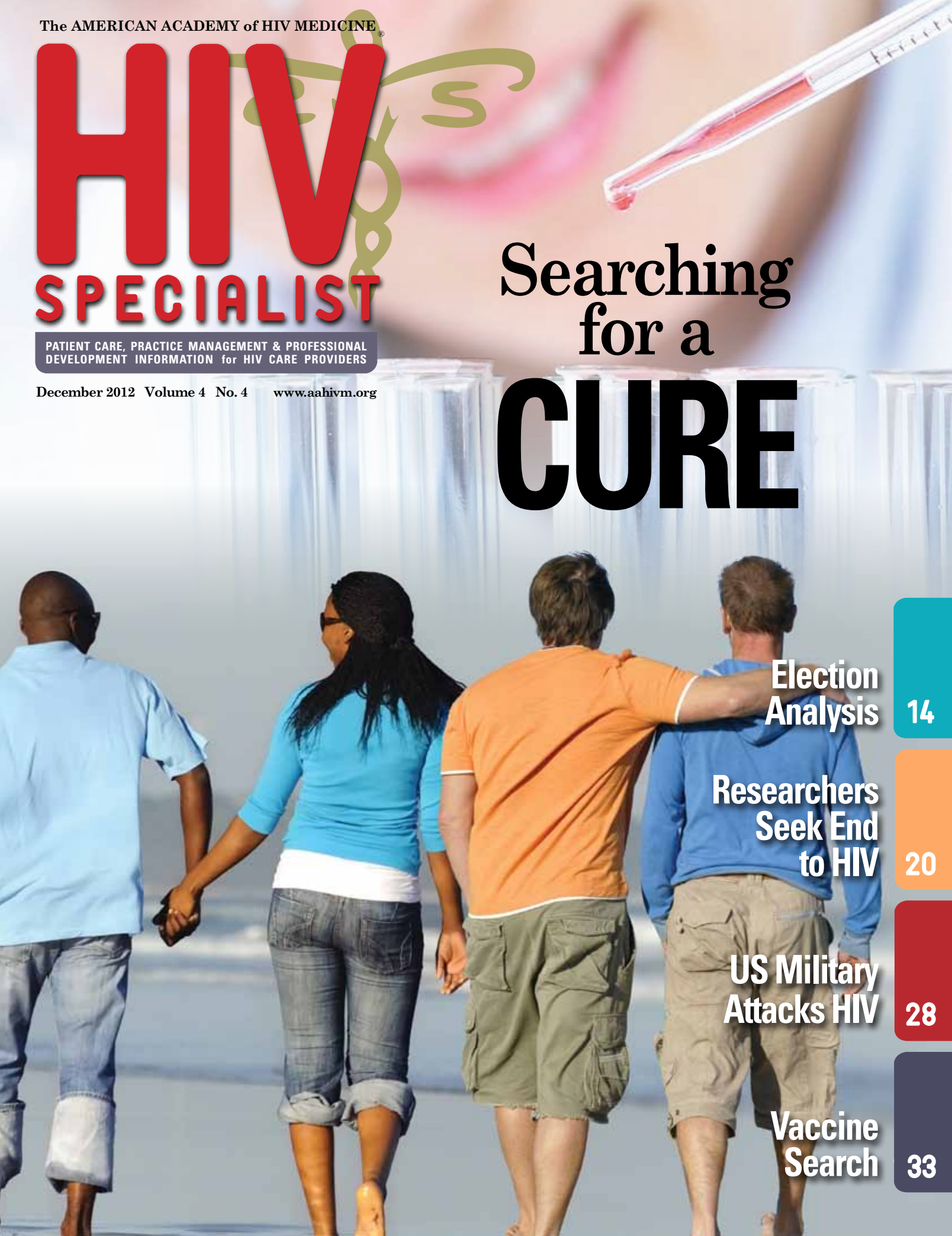
The AMERICAN ACADEMY of HIV MEDICINE®

HIV SPECIALIST

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

December 2012 Volume 4 No. 4 www.aahivm.org



Searching for a CURE

AMERICAN CONFERENCE FOR THE TREATMENT OF HIV (ACTHIV)

March 21 - 23, 2013
Sheraton Downtown Hotel
Denver, Colorado

We invite you to attend the American Conference for the Treatment of HIV (ACTHIV), to be held March 21 - 23, 2013 in the beautiful Mile High City of Denver, Colorado. The 2013 conference will feature a wide variety of relevant topics, an exhibit hall, poster sessions and great networking opportunities. Go to www.ACTHIV.org to register.

ACTHIV is a state-of-the-science conference specifically targeted toward US frontline providers of care to persons at risk of, or with HIV infection. Physicians, physician's assistants, nurses, pharmacists, medical case managers, social workers, psychologists, mental health and substance abuse workers, treatment advocates, educators, and other healthcare professionals involved in caring for those infected with HIV are encouraged to attend.

EDUCATION HIGHLIGHTS

- AAHIVM Technology Awards Luncheon
- HIV: The Basics
- Breakfast with the Experts to include AAHIVM Certification Exam Preparation with Donna Sweet and Case Studies in the following: HIV and Mental Health Disorders, Pain Management, HIV and Addictions, and Reading the HIV Literature for Clinical Practice
- Opening and Closing Plenary to include John Bartlett, MD, *What's New In HIV Clinical Medicine: Guidelines and Beyond*
- Best Practices: Lessons Learned from the Department of Veterans Affairs
- 4 Half Day Sessions dedicated to: HIV Treatment, Viral Hepatitis, HIV Primary Care and Emerging Issues

ACTHIV also offers a unique opportunity to network with companies and organizations relevant to HIV treatment, prevention and advocacy during all meal functions at the conference in the exhibit hall. The exhibit hall is also home to abstracts and case studies presented during the poster session which give attendees an opportunity to discuss new findings and results with the authors.

www.ACTHIV.org

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

Post Election: Shape and Adapt to a "New Reality"

The last issue of *HIV Specialist* focused on the effect of the Patient Protection and Affordable Care Act (ACA) on HIV care providers and patients. There was much speculation as to how or even if ACA would be relevant after the November elections. Now that the country has exercised its right to vote, it is certain that we will move forward with the implementation of the ACA—bringing approximately 30 million Americans into the health insurance fold.

But there are many other areas where the future is not so clear: dealing with the "Fiscal Cliff," income tax reform, immigration reform, addressing the federal deficit, creating more jobs, climate change, international hot spots—particularly in the Middle East—and hot button social issues at home, such as marriage equality. Running a campaign is far easier than addressing and solving these problems. Without good will and commitment to compromise on both sides of the aisle, we will fail. But we must also understand that ***when we succeed***, our society and our country will be different. And all of us will have to adapt to a "new reality."

There will be a "new reality" for HIV practitioners as well. And how effectively we both shape that reality and adapt to change will impact how well we meet the healthcare needs of the patients we serve in the years ahead.

As an organization, AAHIVM also has to adapt and look for opportunities to best serve our Members and Credentialed Providers during this time of change. The Academy is seeking funding support for two new long term programs that will help HIV practitioners in this post-election world. While both of these programs were initially developed to meet the needs of practitioners in a healthcare reform environment, over time they certainly will evolve into much broader programs.

