifth of participants in both arms experienced serious adverse events, but boceprevir recipients were about twice as likely to discontinue therapy due to adverse events (20 percent vs 9 percent, respectively).
- Boceprevir recipients were more likely than placebo recipients to report several symptoms including fever, loss of appetite, vomiting, dysgeusia (unusual taste sensations), anemia, and neutropenia.
- Absolute CD4 T-cell counts decreased in both groups—a known side effect of interferon—but CD4 cell percentages remained stable.

"The addition of boceprevir to [pegylated interferon/ribavirin] was associated with higher rates of undetectable HCV RNA at all time points," the researchers said. "The safety and tolerability profile was consistent with that observed in HCV monoinfected patients."

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EXCLUSIVE INTERVIEW

Dr. Grant Colfax

Director of the Office of National AIDS Policy

Former HIV Clinician Leads U.S. Fight Against HIV

Among priorities: Focus resources on populations at greatest risk; tackle HIV workforce shortage

ON MARCH 14, 2012, President Obama announced the appointment of Grant Colfax, MD, as director of the Office of National AIDS Policy (ONAP). One of the nation's leading public health policy experts, Dr. Colfax previously was director of the HIV Prevention Section in the San Francisco Department of Public Health. He is charged with leading the continuing efforts of the government to reduce the number of HIV infections in the U.S.

"Grant Colfax will lead my administration's continued progress in providing care and treatment to people living with HIV/AIDS," said President Obama when he announced the appointment. "Grant's expertise will be key as we continue to face serious challenges and take bold steps to meet them. I look forward to his leadership in the months to come."

Less than two months after his appointment, HIV Specialist interviewed Dr. Colfax to get a sense of his priorities and plans as he tackles his new assignment that is so crucial in the battle against HIV. Here is the text of that interview:

Can you please provide an update on where we stand on the implementation of the National AIDS Strategy and your primary goals for your first year as Director of the Office of National HIV/AIDS Policy? Why is it important to differentiate the needs off specific populations when addressing HIV in this country?

Since the Strategy's release in 2010, we've really arrived at a transformative time in HIV care and prevention. The question is, as we move forward, how do we best implement sustainable interventions that are going to have the greatest impact in meeting the goals of the strategy: reducing new HIV infections, improving health outcomes, and reducing HIV-related disparities? How do we best align resources and integrate efforts? There are no easy answers, but as a recent "on the ground" implementer myself, it's clear that engaging in ongoing dialogue with providers, planners, people living with HIV, and others on how to continue these efforts is critical to their ongoing success.

EXCLUSIVE INTERVIEW

Dr. Grant Colfax

Director of the Office of National AIDS Policy

An administration priority continues to be ensuring that resources go to where the epidemic is. We know the populations at greatest risk for HIV in the United States: men who have sex with men are at highest risk, accounting for nearly two-thirds of all new infections, and infection rates are increasing among young black men who have sex with men.

Among women, who account for just under a quarter of new infections, African-American and Latina women account for three-quarters of new infections. And of course, injection drug users continue to be at high risk for infection. So we are working with federal, state, and local partners to align resources to meet the needs of these populations.

"It's critical that we continue to engage a diversity of providers and clinicians in discussions about how to maximize our efforts to improve HIV prevention and treatment outcomes."

For example, the CDC recently realigned HIV prevention funding to states and local jurisdictions to be proportional to reported HIV cases; the net result was states with more living HIV cases receiving a greater proportion of funding. Of course, there's also an ongoing need for general campaigns to raise general public awareness that HIV continues to be an important public health issue in the United States.

From an intervention standpoint, it's clear we need to focus efforts on increasing diagnoses rates and engaging people in care to reduce HIV viral load. Having one-fifth of persons living with HIV in the country unaware of their status is simply unacceptable.

Increasing testing opportunities and increasing frequency of testing among gay men and women of color in particular, is an ongoing priority. Integration of testing into routine medical care is important. And we know that when done right, testing is extremely cost effective. For instance, the Expanded Testing Initiative, which focused on increasing HIV testing rates among African-Americans, diagnosed thousands of infections, and saved $2 for every $1 spent.

With regard to engaging and linking people to care, we also need to do better. Data released since the strategy was published estimates that only 28 percent of persons living with HIV in the U.S. have a suppressed viral load. There's a lot of room there for improvement. So how do we achieve better outcomes? What models need to be scaled up with regard to improving our HIV care delivery systems? Certainly Affordable Care Act implementation provides an opportunity to do that. And many jurisdictions are testing various linkage to care models, including expanding patient navigator and case management programs. Once these programs have been evaluated, we will have a good sense of what works best.

Measuring our progress is of major importance. Using recommendations from a recently released Institute of Medicine (IOM) report, ONAP is working with HHS and our other federal partners to develop a core set of clinical HIV indicators that will be used to monitor progress with regard to HIV prevention and treatment. Another goal is to reduce data collection and reporting requirements. The expectation is that we will get a more harmonious and parsimonious set of indicators by which to monitor our progress, and reduce local data collection burden.

Achieving the right balance with regard to implementation depends a lot on what the epidemic looks like at the state and local level. To focus attention on how jurisdictions are working to "get it right," and challenges moving forward, ONAP is continuing to engage in discussion with state and local partners.

ONAP sponsored a series of "Implementation Dialogues" in five jurisdictions (Birmingham, AL, Seattle, WA, Philadelphia, PA, Baton Rouge LA and Des Moines, IA) last fall, and recently co-hosted a White House event at the Morehouse School of Medicine in Atlanta, GA that focused largely on implementation. What stands out about these meetings is that there are a number of challenges in moving forward, including the need for providing technical assistance, integrating prevention and care delivery programs, and updating data collection and evaluation systems. What's also clear is that there's a renewed sense of enthusiasm and hope in the HIV prevention and care field.

In addition to implementation, is there anything else that you will focus on during the next year?

The Ryan White Program will also be a focus, given that it is scheduled to be reauthorized in 2013. The administration's support for Ryan White has been steadfast, and the President's budget includes $1 billion for ADAP in 2013. Certainly Ryan White support is critical to the success of the Strategy.

ONAP is supporting research to help determine how the Ryan White Program will be most effective, especially in the setting of the Affordable Care Act implementation. Moving forward, there will be ample opportunity for input from providers, patients, and other stakeholders on the future of the program.

And of course, the International AIDS Society (IAS) will host the International AIDS Conference, AIDS 2012, July 22-27 here in Washington DC. Thanks to the administration's lifting the entry ban on persons living with HIV, this will be the first International AIDS Conference held in the U.S. in 22 years. ONAP is coordinating the government's conference activities, which will focus on science and policy.

What approach will you take towards reaching out to providers and clinicians who treat HIV/AIDS patients?

It's critical that we continue to engage a diversity of providers and clinicians in discussions about how to maximize our efforts to improve HIV prevention and treatment outcomes. There's no substitution for on-the-ground clinical experience, and we need to hear what's working and what's not.

One of my first meetings as director of ONAP was with a delegation of Ryan White Care providers, and it was extremely helpful to hear about their concerns and solutions moving forward. I'm committed to keeping all lines of communication open and look forward to working with the community in the future.

With increasing numbers of HIV providers retiring, the workforce will be an issue in providing quality care. What are your thoughts for addressing the workforce shortage?

The healthcare provider workforce issue is an important one, and one that extends beyond HIV.

With regard to HIV, there's an ongoing study at HRSA that will help quantify the extent of the possible shortage. It's likely the solution to the shortage will need to be multifaceted, and could include providing incentives for providers to work in HIV care, shifting the care model to emphasize a team-based approach, and taking further advantage of technological advances such as electronic medical records and telemedicine.

One model may be that after initiation and stabilization on therapy as managed by an HIV specialist, patients are then seen by a primary care provider and referred back as needed. Further implementation research is needed to determine the sustainability of these models and, most important their effects on health outcomes.

Can you please discuss the importance of the Affordable Care Act with respect to HIV/AIDS?

The Affordable Care Act is a game changer on multiple levels. A few of the highlights: 54 million additional Americans are receiving preventive services coverage without cost-sharing, including coverage for HIV screening. Insurance companies can no longer deny coverage to children living with HIV. Pre-existing condition insurance plans are providing coverage to hundreds of individuals living with HIV who are otherwise unable to find coverage due to pre-existing conditions. Insurance companies can no longer impose a lifetime ban on essential health benefits.

Starting in 2014, the Affordable Care Act will forbid insurance companies from denying people coverage based on pre-existing conditions, removing a huge barrier for people living with HIV who cannot get coverage now. This also removes a barrier for people who don't get HIV tested out of fear of being denied health coverage.

"It's likely the solution to the (HIV workforce) shortage will need to be multifaceted, and could include providing incentives for providers to work in HIV care…"

The Affordable Care Act increases the Medicaid eligibility level to 133 percent of the federal poverty level, which means thousands of persons with HIV will be eligible for coverage. ONAP is working especially closely with HHS to help prepare for changes. One focus is on how systems are best supported to help link and consistently engage people in HIV care.

What is the greatest single challenge for implementing the President's National Strategy?

Keeping the focus on the goals of the Strategy at every level and stage of implementation. We've made continued progress, but there is always room to grow. And with continued research, better data, ongoing dialogue and collective problem solving, we will get there. HIV

About Grant Colfax, MD

Dr. Colfax was most recently director of the HIV Prevention Section in the San Francisco Department of Public Health. He is a graduate of Harvard Medical School and completed his medical residency at the University of California, San Francisco. His work focused on collaborating with community stakeholders to implement sustainable, evidence-based HIV prevention and treatment interventions and policies in public health settings and measuring their effectiveness. Under his leadership, San Francisco expanded HIV testing and treatment support efforts. Until assuming his ONAP role, Dr. Colfax was also an NIH-and CDC-supported scientist studying HIV testing strategies, clinical trials of medications to treat substance dependence, and biomedical HIV prevention interventions. He was a practicing clinician at the Positive Health Program, a major public HIV clinic in San Francisco.

HEALTHY RELATIONSHIPS

Diverse Challenges; Tools to Respond

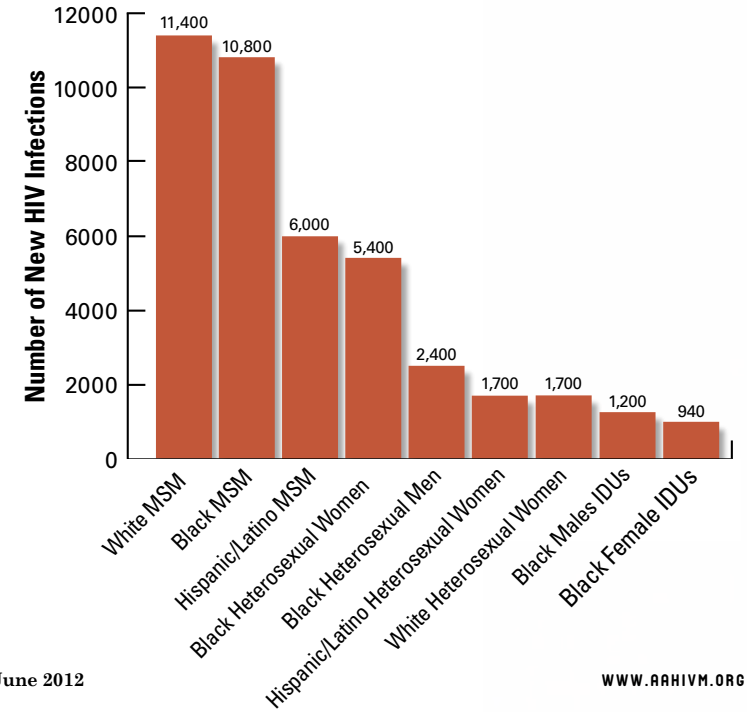
BY BOB GATTY

With at least 1.2 million people in the United States living with HIV, an important challenge for those who treat and care for them is to encourage intimate relationships that are healthy; relationships that, rather than spreading the virus, encourage positive lifestyles and even help to improve patient adherence to medication.

The complexities in this challenge are many with an estimated 56,000 Americans becoming infected with HIV each year. Providers must recognize and understand the unique problems and concerns faced by individual patients, whether they are men having sex with men (MSM), women, young people, African American, Latino, transgenders or others. All factors, from social status, education and financial resources to stigma and substance abuse must be recognized and understood.