James M. Friedman

The first of these proposals is a program to provide summarized state-specific information to HIV providers during the implementation of the Affordable Care Act. For example, if a state is contemplating a restricted drug formulary for its expanded Medicaid program, this proposal might advise HIV practitioners in that state to send letters to state officials to explain why that approach is dangerous and counterproductive for HIV patients. In another example, where a state might require all Medicaid providers become associated with a healthcare "network," this proposal would give HIV providers information on how to become part of that "system."

In later years, this proposal will also assist HIV providers adapt to possible changes to the Ryan White Program—which also may differ from state to state.

The second of these proposals is being developed in partnership with MedScape. This proposed program will provide on-line HIV CME to non-HIV specialists who will increasingly be caring for HIV patients. This proposal envisions a brief pre-test followed by five or more CME HIV chapters drawn from the pages of the *Fundamentals of HIV Medicine*, and finally a brief post-test to measure learning. The Academy will then issue a Certificate of Advanced Knowledge to those successfully passing that post-test. This is a multi-year proposal which will be updated to reflect changes in best practices.

These two proposals, if funded, will become centerpieces of the Academy's offering, similar to our publishing of *Fundamentals of HIV Medicine* and our Credentialing Program.

The Academy is committed to helping HIV practitioners navigate the new waters of healthcare reform. We want to hear from you. Let us know your experiences and your needs so that we can continue to tailor our offerings to our Members and Credential Providers. You can always reach me at jfriedman@aahivm.org.

Just remember... it's only through change that we grow. HIV

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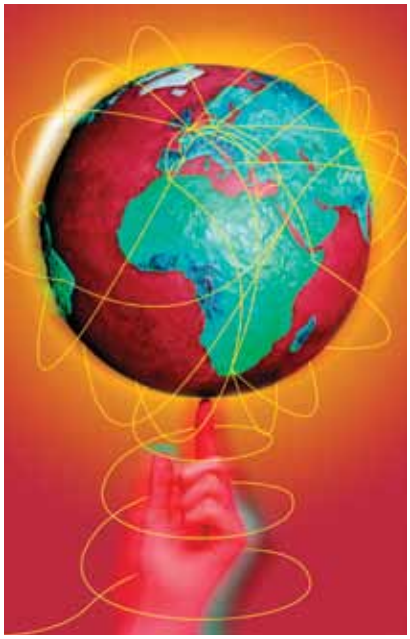

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IN THE NEWS

HIV Providers call for Increased Access to Lifesaving Drug Therapy

The American Academy of HIV Medicine (AAHIVM) and the HIV Medicine Association (HIVMA) have released a joint statement expressing concern over current HIV drug pricing. The statement provides detailed recommendations for improving access to effective HIV antiretrovirals both in the U.S. and abroad.

AAHIVM and HIVMA membership represent the vast majority of frontline HIV care providers in the United States. The organizations delivered the recommendations to pharmaceutical companies, insurers and the Centers for Medicare and Medicaid Services (CMS).

The joint statement recognizes the pharmaceutical industry for its unprecedented advancement in research and development of life-saving HIV therapies over the past 30 years. However, the groups urge pharmaceutical companies to set prices for antiretrovirals at levels that support access for the populations most in need.

Twenty-five percent of people with HIV infection are uninsured, with fewer than 15 percent having private insurance coverage. Drug accessibility based on price can unduly affect individuals with HIV. In addition to setting fair drug prices, HIVMA and AAHIVM call upon industry to participate in innovative programs like HarborPath and to work with U.S. policymakers and public and private insurers to reduce burdensome restrictions that are barriers to expediting access to lifesaving HIV drugs.

"HIV care providers across the country can prescribe the therapies available to treat patients to properly manage their disease," said Michael Horberg, MD, MAS, Chair of the Board of Directors of HIVMA. "However, if patients are unable to afford to fill the prescription, the treatment link is broken. Reliable access to HIV medications is imperative for viral suppression and effective management of HIV infection, not only to improve the patient's health but also to help prevent the spread of the disease."

Of the 1.1 million people living with HIV infection in the U.S., just 37 percent are retained in regular care and only 25 percent have undetectable levels of HIV in their blood. The Patient Protection and Affordable Care Act (ACA) offers an opportunity to dramatically increase access to HIV treatment and care.

"The provider community is pleased that ACA will expand care options for the HIV patient," said Dr. Donna Sweet, chair of the AAHIVM Board of Directors. "But if the full range of treatment options is not included in the drug formularies and costs aren't kept down for third-party payers and individuals, the full benefit to HIV patients through the ACA will not be achieved."

To view the statement in its entirety, visit the HIVMA website at www.hivma.org or the AAHIVM website at www.aahivm.org.

White House Honors World AIDS Day 2012

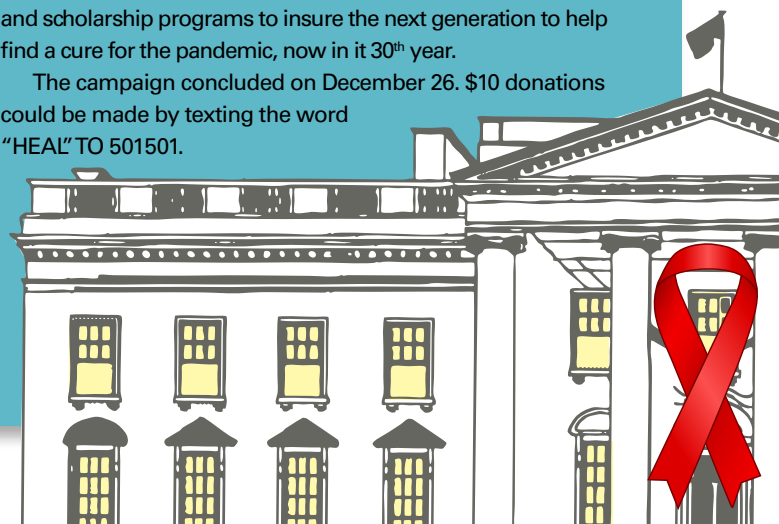
Erin Lindsay, deputy director of online engagement for the Office of Digital Strategy at the White House, posted a blog on December 1, World AIDS Day, noting that last year President Obama announced ambitious targets in the global fight against HIV/AIDS, and on the domestic front investment in the first comprehensive National HIV/AIDS Strategy to fight the epidemic.

"One year later, the President's commitments have translated into real measurable progress," the blog noted. "As of today, we are treating over 5 million people with lifesaving medicines for AIDS, up from 1.7 million in 2008, and are on track to treat 6 million people by the end of 2013."

"This year, we have also reached over 700,000 HIV-positive pregnant women with antiretroviral drugs that will prevent them from passing the virus to their children. We are making real progress, but the fight is not over."

Among other activities worldwide, AT&T and the National AIDS Memorial teamed up to help raise awareness and funding for programs to support the Memorial. All donations to the text-to-donate campaign support the Memorial's mission to honor and pay tribute to those who have lost their lives to HIV/AIDS, create and maintain a permanent memorial grave located in San Francisco as a place for healing, and expand youth awareness and scholarship programs to insure the next generation to help find a cure for the pandemic, now in it 30th year.