Fortunately, there are resources to help guide the practitioner, including downloadable modules recently developed by the Centers for Disease Control (CDC) that are tailored to individual patient groups (www.effectiveinterventions.org). There is also a great deal of academic and clinical research, as well as the experience of clinician peers who routinely deal with these situations, that can be drawn upon for guidance.

While the diversity of our nation weaves a rich cultural fabric that benefits us all, it also complicates the challenge for HIV health care providers. The following chart illustrates CDC's estimates of new HIV infections in the United States in 2009 for the most-affected subpopulations.



Women

According to CDC, at some point in her lifetime, one in 139 women will be diagnosed with HIV infection; for black women, that rate is one in 32. In most cases, this is directly attributable to their relationships with partners who are putting them at risk because of their own, often secret, behavior.

Charles B. Collins, Jr., Ph.D., science application team leader at the CDC's Division of HIV/AIDS Prevention Capacity Building Branch helped prepare, with the assistance of outside experts, CDC's evidence-based intervention modules that are designed to help clinicians work effectively with HIV patients and their partners.

"Frequently women in our society take on the role of being the caretaker for their kids," Dr. Collins observed. "But what happens when they need to be cared for? We also have to think about the many HIV-positive women who have negative experiences with domestic violence and the pain involved. So when we talk to them about how important it is to care for their health, to use safer sex, they talk about a sex partner who may, in fact, beat them. For a woman who is HIV-positive to negotiate safer sex with a man who is abusive is a complex issue."

Often, Dr. Collins added, male sex partners refuse to use condoms because of a macho attitude that says, "Hey, I'm a man. I'm not scared of any disease."

"So how does an HIV-positive woman convince a male sex partner to protect himself from becoming HIV-positive when he's got this macho attitude and is not afraid of infection?"

THINKSTOCK

One of the Prevention with Positives intervention modules available from the CDC is designed to help HIV-positive women cope with those and other relationship challenges. It's called "WILLOW" (Women Involved in Life, Learning from Other Women),

and involves four four-hour sessions facilitated by a health educator and an HIV-positive female peer.

"WILLOW is a risk-reduction intervention that also deals with some of the life circumstances HIV-positive women confront, including stigma, child care issues, and domestic violence,"

Through WILLOW, these and other challenges are addressed in content that emphasizes gender pride, benefits of maintaining current and developing new social support network members, stress management and coping strategies development, HIV/STD transmission risk-reduction skills, and assertive communication and condom use skills.

Two years ago, a study published in the Journal of Prevention & Intervention in the Community, assessed the effectiveness of woman-focused HIV intervention on condom use and negotiation skills through a training program administered to at-risk women in Pretoria, South Africa.

The study concluded that teaching women to negotiate with primary sexual partners appears to be an effective way to increase condom use and reduce heterosexual HIV transmission. As in the U.S., many South African women lack the sociocultural and economic power to control sexual relationships and practice safer sex with their male partners—particularly poor, uneducated women who depend on their partners for basic substance.

African Americans

In 2009, the estimated rate of new HIV infections among black men was six and a half times as high as that of white men, and more than two and a half times as high as that of Hispanic/Latino men and of black women. In the same

year, the estimated rate of new HIV infections among black women was 15 times that of white women and over three times that of Hispanic/ Latina women.

As Phil Wilson, chief executive and president of the Black AIDS Institute has said, "AIDS is the fire that is ravaging the black community."

While there are many reasons, including poverty, economic stability, racism, lack of quality health care and poor access to health care, gender inequality, domestic violence, homophobia, intravenous drug use, and untreated sexually transmitted diseases, Kellee Terrell, editor of *The Body Pro*, has written that a major problem has been the "black community's own slow response to the epidemic."

"Minus a few exceptions, most black media publications, churches and community leaders set the tone early by turning a blind eye to HIV, believing that this epidemic was not their problem and that HIV was a moral issue as opposed to a public health crisis," she wrote. "In the end, we have all paid a price for their unwillingness to address the disease early on." And then, she added: "The culture of ignorance, stigma, silence and fear is very real, and it is killing us."

In April, Terrell reported on a roundtable conversation conducted to explore the difficulties of reaching heterosexual black men regarding HIV prevention. She spoke with Ingrid Floyd, executive director of Iris House in New York City and Larry Bryant, national field organizer for Housing Works in Washington, DC.

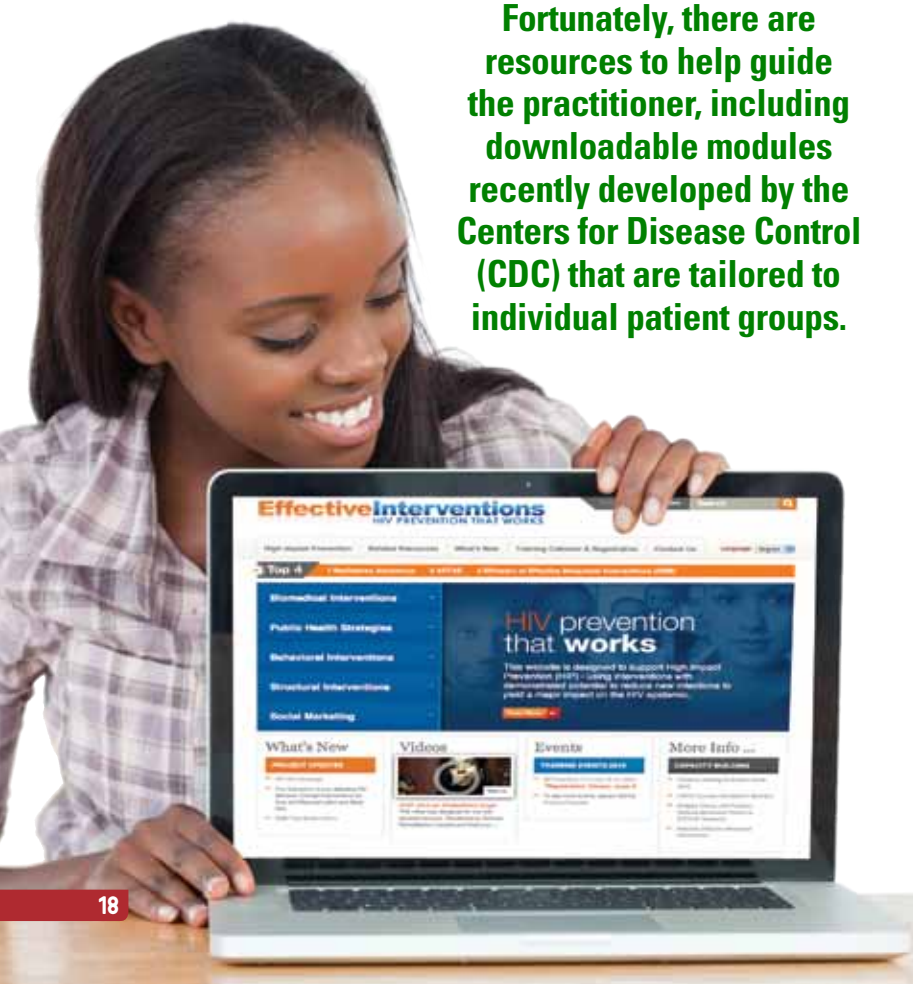
Here are some of the key points from that discussion:

- Talking about sex and sexuality in a way other than about dominating a woman is not easy. Historically, African-American heterosexuals have been sexually fetishized and stereotyped, and instead of being seen as emotional creatures who communicate, they are cast as strong, silent, overly sexual types. Where can men go to talk about sex and emotions?
- Overall, people of color in general have a hard time gaining access to health care, but once young black men age out of pediatric care, it's hard for them to get back into care on a consistent basis. Young women and women in general have a reason to go to the OB/GYN and are more connected to the health care system; men don't have those same experiences and with that comes missed opportunities to be tested for HIV and STDs.
- How much research is really being done around heterosexual men and HIV? And when research is being done, is it advertised in a way that encourages straight men to show up and be counted?
- Heterosexual black men, both those living with HIV and those not, need to see other men that they can identify with serving as role models and urging them to get tested. Where are those examples?

As *HIV Specialist* reports in our *In The News* section, a study from the University of Michigan found that African Americans are less likely to adhere to their HIV meds compared to other people living with HIV/AIDS. Fewer than 30 percent of the African Americans who participated in the study had "optimal" adherence (more than 90 percent of the time), compared to 40 percent of HIV-positive participants of other races and ethnicities.

The study reported that depression plays a factor in adherence and that antidepressant treatment nearly doubled the odds of optimal ART adherence among patients of all races who reported depression.

Fortunately, there are resources to help guide the practitioner, including downloadable modules recently developed by the Centers for Disease Control (CDC) that are tailored to individual patient groups.



THINKSTOCK, BONOTOM STUDIO

Latinos and HIV

Latinos are the largest and fastest growing ethnic minority group in the U.S. and the rate of diagnoses per 100,000 among Latino adults/adolescents was the third highest of any racial/ethnic group in the U.S. in 2010—about three times that of whites, but one third that of Blacks. Latinos account for a growing share of annual AIDS diagnoses, rising from 15 percent in 1985 to 22 percent in 2010, although that number has been declining since 2007.

According to experts at the Henry J. Kaiser Family Foundation, HIV transmission patterns among Latino men vary from those of white men. While both groups are most likely to be infected through sex with other men, Latinas are somewhat more likely to have been infected through heterosexual transmission than white women, who are more likely to have been infected through injection drug use than Latinas.

"With Hispanic women, the situation differs according to the subgroup they belong to," said Beatrice J. Krauss, Ph.D.,

Professor of Urban Public Health at CUNY School of Public Health and executive director of the Center for Community and Urban Health in New York City. "There is a lot of bad substance abuse and unsafe injection practices among Puerto Ricans who frequently travel back and forth between their home country and places like New York City, for example. Shooting galleries may be pretty safe in New York City, but not in Puerto Rico."

The migration of labor also affects the HIV rate among Latinos, she added, noting that when migrant farm workers are separated from their partners as they move from state to state following the crops, there is "temptation for sexual acting out."

So, Dr. Krauss said, "migrant laborers are often returning home and giving HIV to their perfectly fidelitous wife. When you separate families, you put each person at risk."

Bea Krauss

"Comfort with sexuality must be addressed at three levels: sexual socialization, information about sexuality, and greater openness about sexual behaviors"

According to HIV InSite, an HIV resource of the University of California, San Francisco, sexuality appears to be even more intensely private and personal in the Latino culture than in others, so sexual issues are often not discussed even between partners. "In the Latino culture, the 'good' woman is not supposed to know about sex, so it is inappropriate for her to bring up subjects like AIDS and condoms," HIV InSite says.

"Comfort with sexuality must be addressed at three levels: sexual socialization, information about sexuality, and greater openness about sexual behaviors," HIV InSite states. "In order to socialize children more appropriately about sexuality, Latino parents must be taught both basic information about sex and methods to communicate with their children about this topic. Despite a strong emphasis on family interactions, Latinos are currently less likely than other groups to provide their children with critical information about sex and AIDS. In many cases, parents do not have the necessary information. Increasing information and openness about sexuality among adults will also increase comfort with condoms and with discussion of sexual activities."

HIV InSite says programs that address sexual impulses are "urgently needed," because sexual feelings are often not discussed at school or in the home, which may contribute to sexual discomfort and reports of many adolescents that sexual activity "just happened."

"Acceptance and discussion of sexual feelings should make such feelings more accessible and therefore manageable. Careful examination of these issues is also likely to be productive in interventions aimed at adults in sexually transmitted disease (STD) clinics, men in prison, and other settings in which high risk men are found," InSite says.

The report closes with this comment:

"Even with major efforts to prevent the spread of HIV, AIDS will continue to affect Latinos disproportionately in the United States. Multiple sexual partners and use of intravenous drugs are prevalent in some areas. Homophobia and traditional sex roles may impede prevention efforts. At the same time, there are some hopeful signs for the future. Fifty percent of Latino men with multiple partners report consistent condom use with secondary partners. Cultural strengths such as strong family orientation can be used to encourage safe sexual and drug behaviors. A culturally appropriate intervention for Latino STD patients already exists and is available. Greater understanding of and respect for Latino culture will lead to better HIV prevention efforts." (HIV InSite's report was supported in part by grants from the National Institute of Mental Health.)

Transgender People

According to the CDC, transgender communities in the U.S. are among the groups at highest risk for HIV infection. CDC defines transgender as a person whose gender identity does not conform to norms and expectations traditionally associated with a binary classification of gender based on external genitalia.