The campaign concluded on December 26. $10 donations could be made by texting the word "HEAL" TO 501501.



THINKSTOCK, SHUTTERSTOCK

A Single Tablet Regimen That Reaches Many Treatment-Naïve Adults

Indication

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.

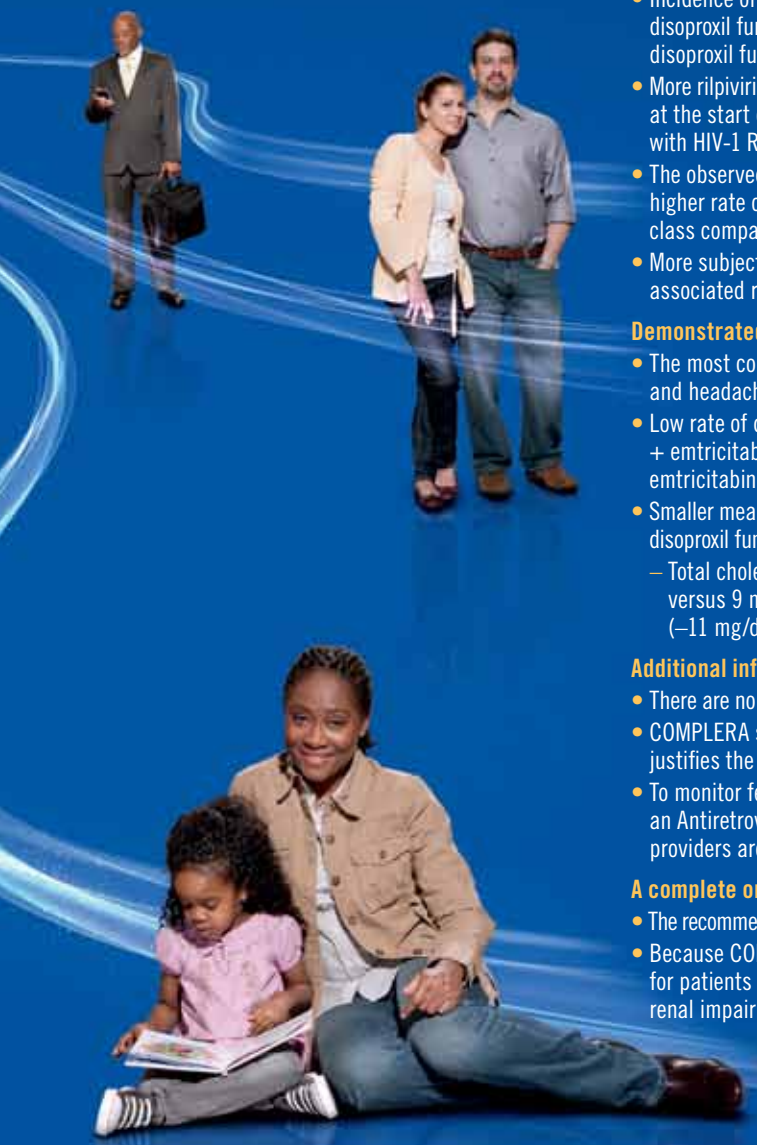
GILEAD

Important Safety Information

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. 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. **2.** 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)[1,2]*

- 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)[1,2]
- Incidence of virologic failure: 13% with rilpivirine + emtricitabine/tenofovir disoproxil fumarate (N=550) versus 8% with efavirenz + emtricitabine/tenofovir disoproxil fumarate (N=546)
- 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

Demonstrated safety through 48 weeks

- The most common adverse drug reactions (Grades 2-4, ≥2%) were insomnia and headache
- Low rate of discontinuation due to adverse reactions (2% with rilpivirine + emtricitabine/tenofovir disoproxil fumarate versus 5% with efavirenz + emtricitabine/tenofovir disoproxil fumarate)
- Smaller mean changes in fasting lipid levels (rilpivirine + emtricitabine/tenofovir disoproxil fumarate versus efavirenz + emtricitabine/tenofovir disoproxil fumarate)
  - 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)

Additional information: Pregnancy Category B

- There are no adequate and well-controlled studies in pregnant women
- COMPLERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus
- 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

A complete once-daily, single tablet regimen

- The recommended dose of COMPLERA is one tablet taken orally once daily with a meal
- 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)

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

Scan this QR code to go directly to

complera.com/hcp

*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). The primary endpoint was non-inferior viral suppression to efavirenz through 48 weeks (HIV-1 RNA <50 copies/mL).[1,2]

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 **BOXED WARNINGS** on previous page.

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. Autoimmune disorders may occur in the setting of immune reconstitution

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, including **BOXED WARNINGS**, on following pages.

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 jiroveci* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillian-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

ADVERSE REACTIONS

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/mm^3) 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]*.

Issued: 8/2012

GILEAD

Feds Announce Awards on Prevention of HIV Mother-to-Child Transmission

The U.S. Department of State's Office of U.S. Global AIDS Coordinator, in collaboration with the National Institutes of Health's *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), has announced plans to award grants totaling up to $7.5 million over the next two years to advance efforts to prevent transmission of HIV from mothers to their newborn children.

The funds will support implementation science projects to inform the President's Emergency Plan for AIDS Relief (PEPFAR) as it continues to implement programs for prevention of mother-to-child transmission (PMTCT). The National Institute of Mental Health (NIMH) and the Office of Research on Women's Health (ORWH) at the National Institutes of Health have also provided co-funding for some of the grants.

The funds will support nine implementation science awards to address a variety of topics, including optimizing integrated PMTCT services; increasing uptake and retention of PMTCT services; facilitating HIV testing and education of male partners; examining the effect of 'buddy' systems to help mothers adhere to feeding guidelines; comparing cost-effectiveness of faith-based- and clinic-based approaches; closing the gaps in early infant diagnosis; and measuring the impact of PMTCT programs on maternal and infant health outcomes.

These studies link directly to programs, researchers and institutions in seven countries receiving PEPFAR support.

For additional information, visit www.pepfar.gov.

For more information about NIH-sponsored research, please visit http://www.nih.gov and http://www.nichd.nih.gov.

Chinese Study Challenges Treatment as Prevention Strategy

A large Chinese study claims that treating HIV is less effective at preventing transmission of the virus among serodiscordant couples than previously believed, *MedPage Today* reports.

The study, published in the online edition of *The Lancet*, says treatment only reduced transmission rates by 26 percent.

This finding challenges the HPTN 052 trial of 2011, which found that antiretroviral (ARV) treatment reduced transmission rates by 96 percent. Both the HPTN 052 trial and the Chinese study looked at heterosexual couples, but the Chinese study looked at serodiscordant relationships outside the confines of a tightly controlled research study.

Using records from Chinese epidemiology and treatment databases covering 2003 through 2011, Yiming Shao, MD, of the Chinese Center for Disease Control and Prevention in Beijing and colleagues examined data on 38,862 serodiscordant couples, including 101,295 person-years of follow-up for the HIV-negative partners.

Among the 14,805 couples in which the HIV-positive partner was not on ARVs, the rate of transmission was 2.6 per 100 person years; while among the 24,057 couples in which the HIV-positive partner was on treatment, the rate of transmission was 1.3 per 100 person-years.

Researchers could only state with certainty that the 26 percent reduction in the rate of transmission was significant in the first year of treatment; the reduction lost significance in subsequent years in their statistical analysis.

They said more research is needed to understand whether the benefits of treatment as prevention will endure, and to determine how data from such studies can be applied to the real world.

The *MedPage* report is available at: http://www.medpagetoday.com/clinical-context/HIVAIDS/36200

The Lancet report is available at: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)61898-4/abstract

SHUTTERSTOCK, DREAMSTIME

IN THE NEWS

Grants Announced to Address Gender-Based Violence as Part of the Global HIV Response


Melanne Verveer

IN RECOGNITION of the International Day for the Elimination of Violence Against Women and World AIDS Day, Ambassador-at-large for Global Women's Issues Melanne Verveer has announced $3 million in small grants awarded to dozens of grassroots organizations working to prevent and respond to gender-based violence (GBV) around the world, with a link to HIV prevention, treatment and care.

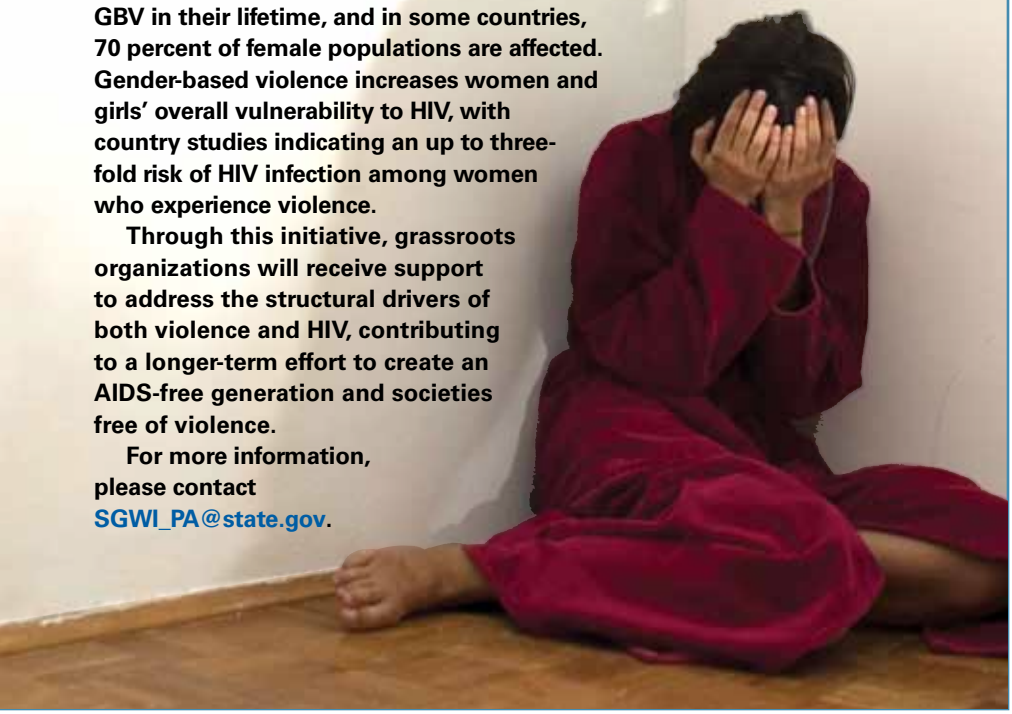
The grants are part of a joint initiative between the Secretary's Office of Global Women's Issues and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) to address the link between HIV infection and GBV, and will support the work of 35 organizations in 28 countries.

Grants of up to $100,000 per organization will fund iprograms that link to HIV prevention, treatment and care platforms, including those programs that work to engage community leaders in the fight against GBV and AIDS, strengthen legal and judicial systems to ensure the full enforcement of anti-GBV laws, enhance prevention and response efforts, and work to reduce stigma and harmful practices.

One in three women worldwide will experience GBV in their lifetime, and in some countries, 70 percent of female populations are affected. Gender-based violence increases women and girls' overall vulnerability to HIV, with country studies indicating an up to three-fold risk of HIV infection among women who experience violence.

Through this initiative, grassroots organizations will receive support to address the structural drivers of both violence and HIV, contributing to a longer-term effort to create an AIDS-free generation and societies free of violence.

For more information, please contact SGWI_PA@state.gov.



HIV Therapy Reduces Malaria Recurrence in Children, Study Shows

A combination of protease inhibitors lopinavir and ritonavir has been shown to reduce the risk of recurrent malaria by 40 percent in HIV-positive children, according to a research study funded by the National Institutes of Health (NIH).

The children in the study ranged from infants to those up to age 6 in Uganda and were also being treated with anti-malaria drugs. The reduction was in comparison to malaria incidence among children receiving treatment with non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Researchers said the protease inhibitor combination did not appear to inhibit an initial bout of malaria, but did reduce the chances of a recurrence of the disease after treatment. They found blood levels of anti-malarial drugs were higher in children who had received the protease inhibitors.

"It's possible that these protease inhibitors prevent antimalarial drugs from breaking down or have some other additive effect against the malarial parasite," said Lynne Mofenson, M.D., chief of the Pediatric, Adolescent, and Maternal AIDS Branch at the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the NIH institute that funded the study. "Laboratory studies also suggest that protease inhibitors can block the malaria parasite outright. Finding out why this drug combination is effective is an area for further study."

SHUTTERSTOCK

Vitamin D May Boost Women's Ability to Fight HIV

According to research published online in *AIDS*, women who start HIV treatment late in the course of their infection gain significantly fewer CD4 immune cells if their vitamin D levels are insufficient.

The researchers assessed 204 HIV-positive women who began ART later than usual in the course of their infection. Eighty-nine percent were vitamin D deficient. The researchers found that after two years of therapy, the women with insufficient vitamin D gained an average of 134 CD4 cells, while those who had sufficient vitamin D levels gained 188 CD4 cells.

"There may be biological mechanisms that explain the effect of vitamin D insufficiency on late CD4 cell recovery after HAART (highly active antiretroviral therapy) initiation," the authors concluded.

Source: Aziz AM, et al. Vitamin D insufficiency may impair CD4 recovery among women's interagency HiV study (WIHS) participants with advanced disease on HAART. AIDS. Nov 6, 2012.

Hep C and HIV Linked to Hip Fractures

A TEAM OF RESEARCHERS in the U.S. has grown concerned about the strength of bones in the hips of people with HCV, HIV or both viral infections, reports *THE BODY PRO*.

Among HIV-negative people, when hip bones/joints become broken, their survival subsequently decreases. Moreover, the U.S. researchers noted:

"Hip fractures cause significant pain and disability and typically require an emergency department visit, hospitalization, surgery and rehabilitation stay, resulting in substantial healthcare costs."

The U.S. research team (based at the University of Pennsylvania) conducted a massive study of three million people, both with and without different viral infections. They found that people co-infected with HIV and HCV were at greatest risk of hip fracture compared to participants with HCV infection alone (monoinfection) or to people who had neither infection.