Key issues involving transgender individuals and HIV, CDC says, include:

- High levels of HIV risk behaviors, with multiple sex partners and unprotected receptive or insertive anal intercourse.
- High levels of alcohol and substance abuse, which can affect judgment and lead to unsafe sexual practices.
- Multiple male sex partners engaging in unprotected receptive anal or vaginal intercourse.
- Discrimination and social stigma, hindering access to education, employment, and housing opportunities, often leading to high-risk activities such as commercial sex work.
- Health care provider insensitivity to transgender identity or sexuality, which can discourage individuals from seeking health care.

For treatment guidelines from the University of California at San Francisco, see sidebar: Transgenders & Sexual Health.

'Die Young, Stay Pretty'

Young people aged 13-29 accounted for 39 percent of all new HIV infections in 2009, although they comprised just 21 percent of the U.S. population in 2010.

Young MSM, especially those of minority races and ethnicities, are at increased risk for HIV infection, the CDC reports.

According to CDC's 2009 National Youth Risk Behavior Survey (YRBS), 46 percent of high school students say they have had intercourse, with 5.9 percent reporting their first sexual encounter before age 13. Of the 34.2 percent of students reporting sexual intercourse during the three months before the survey, 38.9 percent did not use a condom.

"Young people with older sex partners may be at increased risk for HIV," CDC observes on its Website. "HIV education needs to take place before young people engage in sexual behaviors that put them at risk. Parent communication and monitoring may play an important role in reaching youth early with prevention messages."

CDC data have shown that young gay, bisexual, and other MSM, especially young African American and young Latino MSM, have high rates of new HIV infections. Another CDC study showed that young MSM and minority MSM were more likely to be unaware of their HIV infection, a situation that puts their health and the health of their partners at risk.

CDC points out that young MSM may be at risk because they have not always been reached by effective HIV interventions or prevention education, "especially because some sex education programs exclude information about sexual orientation." CDC also notes that young MSM may have increased risk factors for HIV, such as risky sexual behavior, due to isolation and lack of support, and that young adults who have experienced sexual abuse are more likely to engage in sexual or drug-related behaviors that could put them at risk for HIV infection.

Substance abuse can also cause young people to engage in high-risk behaviors. Runaways, homeless young people, and young persons who have become dependent on drugs are at high risk if they exchange sex for drugs, money or shelter.

Mary Jane Rotherman-Borus, Ph.D., a child psychologist who directs the Global Center for Children and Families and the Center for HIV Identification Prevention & Treatment Services (CHIPTS) in Los Angeles, CA, concurs with those conclusions from the CDC.

Healthy Relationships:

Gay, bisexual, and other men who have sex with men of all races and ethnicities remain the population most severely affected by HIV. While MSM account for just 2 percent of the U.S. population, they accounted for 61 percent of all new HIV infections in 2009. MSM accounted for 49 percent of people living with HIV in 2008, the most recent year national prevalence data are available.

In 2009, white MSM continued to account for the largest number of HIV cases of any group in the U.S., with 11,400, followed by black MSM at 10,800. Young, black MSM were the only risk group in the U.S. to experience statistically significant increases in new HIV infections from 2006-2009—from 4,400 in 2006 to 6,500 in 2009.

Blacks continue to experience the most severe burden of HIV, compared to other races and ethnicities. Blacks represent approximately 14 percent of the U.S. population, but accounted for an estimated 44 percent of new HIV infections in 2009. Blacks accounted for 46 percent of people living with HIV infection in 2008. At some point in their life, approximately one in 16 black men will be diagnosed with HIV infection, as will one in 32 black women.

In 2009, the estimated rate of new HIV infections among black men was six and a half times as high as that of white men, and more than two and a half times as high as that of Hispanic/Latino men and of black women. In the same year, the estimated rate of new HIV infections among black women was 15 times that of white women and over three times that of Hispanic/Latina women.

HIV also disproportionately affects Hispanics/Latinos. In 2009, Hispanics/Latinos represented 16 percent of the population, but accounted for 20 percent of new HIV infections. They accounted for 17 percent of people living with HIV infection in 2008 and 22 percent of new AIDS diagnoses in 2010.

Heterosexuals and injection drug users also continue to be affected by HIV. Heterosexuals accounted for 27 percent of estimated new HIV infections in 2009 and 28 percent of people living with HIV infection in 2008.

She pointed out that only about 250 HIV-positive babies are born annually, so the vast majority of young people with HIV have acquired the virus as a result of their activities, with most being gay boys, MSM, and some African American young girls "who live in the wrong neighborhood" with their older boyfriends injecting drugs or engaging in MSM activities without their knowledge.

All too often kids are on the street, many having been turned away by their families after coming out. Those adolescents are in high demand by older MSMs, she said, and are vulnerable to acquiring HIV.

Often, the concept for life is "Die young, stay pretty," because being attractive and beautiful is so important. "So what if you are going to die? You are going to be pretty your entire life and highly desirable to others," Dr. Rotherman-Borus explained.

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46 percent of high school students say they have had intercourse, with 5.9 percent reporting their first sexual encounter before age 13.

Many turn to methamphetamine because of its powerful sexual effect which lead to users often having several sexual partners in quick succession, but which also can lead to impotence only months later. That, Dr. Rotherman-Borus, explained, often leads young men to try other avenues for sexual fulfillment, including practices risky for HIV.

"It pulls you in," she said. "It is an epidemic, especially among young gay men, and has become their drug of choice."

For the clinician, all of these behaviors pose challenges. "Adolescents are the ones who are going to lie to you," Dr. Rotherman-Borus said, "because they want you to like them. They are not going to tell you a lot of detail unless you ask directly about it. Young people are often too embarrassed to be honest with their physicians or with anybody."

The Numbers

HIV infections among women are primarily attributed to heterosexual contact or injection drug use. Women accounted for 23 percent of estimated new HIV infections in 2009 and 25 percent of those living with HIV infection in 2008. Injection drug users represented 9 percent of new HIV infections in 2009 and 17 percent of those living with HIV in 2008.

Of the total number of new HIV infections among women in the U.S. in 2009, 57 percent occurred in blacks, 21 percent in whites, and 16 percent were Hispanics/Latinas. In 1009, the rate of new HIV infections among black women was 15 times that of white women, and over three times the rate among Hispanic/Latina women.

In 2009 young MSM accounted for 27 percent of new HIV infections in the U.S. and 69 percent of new HIV infections among persons aged 13-29. Among young black MSM, new HIV infections increased 48 percent from 2006 through 2009 when an estimated 8,294 young persons were diagnosed with HIV in the 40 states with long-term HIV reporting, representing about 20 percent of the persons diagnosed that year. Those aged 20-24 had the highest number and rate of HIV diagnoses of any age group (36.9 new HIV diagnoses/100,000 people).

Data from CDC-funded HIV testing programs show high percentages of newly identified HIV infections among transgender people. In 2009, about 4,100 of 2.6 million HIV testing events were conducted with someone who identified as transgender. Newly identified HIV infection was 2.6 percent among transgender persons compared to 0.9 percent for males and 0.3 percent for females. The highest percentage of newly identified HIV infection was among Blacks (4.4 percent) and Hispanics (2.5 percent). More than half (52 percent) of testing events with transgender persons occurred in non-clinical settings.

Partners & Peers

"For clinicians concerned about prevention to treat HIV-positive individuals, a primary tool could be partner interventions," the CDC's Dr. Collins said, pointing to "CONNECT," a couples-level intervention from CDC for heterosexuals at risk for HIV. It teaches couples communication techniques, HIV-risk reduction knowledge and skills, while addressing the power dynamics of the relationship that may serve as barriers to safer sex behaviors.

"The partner is a valuable resource for the HIV-positive person," Dr. Collins said. "It's not just status disclosure or helping couples practice safer sex, but the partner can also be involved in helping the person with medication and treatment adherence."

The active, managed support of peers can be a powerful asset for the clinician in treating the HIV-positive patient, observed Jane M. Simoni, PhD, professor, Department of Psychology, University of Washington, who has conducted extensive research into the use of nonprofessional community members to complement professional health care providers.

Dr. Simoni, a psychologist, is co-author of a paper published last year by the American Orthopsychiatric Association entitled "Peer Interventions to Promote Health: Conceptual Considerations," and believes peers are underutilized when working with HIV-positive persons and their partners. "I am very passionate about this," she said.

"Peers can be helpful in providing emotional support and by being the patient navigator within the clinic system," she told *HIV Specialist*. "It would be helpful for providers

Transgenders & Sexual Health

EDITOR'S NOTE: ***The Center of Excellence for Transgender Health Medical Advisory Board at the University of California, San Francisco, prepared the following recommendations for providers when managing the care of a transgender person. The recommendations were created with support from Primary Care program manager Jamison Green and intern Charlie DeVries. It was created with support from The California Endowment.***

Take a sexual history: inquire about past and current sexual contacts/total numbers; gender(s) and number of partners. Check for sexual orientation changes; ask if patient is aware that sexual orientation may change as they change their gender presentation or as hormonal changes occur; contraception, condom and barrier use/frequency; STI history; sexual abuse history; potentially risky sex practices (e.g., bondage, S&M, auto-erotic asphyxia, etc.). Self-destructive behaviors may indicate a need for mental health referral (see section Mental Health).

- **HIV and Hepatitis B/C screening/prevention:** if ongoing risk behaviors for sexual or blood-borne transmission (e.g., unprotected penile-vaginal or penile-anal intercourse, history of prior STIs, sharing needles for injection of hormones or illicit drugs), consider HIV and Hepatitis B/C screening every 6-12 months; otherwise consider HIV and Hepatitis B/C screening at least once during lifetime. Treat STIs according to recommended guidelines for non-transgender patients; offer Hepatitis B vaccination if patient is not already immune.
- HIV is not a contraindication or precaution for any transgender treatment. Treatment with hormones is frequently an incentive for patients to address their HIV disease. Providers of care for transgender people should enhance their HIV expertise, and vice versa.
- **Considerations for both transwomen and transmen:** If patient reports ongoing risk factors (recurrent STIs, unprotected sex with a partner who might be at risk, unprotected anal/vaginal sex with more than one partner, psychosocial cofactors relating to unsafe sex), screen every six months for gonorrhea, chlamydia, and syphilis. Treat all patients with STIs and their partners according to recommended guidelines.
- Internal genital exam should be based on patient's past and recent sexual history and comfort with exam, and discussion of the risks and benefit of the procedure. Use a gloved finger and/or an appropriate-sized speculum. Discuss fertility issues with patients considering hormone therapy. Cross-sex hormone use may reduce fertility, and this may be permanent even if hormones are discontinued. Estrogen may have the effect of reducing libido, erectile function, and ejaculation. Testosterone generally increases libido. Note: Even though testosterone reduces fertility in patients, testosterone is not a contraceptive substance; transmen having unprotected sex with non-trans men are at risk for pregnancy as well as STIs.

Special considerations for transwomen: Pap smears in neovaginas are not indicated. Perform periodic visual inspection with a speculum, looking for genital warts, erosions, and other lesions. If STI is suspected, do a culture swab, not PCR. Neovaginal walls are usually skin, not mucosa; when it is mucosa, it is urethral or colon mucosa.

to have peer programs that are formalized and connected to the patient." Programs can be as simple as coffee and donut meetings for patients to discuss their treatment with their peers, as well as one-on-one discussions, but they need to be effectively managed and peers need to be adequately trained. She has developed a training manual for this purpose.

"You have to have face-to-face training of peers, teach them about respecting boundaries, confidentiality, how to help work things out, making referrals, sharing what's been successful, stigma reduction," she explained. "We try to make it social, fun, so people have a chance to talk and share." The facilitator, she added, can be a more experienced peer or a social worker and is responsible for keeping the conversation on target.

Stigma, Fear

Dr. Rotherman-Borus, who is also Bat-Yaacov Professor of Child Psychiatry and Biobehaviorial Sciences at University of California at Los Angeles, is an advocate of the CDC's "CLEAR" (Choosing Life: Empowerment, Action, Results!) intervention module developed to help clinicians in their work with youth and adults, ages 16 and older, who are living with HIV.

According to Dr. Collins, CLEAR helps youth and adults decrease risky sexual behavior. Based on Social Action Theory, it consists of five required core skill sessions, 21 menu sessions, and one wrap-up session. Through the use of menu sessions in six domains (sexual risk, substance use risk, health care and self care, medication adherence, disclosure, and HIV stigma), the counselor is able to tailor the intervention to fit each client's circumstance, he explained.