THE BODY PRO report said the study underscores the need to understand why thinning bones, particularly in the hips, occur in people with HIV, HCV or both. Furthermore, ways to improve the bone health of people with chronic viral infections are needed.

Read more at: http://www.thebodypro.com/content/69819/viral-infections--hep-c-and-hiv-linked-to-hip-frac.html

SHUTTERSTOCK, THINKSTOCK

Canadian HIV Meeting Emphasizes Research with Real-Life Impact

THE ONTARIO HIV TREATMENT NETWORK (OHTN) is a collaborative network of researchers, health service providers, policy makers, community members and people with HIV who work together to promote excellence and innovation in HIV treatment, research, and education.

The annual OHTN HIV research meeting (Nov 11-13) entitled "Research with Real-Life Impact" provided cutting-edge updates on critical domains in HIV research. The organizers emphasized that the goal of the conference was to solve problems. Attendees heard from some of the most distinguished researchers in the field from across Canada, the United States, Britain, New Zealand and Australia (Conference summary notes as well as all PowerPoint presentations can be gotten at http://www.ohtn.on.ca/Conference/index.php.).

The small scale of this conference belies the reach and depth of the information presented and discussed. The Plenary panels included "Closer to A Cure" led by Robert Siliciano MD PhD, Professor of Medicine at Johns Hopkins University Medical School, which focused on the promising and provocative work on resting and activated CD4+ cells. The plenary included a report by Brad Jones, PhD of MIT and Harvard's Ragon Institute on cytoxic T-lymphocytes' elite control and the use of nanoparticles as a treatment modality.

For the plenary "Men Who Have Sex with Men," Patrick Sullivan PhD of Emory's School of Public Health led a team and gave powerful evidence of both the biological and social factors that underlie MSMs accounting for the majority of HIV infections. His data provided a very different data driven perspective on the high HIV burden by the gay communities (MSM) whose high per-act and per-partner HIV transmission probabilities, sex role versatility, and network and structural level risks must be considered.

The challenges of PrEP were detailed by historical and present research data in the plenary "Is Treatment Enough Prevention" led by William Miller, MD, PhD, from Medicine and Epidemiology at the University of North Carolina.

Building Resistance

Many of the Plenaries were relevant to the issue of HIV and aging.

The plenary "Building Resistance" defined the challenges faced by PLWH and their care providers, addressing the multiple issues which drive health management challenges, including those of older adults who are aging with HIV. One of the primary conference sponsors was the Ontario Ministry of Health and Long-Term Care. Canada recognizes the emerging challenges of the older adult with HIV.

Three years ago the Canadian Working Group on HIV and Rehabilitation began to focus on the issue and is now collaborating with ACRIA ((AIDS Community Research Initiative of America) in an Across the Borders effort to train staff in long term care facilities about the needs and fears of the older adult with HIV.

In the last plenary, on HIV and Aging, Canadian researcher David J. Brennan, PhD reported on studies of factors associated with mental health resiliency among older adults living with HIV as well as protective and risk factors associated with HIV. The effects of stigma, gender, ethnicity and certain socio-demographics were predictors of resiliency.

Brain Health

New data and perspectives were presented as part of the plenary "HIV, HAND and Brain Health." Robert K. Heaton, PhD, Professor of Psychiatry, and Scott Letendre, MD, Professor of Medicine, both at UCSD, detailed the neruocognitive findings associated with the varied penetrations of the CNS by a spectrum of anti-retro virals. Data showed the "Effectiveness Rank" of ARTs and a detailed path for the management of HAND was provided. Canadian Sean Rourke, PhD, covered his data and the efforts underway to establish an OHTN Center on NeuroAIDS.

A leader on the issue of cognitive function and HIV, Geriatrician Victor Valcour, M.D., Geriatric Medicine and Neurology, UCSD, reported on his cohort (n=100) of older adults age 60-82 (most are 60-65) who have been living with HIV for two to three decades. Half show Neruocognitive disorders with 5 percent of those having HAD (HIV-associated dementia, n=3). Of those with neurocognitve impairment about 42 percent had Asymptomatic Neruocognitive Impairment (ANI) and 50 percent had MND (Mild Neruocognitive Disorder). He believes there is no difference between the two groups (MND vs. ANI). He thought the ANI group was less aware of their real functional status.

Consequently, Valcour said he did not

see any progression from one group to another and that in using measures of cognitive function and day-to-day functionality tests there were no differences between these two groups. He also showed preliminary evidence of structural and connectively changes in the CNS using diffusion tensor imaging scans as well as brain size measurements when comparing HIV+ individuals to HIV- controls.

These changes in morphology were not correlated with cognitive deficit measures. His data shows that the duration of HIV infection is not a predictor of cognitive impairment. This may be in part due to survival bias. The CD4 nadir as well as a diagnosis of diabetes are predictors as well as APOe4 genotype measures and the Monocyte Effectiveness (ME) score. Non-predictors were CNS penetration by ARTs (CPE scores), age and duration of infection, VL and CD4 lymphocyte counts. Dr. Valcour speculated that the cognitive deficits seen may find their etiology in cerebrovascular changes or the HIV associated inflammatory response. Emerging risk factors are glucoregulatory disorders, APOe4, and the inability of ARTs to treat sequestered reservoirs of HIV in Monocytes which can carry the virus into the brain.

Living Longer = Living Well? Aging with HIV

The last Plenary was entitled "Living Longer = Living Well? Aging with HIV." It was moderated by two local participants who have been living with HIV for over two decades.

Lisa Power reminded the group "HIV systematically disadvantages you across a lifetime."

Stephen Kapriak PhD, Associate Director for Research at ACRIA and a faculty member at New York University College of Nursing, provided an overview of the older adult epidemiology in North America, as well as Africa, where there are now 3 million people over age 50 living with HIV. The CDC predicts that half the US HIV population will be age 50 and older by 2015.

Karpiak described how people at a young age (50-65) aging with HIV face unexpected non-AIDS associated complications from the development of illnesses typically associated with the very old (including cardiovascular disease, cancer, renal disease, arthritis and osteoporosis).

He detailed the increasing incidence of multimorbidity in this population and described how the AAHIVM, ACRIA and the AGS's two-year project provided guides for clinicians. That detailed report embraces the need to use established geriatric care elements in order to optimize the health of these older adults.

ACRIA's research on service utilization in New York and Chicago underline the needs of this older population and the growing toxicity of stigma driven social isolation, which is reflected in high rates of unmanaged depression. Depression, vestiges of substance use and fragile social networks (70 percent live alone) contribute to poor health outcomes in part driven by poor medication adherence. Dr. Karpiak emphasized how the research data generated by ACRIA (especially ACRIA's large seminal comprehensive research study, "ROAH: Research on Older Adults with HIV," was a voice of the often invisible and marginalized older adult with HIV.

Bone Fractures

Michael Yin, Assistant Professor of Clinical Medicine in the Division of Infectious Diseases, Columbia University Medical Center, New York, showed the increases in fractures that were occurring in the older adult HIV populations as a result of osteoporosis. Data show decreases in bone density occur after ART initiation in the first six months followed by a gradual improvement to baseline that remains stable. Losses in bone density were not different in both males and females who were HIV+ when compared to controls.