"CLEAR is a module that can be downloaded," Dr. Rotherman-Borus said. "If doctors endorse it, kids are going to do it. You can have a paraprofessional in your office run it, and if you congregate all young HIV-positive patients during the same time period, based on age, it can be very efficient."

Dr. Krauss has done a great deal of work regarding stigma and believes strongly that the term is mired in attitudes, that it goes to social awkwardness about misunderstood conditions and can be spawned by fear and ignorance, which can be dangerous.

"When we keep silent about certain things, about taboo topics, people may think they must be OK. When we start stigmatizing and becoming silent, we prevent ourselves from doing the very prevention that is needed to protect one another. Our highest value ought to be protecting," she said.

"When we keep silent about certain things, about taboo topics, people may think they must be OK. When we start stigmatizing and becoming silent, we prevent ourselves from doing the very prevention that is needed to protect one another. Our highest value ought to be protecting."

Based on her research and work, Dr. Krauss said that even in a community where 10 percent of adults are living with HIV, both children and adults have moderate levels of useful HIV knowledge, including knowledge of prevention practices, and high levels of unrealistic HIV worry. Children, she said, worry a lot that someone they know has HIV/AIDS and hasn't told them, or that someone they know will contract the virus.

Her message is clear: being kind and helpful to those with HIV is in everyone's interest, while being unkind prevents people with HIV from getting treatment because they are afraid that by even going to a clinic or taking their medicines their status will be revealed with negative effects on relationships, housing, employment and their own emotional and physical health.

"The virus does not do an 'interview' to determine whom to infect," she said. "Use of infected, non-sterile syringes or needles can transmit HIV regardless of whether what is being injected is an illegal drug, insulin, or a vitamin."

Dr. Krauss says it doesn't matter how or where HIV started; that all diseases start somewhere. "With HIV, some made the early mistake of 'blaming' entire regions, just like blaming people for their own misfortune," she said. "When we are unkind to a person living with HIV, we are also being unkind to their family, friends, health care providers, and researchers in the field. They all see and hear how we behave."

That, said Dr. Krauss, is a message that clinicians can use in counseling with youth and others when the topic of stigma is discussed. "Making HIV a difficult topic prevents us from talking openly about how to prevent it," she stressed, adding that people with HIV wish to be treated like everyone else and as a complex human being with multiple roles, relationships interests, attitudes and feelings. HIV

ABOUT THE AUTHOR: *Editor of HIV Specialist*, **Bob Gatty** is a Washington, DC-area health policy writer and publications professional. He is founder of G-Net Strategic Communications and can be reached at bob@gattyedits.com.

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HEALTHY RELATIONSHIPS AND HIV STATUS DISCLOSURE

What's Love Got to Do with It?

BY CHARLES B. COLLINS, JR. PH.D.

"When do I tell? Before we have sex? After we have sex?"

For sexually active HIV-positive people, revealing their HIV status to their sex partner/s is a critical concern. We encourage and hope our HIV-positive patients have safer sex with their partners. We encourage and hope our HIV-positive patients thoughtfully disclose their HIV status.

But for the HIV-positive patient, sex is difficult to separate from love and relationship and HIV status disclosure is difficult to separate from trust and intimacy. For many HIV-positive people, safer sex practice and HIV status disclosure are combined into an issue with both ethical and romantic repercussions.

Healthy Relationships, a behavioral intervention available through the CDC, addresses these issues in five group sessions for HIV-positive people. Healthy Relationships can be delivered in community-based or clinical settings. Some providers may wish to implement the intervention in their clinic whereas others may wish to refer their patients to a Healthy Relationships group in the community. Health departments can be contacted to find out whether a Healthy Relationships group is locally available.

"I have fallen in love with a woman in my apartment complex. I know she is attracted to me and has asked me to come watch television with her tonight. I plan on having condoms with me because I am almost certain she will ask me to spend the night with her. I always practice safer sex with all partners. But what if she is the one for me? Should I tell her I am HIV-positive before we start to kiss or after we have our clothes off? Telling her after we have had intercourse and just relaxing with each other before falling asleep would probably not be cool. "

"There is a guy I have been dating for about a month. We kiss and play around but we have not had 'real' sex yet. I think he is in love with me, at least he hinted that he was falling for me. I know I am falling in love with him. I am so afraid that if I tell him I am HIV-positive, that it will scare him away. Should we begin a sexual relationship and then when we both are committed, let him know I am HIV-positive? Would this be a violation of his trust? Would he ever trust me again? Would he leave me just at a time when we are fully opening ourselves up to each other?"

These are the type of comments made by HIV-positive persons in the Healthy Relationships intervention. They reflect the complex adult situations in which HIV-positive people find themselves when they consider how to reveal their HIV status and negotiate safer sex with new romantic interests in their lives. The Healthy Relationships behavioral intervention helps HIV-positive persons deal with these critical issue of determining when, where, and how to reveal HIV status to potential or current sex partners. The name for the intervention reflects the need for HIV-positive persons to have emotional and sexual relationships that are based on safety, trust and intimacy. Challenges with HIV status disclosure for some positive people may be a barrier to building the trust, intimacy and a safer sexual relationship that protects their partner's health.

Seth Kalichman and his colleagues developed the Healthy Relationships intervention for HIV-positive persons and published their findings in the American Journal of Preventive Medicine in 2001. Clients in the Healthy Relationships condition were significantly more likely to report less unprotected intercourse at the three-month and six-month follow-up as compared to the control clients.

When Kalichman and his colleagues were developing the intervention, in focus groups with HIV-positive heterosexual men and women and with gay men, they asked how people negotiated for safer sex. The responses they received from HIV-positive people are very telling as to the complexity of safer sex and new relationships for HIV-positive people. They often heard from HIV-positive people: "For HIV-negative folks, safer sex discussion and negotiation is more straight-forward. For an HIV-positive person, with a new sex partner, you have to not only discuss and negotiate safer sex but you also have to figure how when and under what circumstances do you reveal that you are HIV-positive."

This led Dr. Kalichman and his colleagues to develop an intervention that builds self-confidence in status disclosure to family and friends before moving on to building self-confidence in status disclosure with sex partners. After a client feels increased confidence to disclose his/her status to family, they are better prepared to work

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Partnership for Health

How do we best convey HIV transmission prevention messages?

TWO HIV-POSITIVE PATIENTS visit their physicians.

The first physician says to his patient: "Look on the bright side. If you use condoms when you have sex you will not have to worry about syphilis, you won't have to worry about gonorrhea. You won't have to worry about infecting your partner with HIV and you can relax and enjoy sex."

The second physician says to his patient: "Think about the consequences of not using condoms when you have sex. If you become infected with a sexually transmitted infection then this can negatively impact your immune system and may complicate your HIV treatment. You certainly can infect others with HIV if you don't use a condom and then you would probably feel pretty bad that you infected someone else."

Which message, the first 'gain-framed' message or the second 'loss-framed' message might have the greater impact in helping your patients practice safer sex?

The research of Drs. Jean Richardson and Jessie Milam and colleagues at the University of Southern California indicate that the loss-frame message is significantly more persuasive in helping HIV-positive patients maintain safer sex practice. This led Drs. Richardson and Milam to develop Partnership for Health, an intervention that teaches physicians how to give HIV-positive patients with risk behaviors a loss-framed prevention message at each clinic visit. The intervention takes only four minutes of clinic visit time and once trained, physicians indicate that giving a loss-framed message to patients becomes second nature in provider or physician conversation. Drs. Richardson and Milam published their findings in the *Journal of Acquired Immune Deficiency Syndrome* in 2004.

Partnership for Health is a clinic-based intervention that supports clinician-patient messaging with posters for the waiting and examination rooms along with brochures for patients which help support the messages provided by the provider to the HIV-positive patient. Training for Partnership for Health is available free from the Centers for Disease Control and Preventionand is provided by the CDC's HIV/STD Prevention Training Centers. Training registration can be accessed through www.effectiveinterventions.org. The Partnership for Health training takes four hours and is meant to be a clinic-based training so that multiple providers, nurses, case-managers are all trained on the intervention.

There has been considerable interest in this evidence-based behavioral intervention, and 324 providers at 53 clinics have been trained to implement the intervention. Training is also available in Spanish for those clinics where clinic staff converse with Spanish-speaking patients.

on increasing their confidence to disclose his/her HIV status with a sex partner. After the client has built confidence around status disclosure with family, friends, and sex partners, the intervention then addresses safer sex negotiation with sex partners. The intervention never 'forces' someone to disclose their status to their sex partner/s. Rather the intervention helps support the development of skills so that the patients can ascertain when, where, and how to disclose their HIV status to family, friends, and sexual partners.

One unique feature of Healthy Relationships is the use of 5-minute clips from motion pictures that stimulate the group discussions around status disclosure. Healthy Relationships facilitators are trained to 'set the stage' by saying which actor or actress is HIV-positive in the film segment and then show a segment of a motion picture where that actor or actress is trying to tell something to someone else. The group then discusses how the HIV-positive person in the film could approach status disclosure.

The first two of the five group sessions focus on status disclosure to family and friends. Sessions three and four focus on status disclosure to sex partners. The fifth and final session deals with safer sex negotiation and practice.

Healthy Relationships is disseminated by the CDC Division of HIV/AIDS Prevention, Capacity Building Branch. The intervention has proven to be very popular. CDC-sponsored trainers have trained 340 community-based organizations and 122 clinics how to implement the intervention with HIV-positive patients.

A provider may wish to implement the intervention in the clinic or refer HIV-positive patients to community-based organizations that provide Healthy Relationships. More information and resources for Healthy Relationships are available on the website, www.effectiveinterventions.org. Free training is available from CDC-sponsored training partners. Registration for training is available on www.effectiveinterventions.org.

Disclaimer

The findings and conclusions in this article are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention. HIV

ABOUT THE AUTHOR: **Charles B. Collins, Jr., PhD**, is team leader, Science Application Team, Capacity Building Branch, Division of HIV AIDS Prevention in the National Center for HIV, Hepatitis, STD and TB Prevention at the Centers for Disease Control and Prevention in Atlanta, GA.

HEALTH CARE REFORM CALIFORNIA'S

Initial Implementation of

BY ANNE DONNELLY AND COURTNEY MULHERN-PEARSON

While health care reform holds great promise for people living with HIV/AIDS (PLWHA) to gain increased access to secure and affordable insurance coverage, it presents a significant challenge for most HIV positive uninsured Americans who will be transitioning from Ryan White programs including the AIDS Drug Assistance Program (ADAP). It will be essential to ensure that the Ryan White Program continues to address the significant gaps in HIV care that will exist even after full implementation of the Affordable Care Act (ACA).

California has moved quickly toward health care reform by implementing a Medicaid 1115 Waiver approved in late 2010. The waiver was intended to expand Medicaid (Medi-Cal in California) to 500,000 low income Californians, move people with disabilities, including HIV, and seniors into Medi-Cal managed care and strengthen the safety net in anticipation of full Medi-Cal expansion in 2014.

Although California's experience is still unfolding, there are several important lessons regarding care for people with HIV under Medicaid expansion that may prove helpful to other state advocates and people with HIV as health care reform is implemented nationwide.

The two components of the California experience most affecting people with HIV are the Medi-Cal expansion and the movement of seniors and people with disabilities, including HIV, into Medi-Cal managed care. The Medi-Cal expansion

LESSONS LEARNED

California's 1115 Medicaid Waiver, "A Bridge to Health Care Reform"

programs are developed, run and financed by the participating counties and called the Low Income Health Program (LIHPs). The counties set the income eligibility and can go up to 200 percent of the Federal Poverty Level (FPL). Currently, they range from 25 percent to 200 percent FPL. The counties also may cap the program and create waiting lists. The other important component is the movement into managed care. California is requiring all Medi-Cal beneficiaries who are seniors and people with disabilities, including people with HIV, to move into mandatory Medi-Cal managed care.