The overall data show increased fracture rates occurring in the older adult HIV+ populations when compared to controls. This is particularly evident in post-menopausal women. Cohort data suggests that HIV infection contributes to this as well as risk factors such as HepC, smoking, being postmenopausal as well as other medications used to manage multiple comorbid illnesses. Treatment approaches were discussed by Dr. Yin who stated there was a need to personalize treatments for this population as demands on resource allocation increases.

HIV systematically disadvantages you across a lifetime

Lisa Power, policy director at the UK's Terence Higgins Trust (THT), showed how they use research data to shape their direct service programs, noting that the over-50 HIV community is the fastest growing segment in the UK.

Their online research survey data shows that economic constraints are causing the older adult with HIV, who never expected to live as long, to worry about their future as they face increased financial insecurity, unmanaged mental health issues and stigma driven barriers to accessing health care providers. Their data show that half have mobility and self-care problems. The older adults with HIV finds themselves socially isolated, living with unmanaged depression, and increasingly facing discrimination due to their HIV status, age and sexual identify. These factors cause them to be fearful of engaging social services in their communities as well as medical providers who are needed to address their comorbidities.

THT has begun programs to educate those who provide health and social services of the need to be welcoming and non-judgmental. Their research showed that the older adult HIV populations fear not having a voice. With establishment of an HIV over 50 online community, THT helped to give them a voice. The THT research also found high levels of financial difficulties, as well as mental health and depression issues that persist together with social isolation. Survey respondents expressed fear of AIDS stigma, homophobia and ageism when engaging mainstream social service entities and heath specialists. The online community provides resources that empower the older adult, as well as the support of peers (www.tht.org.uk/50plus). The site hopes to build viable social networks, promote employment efforts, money skills and welfare advice, as well as the need to adjust lifestyle to blunt the occurrence of comorbidities. These THT efforts reflect the need for the patient to become more involved in their health management as detailed in the AAHIVM Consensus report. HIV

ABOUT THE AUTHOR: **Stephen E Kapriak PhD**, is with ACRIA (AIDS Community Research Initative of America and New York University College of Medicine.

CAU in MID

Will President Obama's re-election mean better health care and support for providers?

The elections of 2012 meant both everything and nothing. Long months and millions of dollars left much as it had been before. The re-election of President Obama, and the retention a Democratic majority in the Senate and a Republican majority in the House added up to a very firm maintenance of the status quo on election day.

All of this points to a continuation of current polices and initiatives by the federal government, and a likely continuation of the all the political dynamics that have been seen for the last four years. The same tensions, roadblocks, and standoffs will no doubt carry on.

What Could Have Been

If Mitt Romney had attained the presidency, he vowed a repeal, replacement, or slow and steady gutting of the Affordable Care Act (ACA). He talked about block-granting of Medicaid and overhauling Medicare's design in some form. After Inauguration Day, Romney promised, implementation of ACA would come to a crashing halt.

For many in health care industry and policy, the biggest concern following the election was the fear of being left with an enormous mess because of all of the work that has been underway as federal regulators and state lawmakers have already begun implementation. The architecture for ACA program changes has been built in many states and has been drawn up in others. Grants have gone out, billions of dollars have already been spent, and two years of planning and implementation have taken place.

Insurance companies, hospitals, and physician groups, too, have begun work to comply with and prepare for ACA. Hospitals are working on bundled payments, meaningful use, and becoming accountable care organizations. Halting all of the wheels that are turning would have created chaos.

Across the country, Medicare beneficiaries have begun to see drug rebates. Previously uninsured young adults have been added to their parent's insurance policies. Previously uninsured HIV patients have attained coverage through the Pre-Existing Insurance Plans. Had Romney realized his goal, these benefits would likely have been halted.

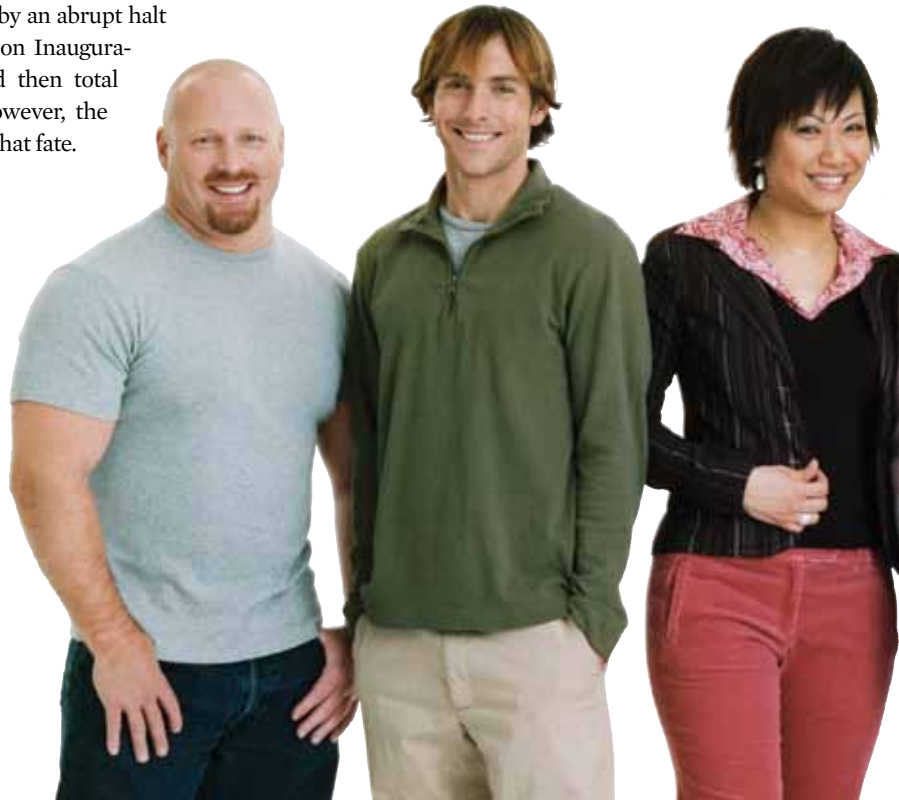
Future of The ACA Law

The President's re-election made secure his signature legislative achievement, the ACA. At least in the short term, full throated attempts to overturn the ACA have probably been silenced as enough stayed the same in Congress to make it clear that the ACA will not be repealed. Similar attempts to gut the law through the budget reconciliation process would have required 51 Republican votes in the Senate, which the party did not acquire.

So, for now, continuing challenges to the law will be limited to funding battles—that is, until after the law is fully implemented, when opponents will gain a new platform for battle – Congressional oversight.

Challenges to the law in court were also put to rest when the Supreme Court this past summer upheld the constitutionality of the biggest parts of the law. The law's legitimacy was confirmed, even though one significant aspect of it was struck down – mandatory implementation of the Medicaid expansion. Nevertheless, for the next few years, the course of the law is set. Implementation will proceed, and likely at a rapid pace.