The Low Income Health Program (LIHP) and People with HIV

During the development of the waiver and its initial implementation, the Department of Health Care Services (DHCS) failed to include HIV care expertise in its Stakeholder Advisory Committee. The State Office of AIDS (SOA), which oversees much of Ryan White, and the DHCS did not communicate about LIHP coverage for uninsured people with HIV. Nor did the Centers for Medicare and Medicaid Services (CMS) communicate with the Health Resources and Services Agency (HRSA), the federal agency which oversees the Ryan White Program. As a result, the State failed to plan to cover people with HIV under the LIHP. The key misunderstanding was that the counties, lacking any guidance, believed Ryan White Programs, including ADAP, could continue to provide primary care and medications to people with HIV.

Neither the state nor the counties understood that Ryan White is the "payer of last resort," and prohibited from covering benefits provided in a Medicaid program. Thus, the counties did not plan for costs, provider networks, or transition of people with HIV from Ryan White services to LIHPs. When the oversight was discovered, people with HIV and their providers faced an abrupt and unplanned transition.

It was extremely difficult to plan quickly because Ryan White funds and services are administered locally and through the SOA, a part of the Department of Public Health, while the LIHP is administered by the Department of Health Care Services. There was no formal liaison between the two departments, little communication, and no joint work groups or advisory committees. As a result there was no one agency or individual in charge of the inclusion and transition.

The Movement of Senior and People with Disabilities into Managed Care

Most Medicaid programs across the nation are moving towards managed care. In addition to providing better coordinate care, state Medicaids are hoping managed care will save money. However, many people with HIV already have coordinated care at clinics that utilize Ryan White funding to provide coordinated services not available under Medicaid fee-for-service structures.

California's Medi-Cal services did a poor job of informing providers who were not already contracted with managed care plans, including many HIV providers of upcoming changes. As a result, many HIV providers had not begun the often complex contracting process with Medi-Cal managed care when the transition began.

Patient protection processes, the Medical Exemption Request (MER) and the Continuity of Care Provisions (CoC), that were intended to allow vulnerable beneficiaries to continue to see their fee-for-service providers, and thus minimize disruption to essential care, were poorly understood prior to the transition due to lack of information and education. Moreover, despite protections written in law, DHCS did not implement the system appropriately.

As a result, the system failed, leading to serious disruptions in care for many with HIV. Ten months into implementation of 12,800 MERs submitted only 1,900 have been approved, 3,400 have been denied and 7,500 have been returned as incomplete. In spite of significant advocacy work at the state and federal level the system remains dysfunctional, arbitrary and subjective.

Lessons Learned and Recommendations

Leadership and Collaboration—No one agency at the state or federal level is formally charged with securing the transition for PLWHA and planning for coordinated care after 2014. A new level of innovative and collaborative leadership from HIV-specific agencies at the state and federal level, such as State Office of AIDS (SOA) or State Health Departments, and the Health Resources and Services Agency's (HRSA) HIV Advisory Board (HAB), will be essential to successfully plan and implement transitions to and retention in new coverage options in 2014, as well as continuing to fill gaps in services and benefits post 2014.

Specifically:

1. New alignment and collaboration will be necessary between CMS and HRSA and their equivalents at the state level are critical to ensure integration of HIV services into broader health care systems and develop ongoing Ryan White programs for coverage and benefit gaps after 2014.
2. New structures that support collaboration should be explored such as joint stakeholders groups and department liaisons where offices are

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in different agencies or departments.

3. HRSA and HAB must develop their role in health care reform efforts to include adequate, timely, formal and informal guidance to assist RW providers to appropriately integrate with and wrap around broad health care coverage
4. State-level HIV agencies must provide leadership working with stakeholders to identify and address transition issues, assist Ryan White grantees in planning, and issue technical assistance guidance.

Planning and Engagement—Many critical decisions regarding health care reform implementation are being made at the federal and state level, including the essential health benefit package, development of the Health Benefit Exchange, and Medicaid expansion plans. Planning for the integration of HIV care services into broader systems of care and the structures and programs that will fill gaps in HIV care post 2014 must begin now to be successful.

Specifically:

1. Planning for health care reform transitions, new coverage and filling gaps post 2014 must start now at the federal, state and local level
2. HIV care expertise, including providers, advocates and PLWHA representing the diverse scope of the epidemic, must engage in implementation decisions at the federal, state and local. Advocates must find out where decisions are being made and get involved.
3. HIV care system experts must also engage with and learn about new systems of care, including Medicaid programs and private insurance options.
4. It is critical to work with other state health advocates who often bring expertise and developed relationships with decision makers.

Transition—Most uninsured people with HIV will be moving from Ryan White to new coverage. It is unlikely that new health care systems will be fully ready to support a smooth transition for all eligible HIV-positive people without disruptions or loss to care. In order to fulfill the promise of health care reform for people with HIV, transition strategies, including communication and education, must be developed that will minimize disruption to care.

Specifically:

1. Developing health care reform task forces at the federal, state and where appropriate local level is important
2. HRSA should consider allowing Ryan White grantees to phase-in screening for new coverage over the course of one year, using clients' birth month, allowing for a more manageable transition for PLWHA, case managers and administrators.
3. Federal, state, and local agencies should plan now for what types of flexibility in funding may be needed to facilitate a more secure transition. Where might ADAP need to fill gaps in access of new systems or between systems?
4. Local and state agencies should begin planning resource allocation that addresses outreach, linkage, engagement and retention in new care systems. One example would be to increase the medical case management and health benefit counseling resources available to PLWHA.
5. Some transitions have already occurred. In those cases, best practices need to be collected and shared as widely as possible.
6. Patient protections need to be developed, with stakeholders, and disseminated to both providers and patients prior to transition. Problem resolution protocols must be clear and usable by both providers and clients.

The Ryan White Program—Many Ryan White providers will integrate into larger systems of care after coverage expansion in 2014. However, Ryan White programs will continue to be essential in filling gaps in coverage and benefits under full ACA implementation.

Specifically:

1. HRSA and community stakeholders need to articulate and plan for the discrete services that are likely to need continued funding through Ryan White to ensure successful implementation of the testing, linkage to and engagement in care goals of the National HIV/AIDS Strategy (NHAS)
   - HRSA should also participate in defining the unique HIV needs in services such as medical case management and peer advocacy and determining if additional training or certification should be required for those services.
2. As payer of last resort, Ryan White cannot pay for services covered under other programs for which the client is eligible. Operating within this statute presents challenges during a transition as large and complex as that of health care reform. HRSA needs to allow for the broadest interpretation of payer of last resort in order to appropriately leverage Ryan White funds to wrap around other payer sources.
   - When Ryan White funds cannot be used, states should explore the use of other funds, such as state and rebate monies, to ensure continuity of care.
3. Advocates should also consider the feasibility of other legislative vehicles to broaden HRSA's authority to waive payer-of-last-resort for limited periods of time under specified circumstances during the health care reform transition.

Capacity Building, Technical Assistance and Infrastructure—To ensure successful integration and continuity of all aspects of quality HIV care, Ryan White providers will require timely and reliable information, updates, technical assistance and guidance.

Specifically:

1. HRSA should develop capacity building and technical assistance grants aimed at helping medical providers navigate moving from grant-driven systems to negotiating, contracting, and interacting with multiple coverage products.
2. Non-medical providers will need technical assistance from HRSA, states and localities about how to best align with and wrap around insurance coverage.

Although California's experience is still unfolding, there are several important lessons regarding care for people with HIV under Medicaid expansion that may prove helpful to other state advocates and people with HIV as health care reform is implemented nationwide.

3. State and local AIDS offices may also need technical assistance to develop systems that support and interact with new health care delivery systems.
4. Provider rates, both medical and pharmacy, will be lower under new systems of care and may be completely inadequate under Medicaid programs. Strategies and technical assistance with securing more adequate reimbursement rates will have to be pursued.

Education and Communication—Ryan White providers have developed a relatively seamless continuum of care that PLWHA have come to depend on for necessary information about their health care benefits and rights. However, many PLWHA and their providers in the Ryan White system are not well connected with broader systems of care; therefore general health care education and communication is often inadequate. It will be essential to develop improved stakeholder education and communication networks in this rapidly changing environment. Additionally, more individual assistance for people with HIV will be necessary to navigate, access, and utilize patient protections under new systems of care.

Specifically:

1. HIV entities, including the statewide HIV-specific agencies and the AIDS Education and Training Centers (AETC), need to take a stronger role in creating good communication networks and ensuring that accessible and usable information regarding changes in all systems of care gets distributed regularly.
2. Ryan White allocation planners need to increase resources for individual health benefits counseling and navigation assistance.

Medicaid Programs—People with HIV already rely heavily on Medicaid for their health care services in spite of the disability requirement that still exists in most states. Initial estimates in California suggest that as many as 70 percent of the uninsured HIV positive Ryan White clients will be eligible for Medicaid in 2014. At the same time, most state Medicaid programs are moving to managed care and often instituting increased beneficiary cost burdens and cuts in provider rates to respond to severe budget deficits. HIV Advocates need to directly engage with both traditional and expansion Medicaid programs and policy to ensure that Medicaid programs continue to meet the needs of people with HIV.

Specifically:

1. HIV care experts need to learn about and participate in state Medicaid policy development and implementation, including waiver, expansion programs, and movements to mandatory managed care.
2. CMS needs to ensure adequate oversight of state waivers and should consult with HRSA on any waiver that would affect people with HIV.
3. CMS should direct state Medicaid programs to reach out to Ryan White grantees in addition to other providers during waiver or program development.
4. HIV advocates need to be involved with the development and monitoring of patient protections in Medicaid programs
5. Advocates need to organize and oppose cost-cutting proposals that negatively affect Medicaid benefits.
6. Policies and strategies will need to be developed at the federal and, importantly, state levels to ensure that HIV providers receive adequate reimbursement for the delivery of coordinated chronic care for PLWHA. HIV

ABOUT THE AUTHORS:

Anne Donnelly, MA has been Health Care Policy Director at Project Inform since 2006 after serving as the organization's public policy director. She is responsible for ensuring that health care legislation, funding, program policies and reform at the Federal and California state level reflect the needs of people living with HIV. Ms. Donnelly has worked in the health policy field for more than 17 years and in the HIV field for more than 20 years.

Courtney Hulhern-Pears is the Director of State and Local Affairs for the San Francisco AIDS Foundation, responsible for developing the Foundation's state legislative and budget agenda. In this role, she advocates for full funding of vital HIV care and prevention programs in the California state budget as well as legislation to assure appropriate state policy responses to the HIV/AIDS epidemic.

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MONITORING HIV CARE IN THE UNITED STATES

The Medical Monitoring

IT IS AN EXCITING TIME to be involved in HIV medicine. The development of more effective and tolerable regimens has made it possible to realize the clinical benefits of earlier antiretroviral therapy (ART) initiation and the promise of ART as prevention. For the first time in the history of the epidemic, we have a comprehensive National HIV/AIDS Strategy (NHAS) to achieve the goals of reducing new HIV infections, increasing access to care, improving health outcomes for people living with HIV, and reducing HIV-related health disparities.

Project

BY JACEK SKARBINSKI, MD, AAHIVS, TEAM LEAD, CLINICAL OUTCOMES TEAM, BEHAVIORAL AND CLINICAL SURVEILLANCE BRANCH, DIVISION OF HIV/AIDS PREVENTION, CENTERS FOR DISEASE CONTROL AND PREVENTION

In working towards these goals, we, as providers, constantly strive to better understand *what* we should be doing for our patients, as well as *how well* we are doing by our patients.

Surveillance is a tool that can help us achieve this on a national scale. Although numerous clinical trials and epidemiologic studies are conducted every year, and practice guidelines exist to help establish a standard-of-care for treatment and prevention efforts, there are relatively few data collection activities that assess how well we, as a nation, are delivering these standard-of-care interventions. Since the beginning of the HIV epidemic, we have recognized the need to monitor both clinical outcomes among HIV-infected persons and the behavioral drivers of the HIV epidemic. Surveillance informs us about the current state of the HIV epidemic and provides data that can be used to guide our response.

What is the Medical Monitoring Project (MMP)?

The Medical Monitoring Project (MMP) is a supplemental surveillance system focused on HIV-infected persons receiving medical care that produces nationally representative estimates of behaviors, clinical outcomes, and quality of care for adults living with HIV who are receiving care in the United States.[1] It was created in 2004 in response to an Institute of Medicine recommendation for the Centers for Disease Control and Prevention (CDC) and the Health Resources and Services Administration (HRSA) to coordinate efforts to more accurately measure the delivery of and the need for prevention and care services.