The fact that Obama administration officials will continue to be in charge during the law's full implementation creates assurance of a more orderly rollout process. A change in the White House would have undoubtedly resulted in a crisis of swift efforts to implement as much of the law as possible during the winter, followed by an abrupt halt to all efforts on Inauguration day, and then total upheaval. However, the law escaped that fate.



BY HOLLY A. KILNESS, MA

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The outcome of the budget battle will have a lot to say about that.

ACA Implementation

In the months prior to the election, the Administration went virtually silent in terms of regulations and other communications regarding the ACA and other policy initiatives. It is common practice for an Administration to hold off on an announcement of anything that might cause controversy close to an election. Even Health and Human Services (HHS) Secretary Kathleen Sebelius held fewer news conferences on the law as the election drew near.

These regulations define precisely how the details of the ACA language will work in practice, providing detailed instructions for insurance companies, hospitals and states on how to put the law into practice. Some of these regulations will impact areas such as compliance, increased transparency disclosures, Meaningful Use compliance, and what health services and expenses insurers will be required to cover under the law, and more.

But the seeming inactivity masked the vast amount of work that has been going on behind the scenes — both at HHS and at the state level. As soon as the election was decided, the gears and levers of government bureaucracy started moving at full speed again, and some of the anticipated regulations have already been released. The backlog should be resolved soon as the government gears up for 2014 implementation of the law's biggest policies.

The President wants the law put in place as quickly as possible, but he is not the only one.

The insurance industry wants details on the requirements pertaining to coverage and related policies. The health industry will be required to comply with the law starting in only a few months, and certainly needs to know the details of what must be done.

These types of regulations also pose a challenge for groups like HIV advocates. Many of these rules are incredibly complex in nature, and their impact on specific populations is not easy to discern.

State lawmakers, too, claim they will soon need further direction from the feds on how they are to set up various tenants of the law, including those governing the health insurance exchanges, the individual mandate and the exact parameters for expanding Medicaid in light of the Supreme Court decision.

The States

President Obama's win may have secured the fate of the health law, but the states still control its future. States have considerable sway over how the ACA is carried out, particularly with respect to Medicaid expansion and the insurance exchanges.

Next year, 30 states will be led by Republican governors, and the GOP will control 24 state legislatures, while Democrats will control 18. The rest of the states have split or tied legislatures. These legislatures and governors will decide whether millions of uninsured people get coverage through Medicaid beginning in 2014, as the law envisions. They'll also decide whether to set up exchanges, the online markets where individuals who lack health insurance can shop for coverage, or whether to allow the federal government to set up these markets for them.

Since the Supreme Court's decision, Republican governors in Texas, Florida, Mississippi, South Carolina, Louisiana and Georgia have said they will not participate in the Medicaid expansion at all. However, not all of these governors have the support of the legislature behind them in these decisions.

In Florida, for example, one of the longest serving state lawmakers, Republican Mike Fasano, has

THINKSTOCK

publicly remarked that the state can't afford to miss out on new revenue without having its own plan to help more than 4 million residents who lack health insurance. Fasano went on to say that the GOP-dominated state legislature would "take a hard look" at expanding Medicaid -- despite the opposition of Gov. Rick Scott.

Some analysts believe that eventually, all states will take up the Medicaid expansion, even if not all do so by 2014. The federal government's coverage of 100 percent of the costs of new enrollees through 2016, and at least 90 percent thereafter, is a powerful incentive for states to accept the expansion despite ideological protestations.

State lawmakers also face decisions on whether to set up state-run health insurance marketplaces to regulate individual and small business health plans, or allow the federal government to run them instead. By mid-November, each state was supposed to declare to HHS which of the three Health Insurance Exchange (HIX) models would be used within the state. Most states are planning state-federal partnership exchanges, while 10-15 states are considering purely state-certified exchanges. One or two states may opt for a federally-facilitated exchange model, where the state exchange will be operated by the federal government for an initial time period.

However, some states say they still need more information from HHS before they can make these determinations, which brings the focus back to the regulations that need to be published by HHS.

The Fiscal Cliff

Outside the doors of HHS, political attention shifted to the dramatically-named "fiscal cliff," a combination of several significant economic and budgetary policies all scheduled to come to a head simultaneously. Among these, the expiration of the Bush tax cuts, the scheduled sequestration cuts to all federal spending, the sustainable growth rate, and the federal credit limit, have been projected to create a possible confluence of events that could significantly impact the American economy, American government and the households of American citizens starting early in 2013.

The stakes of these economic considerations are so high that they cloud other issues; yet health care spending, entitlement programs, and the ACA all are included in that conversation. A "grand bargain" on all of the considerations is being called for, but as this is written in early December, appears difficult to reach. The President and Congress must find ways to approach federal spending and fund a wide variety of programs. Medicare and Medicaid both represent substantial bargaining chips in the debate.

…This raises questions about the medical workforce capacity and whether there will be enough providers. Provider network adequacy could be a significant problem, worsened by the inadequacy of Medicaid payment rates.

Unless Congress and the President can reach agreement prior to the end of this year, roughly $1 trillion of cuts are set to go into effect January 1, 2013. One of these cuts is a scheduled reduction to Medicare physician payment of approximately 2 percent for all Medicare payments.

The fiscal cliff debate will hopefully be resolved by the lame-duck Congress before the end of the year. But depending on what it entails, Congress may still face a budget battle when the current continuing resolution expires in March of next year.

Far from a victory lap or clear path to ACA implementation, it is likely that the President will be mired in budget battles much of 2013.

Long Term

Looking beyond the immediate situation, the implementation of the ACA will bring an influx of previously uninsured patients into the health care system starting in 2014. Eleven million people are projected to become eligible for Medicaid, even with expansion becoming a state option. Additional millions of previously uninsured people will obtain coverage though the exchanges.

For health advocates this raises questions about the medical workforce capacity and whether there will be enough providers. Provider network adequacy could be a significant problem, worsened by the inadequacy of Medicaid payment rates. Many doctors currently do not participate in Medicaid or greatly restrict the number of Medicaid patients they treat.

The ACA included an effort to reinvigorate participation in Medicaid via temporary pay increases for certain primary care doctors. But this fails to address the issue of whether the newly covered will have access to high quality care. A significant problem for HIV infected Medicaid enrollees is inadequate access to specialists.

America's physicians should remain at the forefront of policy discussions, as a vital component of both the delivery of health care and the health of our nation. Physician payment systems will need to be addressed long-term as both a component of providing well-coordinated, efficient, high-quality patient care and reducing health care costs. These systems will also encourage or discourage the provider workforce overall. HIV

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BY GLEN PIETRANDONI, RPH, AAHIVP

An Integrated Approach to Patient Care

I have been a pharmacist since the late 1970s and was behind the counter at the beginning of the HIV/AIDS epidemic. I have seen the progress that has been made over these years in terms of therapy and treatment. It has been a remarkable journey.

In the beginning, we could not really do a lot for our patients except to provide emotional support and suffer with them. We dispensed medicines that were prescribed without fully understanding the complications that would result, and we hoped and we prayed. Today, however, the drugs that we dispense are, indeed, helping to save lives.