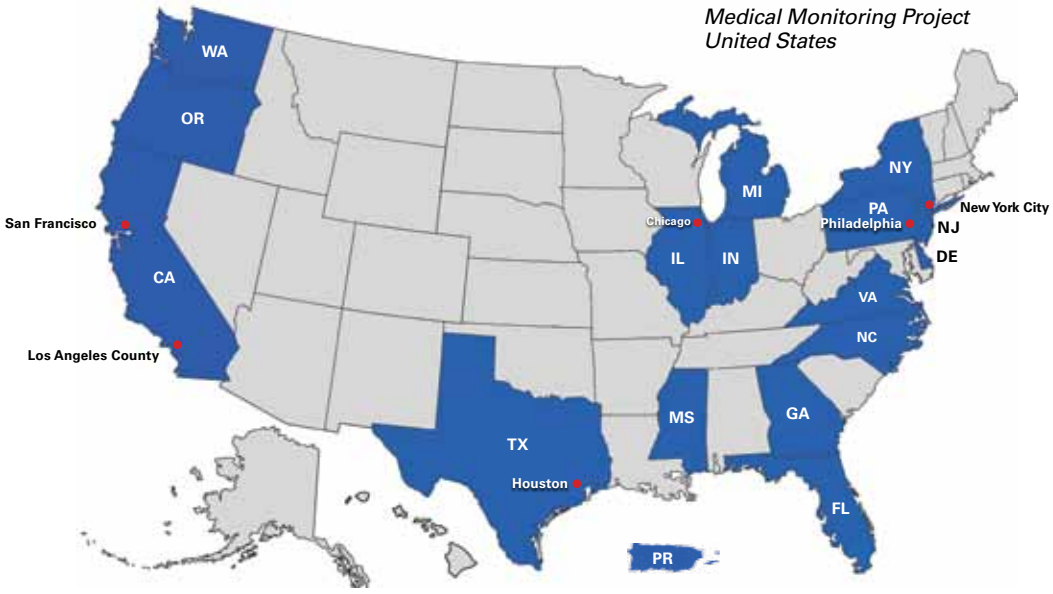
MMP allows for analyses of linked behavioral interview and clinical medical record abstraction data. The information collected via MMP can provide a national "snapshot" or benchmark of how well we are doing caring for people living with HIV and curbing the epidemic. For example, MMP can provide answers to critical questions such as: 1) how many people living with HIV are receiving HIV care; 2) how many people living with HIV in care are on ART and achieve viral suppression; and 3) how many people living with HIV who are in care receive needed prevention and support services.

How MMP Is Conducted

MMP is implemented by state and local health departments in collaboration with the CDC, and is currently conducted in 16 states, one U.S. territory, and six U.S. cities (see map).[2] These areas contain approximately 76 percent of all HIV-diagnosed persons in the United States. MMP is a cross-sectional survey of a patient sample carefully selected to represent all persons receiving HIV care in the United States that has been conducted annually since 2007.

Every year, participating state and local health departments select a random sample of approximately 400 adult patients from between 15-40 HIV care facilities in each jurisdiction. Patients who provide informed consent participate in a 45 minute face-to-face or telephone interview conducted by MMP staff, which includes questions about demographic characteristics, socioeconomic factors, and behaviors--including access to care, adherence to ART, unmet needs, sexual behavior and substance use. Additional information is abstracted by MMP staff from the patient's medical record, such as data on AIDS-defining and other illnesses, labora-

Participating areas - Medical Monitoring Project United States



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tory values, prescription of ART and other medications, substance abuse, and inpatient and outpatient visits. All of the data are kept confidential and names of patients and participating facilities are not collected. MMP staff conduct all project activities except when facility staff prefer to be involved. Additional information about MMP can be found at the MMP web site: http://www.cdc.gov/hiv/topics/treatment/mmp/index.htm.

Key Findings from MMP

Data from MMP have contributed to our overall understanding of the continuum of engagement in HIV care. In a recently published CDC report, MMP data were used to estimate the number and percentage of HIV-infected persons on ART and who achieved viral suppression in the United States (Figure 1).[3] Of the 480,395 persons estimated to be retained in care, 89 percent had been prescribed ART, of whom 77 percent had a suppressed viral load. However, only 28 percent of all persons living with HIV infection in the United States are estimated to be virally suppressed, in large part because only approximately 41 percent are both aware of their infection and receiving ongoing HIV care.

Although use of ART and levels of viral suppression appear high among persons receiving HIV care, more effort is needed to eliminate disparities between subgroups. Analysis of MMP data indicate that smaller percentages of blacks/African Americans and Hispanics/Latinos were prescribed ART and were virally suppressed compared with whites. Differences in rates of ART prescription and viral suppression might reflect differences in insurance coverage, prescription drug costs, health-care providers' perceptions of patients' probability of adherence, or other factors associated with adherence, all of which can be assessed using data from MMP.

In addition, MMP data have been used to highlight the additional efforts needed to incorporate ongoing prevention interventions for persons with HIV infection as a means to reduce HIV transmission. Prevention counseling is recommended as an ongoing part of HIV care for all patients, but MMP data indicate that only 45 percent of patients in the United States reported receiving prevention counseling from their health-care providers during the preceding year. These low percentages indicate a need for more consistent delivery of HIV prevention services by health-care providers, particularly by those caring for men who have sex with men or persons in other highly impacted groups.

Why MMP Is Important to You

The information obtained through MMP will help show how care affects the health of people living with HIV and can be used by HIV prevention community planning groups, Ryan White CARE Act planning councils, providers of HIV care, and others to improve HIV services and outcomes. MMP can inform policy decisions, resource allocation, and evaluation of treatment and prevention initiatives. Through collaboration between HIV providers and state and local health departments to engage patients to participate in MMP, the data can be used to provide a clearer picture of the quality of HIV/AIDS care around the country and to better understand the service needs of people living with HIV.

What you can do to support MMP

Allow your patients the opportunity to participate in MMP if your facility is selected for an MMP cycle. If one of your patients is selected for an interview, encourage them to be a part of this national effort to improve health outcomes and quality of care for people living with HIV in the United States. HIV

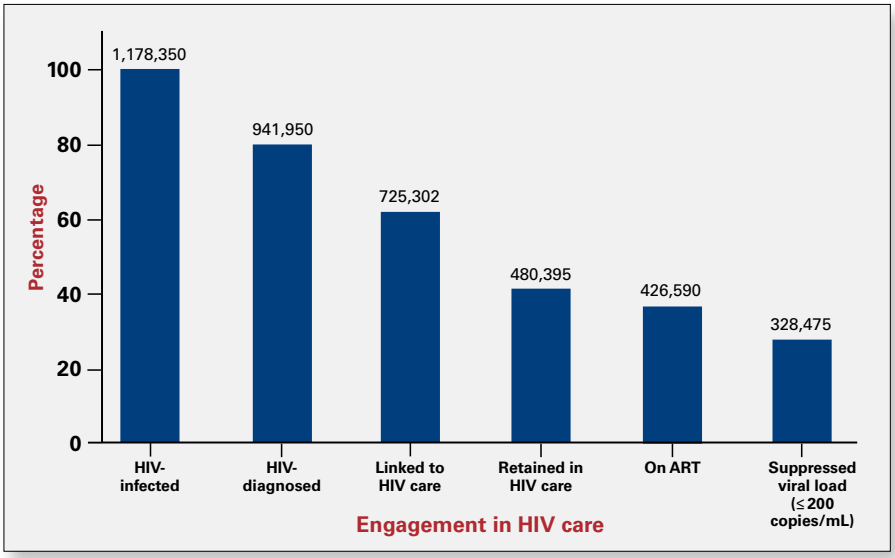

FIGURE 1: Number and percentage of HIV-infected persons engaged in selected stages of the continuum of HIV care — United States

The figure above shows the number and percentage of HIV-infected persons engaged in selected stages of the continuum of HIV care in the United States. CDC synthesized these findings to determine the number of persons in selected categories of the continuum of HIV care, and estimated that 328,475 (35%) of 941,950 persons diagnosed with HIV (or 28% of all 1,178,350 persons with HIV) in the United States are virally suppressed.

Reprinted with permission from: CDC. Vital Signs: HIV prevention through care and treatment, United States. MMWR. December 2, 2011 / 60(47);1618-1623.

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For information on Prevention with Positives including downloadable tools, go to http://www.cdc.gov/PreventionISCare

ABOUT THE AUTHOR:

Dr. Jacek Skarbinski is the team lead of the Clinical Outcomes Team in the Division of HIV/AIDS Prevention at the Centers for Disease Control and Prevention. The Clinical Outcomes Team administers the Medical Monitoring Project (MMP) in collaboration with state and local health departments. He is also a Clinical Assistant Professor of Medicine at the Emory University School of Medicine and provides HIV care at the Ponce De Leon Center associated with the Grady Health System in Atlanta, GA.

BY WILLIAM R. SHORT, MD, MPH AAHIVS AND MARGARET A. LAMPE, RN, MPH

Pregnancy Preparedness

The importance of preconception counseling and care for persons living with HIV

PRECONCEPTION COUNSELING is an essential component of both primary and preventive care and should be considered the standard of care for all individuals of reproductive age living with human immunodeficiency virus (HIV) (CDC, 2006). Healthcare providers who fully understand the impact of HIV infection upon a woman's reproductive health, fertility desires, and family planning needs are better prepared to assist their patients' reproductive health decisions.

The first few weeks of pregnancy are the most vital period in fetal development. During this time, a woman should be healthy and avoid any harmful activities and/or substances which could cause adverse maternal or fetal outcomes. However, as most patients present for prenatal care after this critical time period, preconception counseling is an essential component of HIV care and treatment for HIV-infected women. Both the Infectious Disease Society of America and HIV Medical Association recommend that all HIV-infected women of childbearing age be questioned about their pregnancy plans and desires upon initiation of care and routinely thereafter.

The goals of preconception care in the context of HIV infection are:

1. Prevention of unintended pregnancies.
2. Optimize maternal health prior to pregnancy.
3. Prevention of perinatal HIV transmission.
4. Prevention of HIV transmission to an HIV-uninfected partner when trying to conceive.

Unintended pregnancies are frequent, occurring in approximately 50 percent of all pregnancies in the United States (Feiner & Zolna, 2011). Data from the Women's Interagency HIV Study, a cohort study that showed that 77 percent of pregnancies occurred despite the use of contraception, suggesting that they were unintended

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(Massad LS, 2007). Of the women who had been pregnant since their HIV diagnosis and enrolled in the Medical Monitoring Project, a cross-sectional study of HIV-infected adults in medical care, 85 percent indicated that at least one pregnancy was unplanned (Sutton & Frazier).

The consequences of unintended and unplanned pregnancies are serious and add significant burden to women, men and their families. Women who do not wish to become pregnant should be advised to use an effective method of contraception. While oral contraceptives are safe in this population, it is essential to appreciate the potential drug interactions with certain oral contraceptives.

Table 1 lists many of the commonly prescribed antiretroviral medications and their interactions with the components of oral contraceptives. In addition to contraception, condoms should be recommended not only for their protection against pregnancy, but also to protect against sexually transmitted infections (STI).

Maternal health should be optimized prior to conception to reduce the risk of pregnancy-related morbidities and poor birth outcomes. Table 2 is a preconception healthcare checklist that should serve as a starting point for evaluating all HIV-infected women.

Education and counseling of patients about perinatal transmission is a fundamental component of preconception counseling. Critical elements that need to be addressed are transmission risk and effective methods to reduce these risks; the effects of HIV on pregnancy and pregnancy outcomes; and the additional risk of HIV transmission with breastfeeding after delivery.

In a landmark study, AIDS Clinical Trial Group 076 demonstrated that zidovudine monotherapy administered during pregnancy, labor and delivery and to the newborn, reduced the risk of HIV transmission to the infant by 67 percent (Connor, et al, 1994). Additional studies have demonstrated the effectiveness of combination therapy, further decreasing the risk of HIV transmission to 1-2% (Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, 2011).

The Department of Health and Human Services HIV guidelines, "Recommendations for use of antiretroviral drugs in pregnant HIV-1 infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States," (http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf) recommend that all HIV-positive women who are pregnant receive antiretroviral therapy (ART) regardless of CD4 count to minimize the risk of mother-to-child transmission (Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, 2011).

HIV-discordant couples who desire pregnancy should receive appropriate counseling about methods to minimize risk of transmission to the uninfected partner while trying

TABLE 1. Interactions Between Antiretroviral Drugs and Hormonal Contraceptives		
Antiretroviral Drug	Effect on Drug Levels	Comment
Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)		
Efavirenz	Oral ethinyl estradiol(EE)/norgestimate: no effect on EE; decreased active metabolites of norgestimate (levonorgestrel AUC decreased 83%; norelgestromin AUC decreased 64%)	A reliable form of barrier contraception must be used in addition to hormonal contraception.
Etravirine	Ethinyl estradiol AUC increase 22%	
Norethindrone: no effect	No dose adjustment necessary	
Nevirapine	Ethinyl estradiol AUC decrease 20%	
Norethindrone: AUC decrease 19%	Use an alternate method	
Rilpivirine	Ethinyl estradiol: CMax increase 17%	
Norethindrone: no effect	No dose adjustment necessary	
Ritonavir boosted protease Inhibitors (PI)		
Atazanavir/ritonavir	Decreased ethinly estradiol	
Increased norgestimate	Oral contraceptives should contain at least 35mcg of ethinyl estradiol.	
Darunavir/ritonavir	Ethinyl estradiol AUC decreased 44%	
Norethinfrone AUC deceased 14%	Use alternative or additional method	
Lopinavir/ritonavir	Ethinyl estradiol AUC decreased 42%	
Norethindrone AUC decreased 17%	Use alternative or additional method	
Unboosted Protease Inhibitors		
Atazanavir	Ethinyl estradiol AUC increased 48%	
Norethindrone AUC increased 110%	Oral contraceptive should contain no more than 30mcg of ethinyl estradiol or use an alternative method	
CCR5 antagonist		
Maraviroc	No significant effect on ethinly estradiol or levonorgesterol	Safe to use in combination
Integrase Inhibitor		
Raltegravir	No significant effect on ethinly estradiol or norgestimate	No dose adjustment required

AUC = area under the concentration curve; the total amount of unaltered drug in the patient's blood after a dose
CMax = the peak serum concentration of drug after a dose

to conceive. There are a number of effective methods and techniques which are beyond the scope of this review.

A key component of all methods is the screening and treatment for STIs in both partners and the use of antiretroviral therapy by the HIV-infected individual. HIV Prevention Trials Network (HPTN) 052 unequivocally demonstrated that antiretroviral therapy for the HIV-infected member of the couple significantly reduced the risk of HIV transmission (a 96 percent reduction) (Cohen, et al). It should be noted, however, that this reduction didn't occur in isolation, but it was the use of ART as well as risk-reduction counseling. These are the first data from a randomized clinical trial to demonstrate that the use of ART in those with some preserved immune function (CD4 350—500 cells/mm3) in conjunction with risk-reduction counseling can reduce HIV transmission to an uninfected partner.

Providers of HIV healthcare need to document and update the relationship status, partner HIV status, and fertility desires of their patients, both men and women. Education of their patients should include awareness of referrals and options to assist them to safely conceive when desired and achieve effective contraception when not (Lampe, et al, 2011). HIV

serious and add significant burden to women, men and their families.

TABLE 2. Preconception Healthcare Checklist

Lifestyle
- Regular moderate exercise
- Limit caffeine intake
- Screen for domestic violence

Medical Conditions
- Diabetes Mellitus-optimize control
- Hypertension
- Seizure Disorders
- Deep venous thrombosis-avoid warfarin
- Depression
- Anxiety

Screen for Infectious Diseases
- Syphilis
- Hepatitis B
- Rubella
- Varicella
- Cytomegalovirus

Genetic
- Folic acid supplement
- Carrier screening (ethnic background): sickle cell anemia, thalassemia, Tay-Sachs disease
- Carrier screening(family history): cystic fibrosis

Environmental Toxins
- Smoking cessation
- Screen for alcohol use
- Screen for illicit drug use

TABLE 3. HIV-Related Medications to Avoid During Pregnancy

Medication	Pregnancy Category*	Concern
Efavrienz	D	Contraindicated during the first trimester of pregnancy Potential increased risk of central nervous system birth defects
Ribavirin	X	Absolute contraindication during pregnancy
Combination of Stavudine and Didanosine	C B	Fatal lactic acidosis in pregnant women has been reported

* Food and Drug Administration Pregnancy Categories:

A = Adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

B = Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.

C = Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks

D = There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

X = Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

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ABOUT THE AUTHORS:

William R. Short, MD, MPH, AAHIVS is an Assistant Professor of Medicine at Jefferson Medical College of Thomas Jefferson University in Philadelphia, PA. He has been a member of the AAHIVM Steering committee for the Pennsylvania chapter since 2007. He is also actively involved in clinical research and providing HIV care to patients for over a decade.

Margaret A. Lampe, MPH, RN, is a health education specialist in the Division of HIV/AIDS Prevention at CDC. She is the project officer for the national HIV prevention partnership organizations working on perinatal HIV prevention projects, and the co-author of the HIV screening recommendations MMWR, Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings.

Gonorrhea Rising

What You Need to Know

BEFORE I TOOK OVER as executive director of the National Coalition of STD Directors (NCSD) just over two years ago, I was fairly confident I was well versed regarding reproductive and sexual health issues.

I had spent 10 years running the Washington, DC public policy office of the Sexuality Information and Education Council of the United States (SIECUS), where we spearheaded national efforts against abstinence-only-until-marriage programs during the Bush-years and did all we could to promote evidence-based interventions that averted poor sexual health outcomes, including of course, HIV acquisition.

That and a host of other experiences over the years gave me a good "wheelhouse" from which to work.

But my experience at NCSD has underscored for me that the silos in which we often find ourselves frequently and unwittingly obscure other real and pressing issues. That brings me to the point of this editorial—namely that we have very serious problems on the STD front that must be yelled from the rooftops.

First, as many of you know given your work in care delivery, we have historically low rates of Gonorrhea (GC) in this country. That is the good news. However, there are two looming issues that warrant concern.

First, we are beginning to understand more and more about GC infections in non-genital sites, namely rectal and pharyngeal infections. For years, we've been increasingly taking advantage of advances in diagnostics that meant—particularly for men—that inserting a swab into the penis to gather a urethral swab for culturing is no longer necessary.

That certainly advanced patient acceptability for testing, especially for asymptomatic patients, as the practice of urine-based specimen collection took off. But the decline in culturing generally meant that scaling up the swab –based collections of non-genital infections lagged. Moreover, FDA did not clear the advanced Nucleic Acid Amplification Tests (NAATs) for GC (and chlamydia as well) for non-genital sites (though many labs have now gone through the verification process that allows such testing to occur). Thus, in many instances, non-genital screening did

My experience at NCSD has underscored for me that the silos in which we often find ourselves, frequently and unwittingly, obscure other real and pressing issues... we have very serious problems on the STD front that must be yelled from the rooftops.

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not occur, but a urine-based negative result for urethral infections came back and patients went back into the game assuming they were GC-free.

What we've discovered though is that we're falling short in not conducting these screenings, particularly with gay men and other men who have sex with men (MSM). If we test non-genital sites for GC, we find it. And find it we must, as it is thought that rectal GC infections are a cause of the persistent rates of new HIV infections among MSM.

Recent studies even underscored that identifying these rectal infections are predictive of eventual HIV acquisition among MSM—and the higher number of such infections among patients exponentially increased their likelihood of becoming HIV-positive. To this end, non-genital screening also offers an additional opportunity to engage patients in a discussion among sexual risk-reduction.

The second issue is perhaps a graver one: GC's resistance to treatment.

GC is a tricky bacterium, outsmarting each line of treatment raised against it. Despite being at historic lows, there were 300,000 reported cases in 2011 and because most cases are asymptomatic and go undetected, the CDC estimates the real number of infections to be about 600,000. That's a lot of disease generally, but for something without treatment, it's a public health crisis. And, what penicillin could once easily treat has since outsmarted tetracycline and the fluroquinolone class of drugs, and since 2007, CDC has recommended cephalosporins for treatment of uncomplicated GC accompanied by either azithromycin or doxycycline.

Since 1986 and due to the realization that GC was adapting quickly to new treatments, the CDC invested in the Gonococcal Isolate Surveillance Project (GISP). This effort monitors the minimum level of antibiotics needed to treat infection—as that level rises, it means the bug is getting smarter, stronger and more drug is required to knock it out, with the reality that eventually the antibiotic may become ineffective altogether. It was a wise investment (though shockingly underfunded) and has worrisome evidence that resistance to cephalosporins is growing in the U.S. to the point that it is widely predicted that the Centers for Disease Control and Prevention (CDC) will soon change its treatment guidelines for treatment of GC to an injection-only treatment.

The resulting concern of this approaching storm for increased HIV acquisition is coming into focus…there is no new replacement drug in the pipeline.

While no treatment failures have yet been observed in the United States and cephalosporins remain an effective treatment, such failures have been observed in Norway, Japan and other parts of Asia. The westward move of resistance is not dissimilar from what was observed when fluoroquinolones began to fail and the pattern seems to be repeating itself once more.

In other words, the storm cometh.

The resulting concern of this approaching storm for increased HIV acquisition is coming into focus. We've known that other STD's generally increase susceptibly to HIV, which also among the key reasons why the above issue of non-genital GC infections going untested and untreated must be remedied. Recently the CDC conducted some estimates of the impact of resistant GC itself and NCSD emphasized that during a Congressional briefing we conducted in April, STD Awareness Month. The CDC estimates that due to resistance alone, nearly 800 additional HIV infections would occur over a seven- year period.

If that statistic is not sobering enough, here's the real clincher: there is no new replacement drug in the pipeline.

On every other occasion with GC resistance, there has been another class of drugs waiting, but that is not the case this time. a frightening reality. The reasons for this are multiple, but at the risk of sounding anti-capitalist, which I am not, it is in large part because pharmaceutical manufacturers have shifted focus to drugs one takes for a lifetime—HIV, diabetes, blood pressure, and such. Investing in a one-time treatment doesn't make a great deal of business sense if a patient can take it only once and be done with it.

And if private enterprise failed, blame can be equally shared by a government that has failed to recognize the issue and its implications and has not invested in the wellbeing of the nation. Is that not what government is supposed to do? So, we stand at a precipice without a clear way forward.

While NCSD and other partners work to stimulate the policy, research and drug development processes, healthcare providers can play a key role. The CDC has identified the following:

- Promptly treat all patients diagnosed with gonorrhea according to CDC's Treatment Guidelines; available at http://www.cdc.gov/std/treatment/2010/
- Obtain cultures to test for decreased susceptibility from any patients with suspected or documented gonorrhea treatment failures; and
- Report any suspected treatment failure to local or state public health officials within 24 hours, helping to ensure that any future resistance is recognized early. (Source: http://www.cdc.gov/nchhstp/newsroom/docs/Antibiotic-Treatment-of-GC-fact-sheet.pdf)

I wish there were a rosy way to close. There is not. We are potentially on the verge of a highly untreatable GC epidemic.

Equally important, from my perspective, is that we continue to find new ways of working together—across silos of disease—to promote sexual health efforts. To that end, NCSD is pleased to work alongside AAHIVM and hopes this editorial helps to pull down more siloes and contribute to our collective work.

We have shared interests to educate policymakers and our provider members to ensure whatever duration of GC resistance we experience is a short one and that it does not exacerbate other poor sexual health outcomes, such as increased HIV acquisitions. HIV

ABOUT THE AUTHOR: **William Smith** is Executive Director, National Coalition of STD Directors (NCSD)

Advances in Diagnostic Technologies for HIV-1

Medical and Scientific Affairs, Roche Diagnostics

THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (DHHS) GUIDELINES for the Use of Antiretroviral Agents in HIV-1-infected adults and adolescents updated March 27, 2012[1] provide recommendations for HIV care practitioners for the management and treatment of HIV infected patients. The guidelines recognize the critical role of laboratory tests and discuss the management of treatment experienced patients with low-level detectable viral loads.

DHHS recommendations for managing low level detectable viral load values using HIV RNA rea-time PCR testing (page C-6)

- Low level positive viral load results (typically <200 copies/mL) have been commonly reported with some viral load assays. For patient monitoring, the Panel defines virologic failure as a confirmed viral load >200 copies/mL, which eliminates most cases of viremia caused by isolated blips or assay variability.
- Optimal viral supression is generally defined as a viral load persistently below the level of detection (<20-75 copies/mL, depending on the assay used).
- Isolated "blips" (transiently detectable viral loads typically <400 copies/mL) are not uncommon in successfully treated patients and are not thought to represent viral replication or to predict virologic failure.
- Low level postive load results (typically <200 copies/mL) appear to be more common with some viral load assays than others, and there is no definitive evidence that patients with viral loads quantified as <200 copies/mL using these arrays are ate increased risk for virologic failure.
- For the purposes of clinical trials, the AIDS Clinical Trials Group (ACTG) currently defines virologic failure as a confirmed viral load >200 copies/mL, which eliminates most cases of apparent viremia caused by blips or assay variability. This definition may also be useful in clinical practice

The DHHS provides the following virologic definitions (page C-6)

- Virologic suppression: A confirmed HIV RNA level below the limit of assay detection (e.g., <48 copies/mL).
- Virologic failure: The inability to achieve or maintain suppression of viral replication (to an HIV RNA level <200 copies/mL).
- Incomplete virologic response: Two consecutive plasma HIV RNA levels >200 copies/mL after 24 weeks on an ARV regimen. Baseline HIV RNA may affect the time course of response, and some regimens will take longer than others to suppress HIV RNA levels.
- Virologic rebound: Confirmed detectable HIV RNA (to >200 copies/mL) after virologic suppression.
- Persistent low level viremia: Confirmed detectable HIV RNA levels that are <1,000 copies/mL.
- Virologic blip: After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression.

DHHS Laboratory Viral Load Monitoring Schedule for Patients Prior to and After Initiation of Antiretroviral Therapy
(Updated March 27, 2012) (page C-2)

Laboratory Monitoring Schedule for Patients Prior to and After Initiation of Antiretroviral Therapy

	Entry into care	Follow-up before ART	ART Initiation or modification[1]	2-8 weeks post-ART initiation or modification	Every 3-6 months	Every 6 months	Every 12 months	Treatment failure	Clinically indicated
Viral Load	√	Every 3-6 months	√	√[1]	√[2]			√	√
Resistance Testing	√		√[3]					√	√

[1]ARV modification may be done for treatment failure, adverse effects, or simplification.
[2]For adherent patients with suppressed viral load and stable clinical and immunologic status for >2-3 years, some experts may extend the interval for HIV RNA monitoring to every 6 months.
[3]For ART-naive patients, if resistance testing was performed at entry into care, repeat testing is optional; for patients with viral suppression who are switching therapy for toxicity or convenience, resistance testing will not be possible and therefore is not necessary.

HIV patient management is complex and rapidly evolving. Advances in viral load monitoring provide additional information, such as improvements in test sensitivity with the switch from end point PCR to real time PCR. These improvements may lead to increases in the understanding of disease progression and improvements in patient management and adherence.

Improvements in Sensitivity are Important

Patients: Improved diagnostics support adherence
Providers: Support for clinical decision-making
Support for lower LoD

400	50	48	20	?
1995	1998	2008	2010	Future

Emerging diagnostic technologies support our understanding and management of HIV-1 and could require increased patient education. The following case study discusses a patient managed by Dr. Bill Valenti, Clinical Associate Professor of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY. It is intended for educational purposes only, not to treat or manage actual HIV/AIDS patients.

Case Study:

This case reviews key points related to monitoring serial viral loads using the Roche COBAS® AmpliPrep / COBAS® TaqMan® HIV Test, v2.0, with a lower limit of quantification of 20 HIV-1 RNA copies/mL.

Case Study	
Patient	Male, age 32. Entered care March 2011
Viral load, CD4 (March 2011)	87,500 c/mL, CD4 330 cells/mm^3 (21%)
Viral load, CD4 (May 2011)	85,900 c/mL, CD4 292 cells/mm^3 (22%)
Raltegravir/ritonavir-boosted Darunavir	

The patient, a pharmacist, tested positive for HIV as part of a life insurance application. Although anxious to start antiretroviral therapy, he agreed to mental health counseling first to work on issues related to his unexpected diagnosis.

By May 2011, he was ready to start antiretroviral therapy and was very specific regarding his antiretroviral regimen. He wanted to use agents that were relatively recently approved and when possible, avoid a nucleoside reverse transcriptase inhibitor (NRTI)-containing regimen, even if it meant twice daily therapy and a higher pill count.

After appropriate resistance and tropism testing, we decided on a regimen of raltegravir and ritonavir-boosted darunavir. He was aware that there was limited clinical experience with this type of regimen.[2]

His viral load and CD4 counts after starting therapy are shown in Table 1 (top of next column).

The patient had rapid virological and immunological responses to his antiretroviral therapy and his first viral load <20 copies/mL three weeks after starting treatment. He found the regimen tolerable, easily integrated into his daily routine and experienced no noticeable adverse events.

TABLE 1. Viral load & CD4 Trends

	June 2011	Sept 2011	Dec 2011
VL (copies/mL)	<20*	<20*	<20*
CD4 (%)	530 (33)	501 (31)	710 (36)

*HIV-1 RNA detected, less than 20 HIV-1 RNA cp/mL

He had questions about the sharp decrease in viral load and the significance of the result "HIV-1 RNA detected, less than 20 HIV-1 RNA copies/mL."

I indicated that:

- With his result of "HIV-1 RNA detected, less than 20 HIV-1 RNA copies/mL in conjunction with his clinical presentation and other laboratory test results, we know that the treatment is working, but that the HIV-1 RNA is being detected at a very low level that is below the limit of detection of the test. Thus, it is detectable, but not quantifiable.
- A result that is reported as "target not detected," is different than a viral load that is reported "<20 copies/mL; HIV-1 RNA detected." "Target not detected" indicates that amplification of the HIV-1 target did not occur.
- The rapid fall in viral load to <20 copies/mL in the first three weeks after starting therapy supported the potency of his regimen that included raltegravir.[3-5]
- The Roche test may help with our understanding of emerging concepts in HIV medicine. High viral load is a major risk factor for HIV transmission. Highly sensitive assays may play a role towards HIV eradication by allowing us to measure very low level viremia that may be associated with release of HIV-1 from latent reservoirs.[6,7]

Learning Check:

How have advances in diagnostics increased the need for patient education around viral load monitoring?

What are the potential benefits of being able to quantify down to 20 copies/mL with the COBAS® AmpliPrep / COBAS® TaqMan® HIV Test, v2.0?

HIV

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To learn more about Roche Molecular Virology Portfolio of Real-Time PCR Systems: http://www.roche-diagnostics.us/Pages/default.aspx

BY BHAVIK PATEL, CRISTINA SALAS, SAMI SHAFIQ, PHARMD, CPH, AAHIVE

ART–Hormonal Contraceptive Interaction

Avoiding adverse events

THERE HAS BEEN little progress in the pharmacokinetic studies of hormonal contraceptives and antiretroviral therapy (ARTs). It is known however, that protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) do interact with hormonal contraceptives. DHHS guidelines reports no significant drug interactions between hormonal contraceptives, maraviroc and raltegravir and therefore may be combined safely.

These interactions may result in the failure of ARTs, oral contraceptives, or an increase in adverse effects due to either the contraceptive or ARTs. Adverse events may lead to nonadherence, therefore it is crucial to effectively manage these complex drug interactions and educate patients on the importance of adherence. Having an alternative route of administration may improve adherence in certain cases and prevent unplanned pregnancies.

According to the Center for Disease Control and Prevention (CDC), in the United States alone, almost half of all pregnancies are unintended. This sheds further light on the importance of oral contraceptive use and the concurrent management of oral contraceptives with antiretroviral therapy.

The majority of oral contraceptives available contain a combination of ethinyl estradiol and a progestin. These oral contraceptives can interact with PIs and NNRTIs via cytochrome P450 enzymes. As shown on the chart, pharmacokinetic studies have indicated either an increase or decrease in the levels of oral contraceptives and in a few cases, changes in antiretroviral concentrations.

The clinical significance of these drug interactions is still to be fully determined, but it is important to understand these interactions can result in oral contraceptive failure, antiretroviral failure, and additive toxicity.

In the case of decreased hormone levels due to ARTs, an additional method of contraception is commonly recommended. An increase in hormone levels may result in an increased risk of thromboembolism, breast tenderness, headache and acne among others. The lowering concentrations of ARTs may lead to virologic failure and the development of resistant mutations.

In summary, optimal adherence and effective management of concurrent therapy is important, as it may lead to therapeutic drug concentrations, and minimal adverse effects.

Medroxyprogesterone (Depo-Provera® seems to have the least amount of drug interactions and therefore might be a better choice in those patients who need hormonal contraception concomitantly with ARTs. In some patients, maraviroc or raltegravir with a backbone of two NRTIs might be safely considered due to a lack of significant drug interactions. HIV

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DAVID DAVIS / SHUTTERSTOCK

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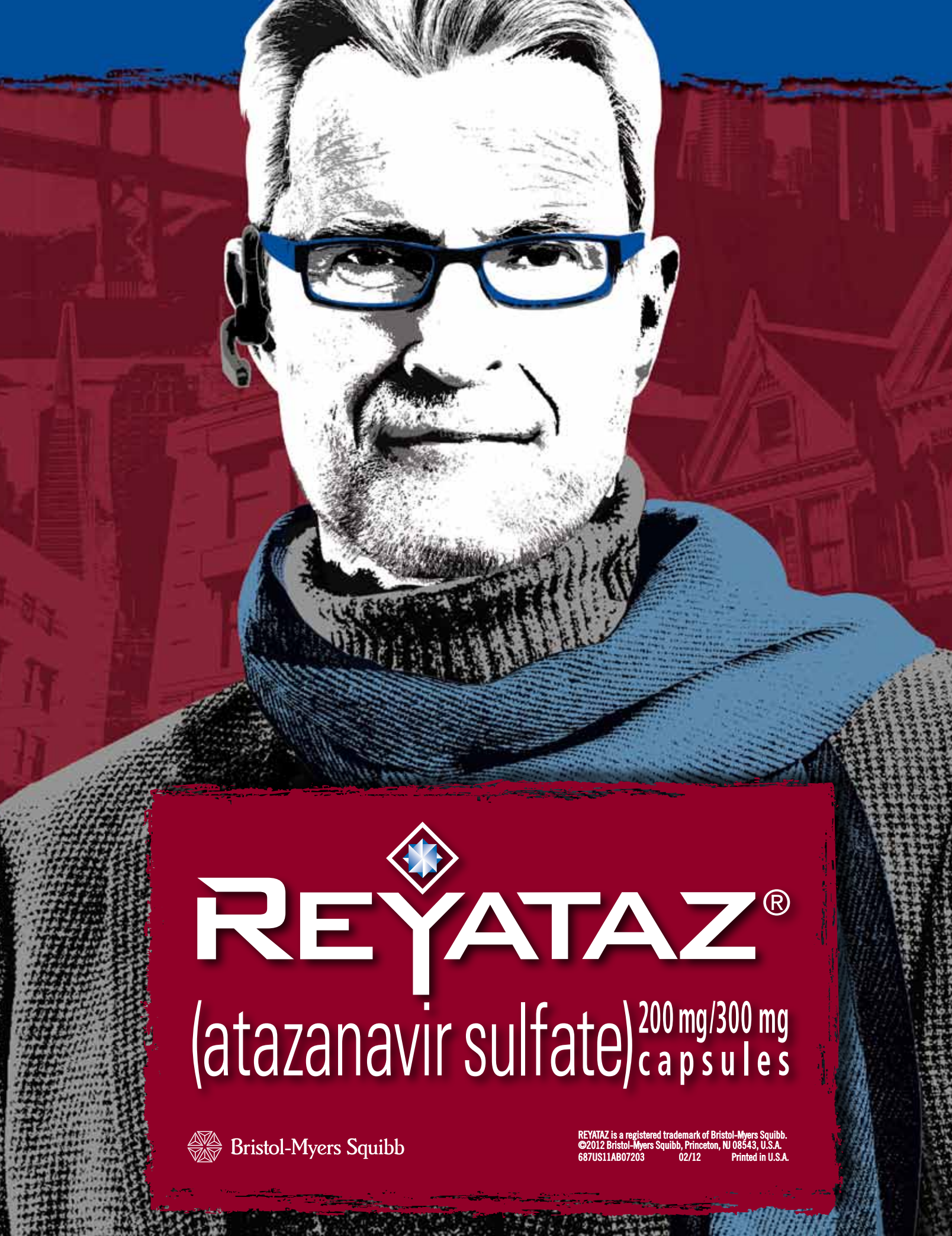
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