But this article is not intended to reminisce about what has been. Rather, I want to draw upon my pharmacy experience and more than 30 years of working in the HIV/AIDS community to encourage providers to take advantage of the resources that we, as pharmacists, can provide as trusted members of your team.

As our profession changes and increasing numbers of HIV specialists retire, it is a fact that many practitioners, with perhaps less experience than their predecessors, are being asked to treat HIV patients. As pharmacists trained in HIV therapy, we can help ensure prescription accuracy so that adverse drug interactions are avoided and that patients receive the therapy that they need.

Working collaboratively with providers every day, we do even more. As a practicing pharmacy in a community setting we are dealing with many issues, including drug combinations and their side effects, insurance and coverage issues, and even personal and employment concerns of our patients. It is an integrated approach that is geared to removing obstacles that can prevent adherence.

At Walgreens, more than 2,000 pharmacists receive 25 additional hours of HIV training a year through a program we developed with the University of Buffalo. Now, that program is being enhanced through a partnership with AAHIVM and the AIDS Education and Training Center. It will be a 25 hour course that will cover all aspects of HIV prevention, treatment, testing, as well as hepatitis C and other co-infections. We are investing in our pharmacists so they can keep abreast of all of the changes that will be coming, and there will be many changes, indeed.

Efforts are under way to develop effective HIV prevention vaccines. If one should become available in the future, Walgreens pharmacists can help deliver that preventative care, just like we do now with other vaccines and immunizations.

About three years ago we established our HIV Centers of Excellence in more than 700 HIV-specialized pharmacies to neighborhood drug stores, community specialty pharmacies, health systems and clinics across the country. Pharmacists at these locations deliver patient-focused care and are accessible to nearly 90 percent of the U.S. HIV population.

These stores provide enhanced services, including specially trained pharmacists whose care is focused on HIV/AIDS, a pharmacy fully stocked with HIV medications, and an integrated care approach to promote HIV prevention and medication adherence.

At each center, we provide our pharmacists with education on cultural competency and sensitivity; we aim to create a safe environment for people living with HIV, and help guide those who want to know how to stay HIV negative. We want to be an important part of the solution, and are investing in these stores, in professionals to staff them and in the necessary inventory. We want to be a community destination for those living with HIV. In addition, we address HIV awareness, prevention, testing and treatment in communities impacted by HIV.

Our pharmacists and HIV-specialized pharmacies are valuable resources and we strive to make a difference in people's lives each day. Working with providers as part of your team, I believe we can help our patients achieve better health outcomes. HIV

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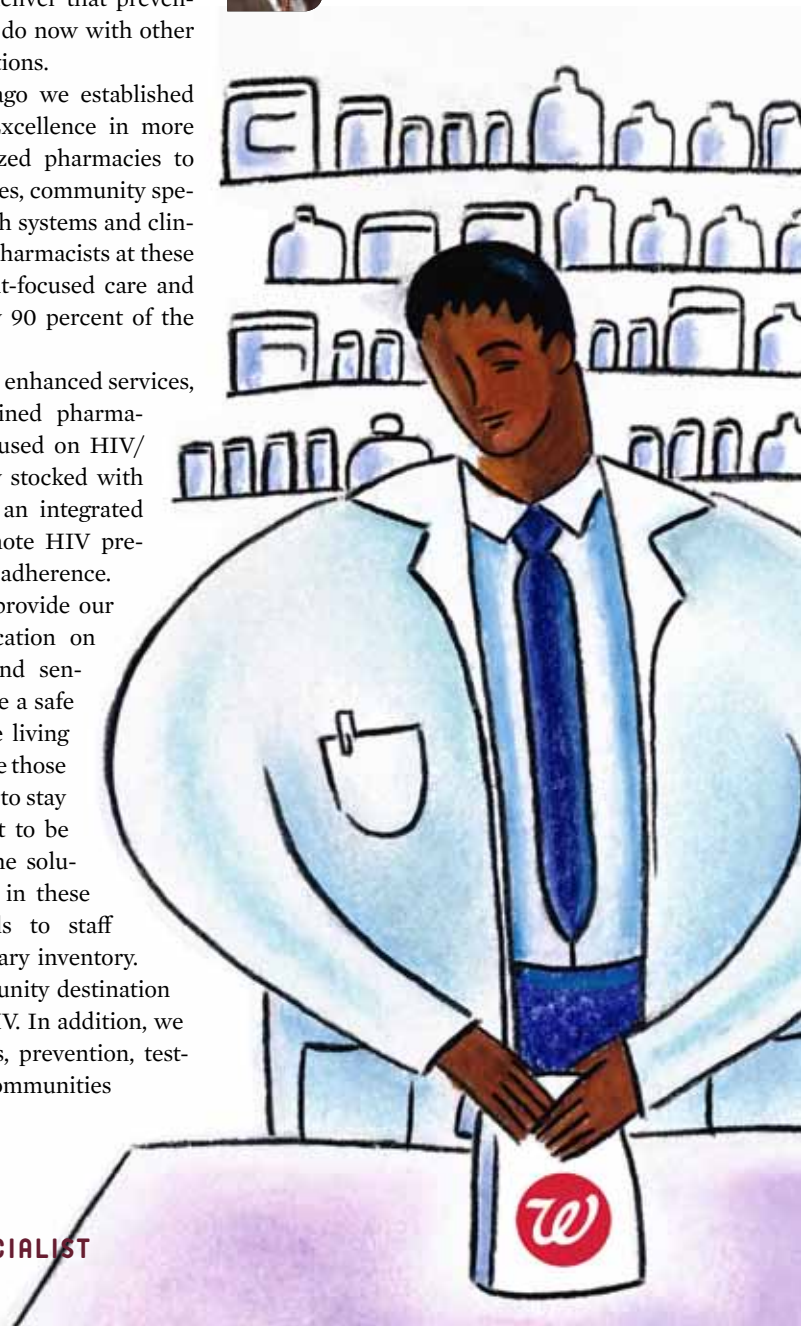


THINKSTOCK, BONOTOM STUDIO

BY JEFFREY T. SCHOUTEN, JD, MD, AAHIVE

What's Next for PrEP

EVEN THOUGH the Food and Drug Administration (FDA) has approved the use of daily Truvada for pre-exposure prophylaxis (PrEP) of HIV infection in men and women, there remain many implementation and research questions.

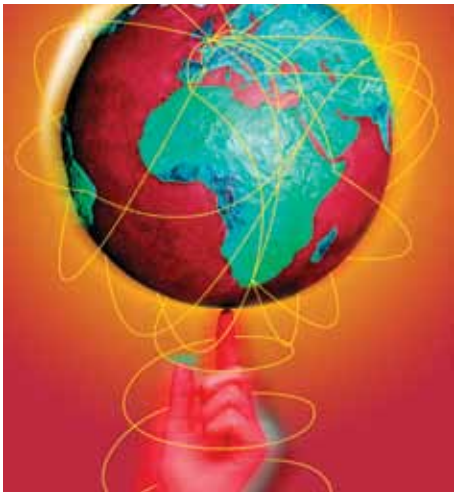
On the implementation front, the Centers for Disease Control and Prevention (CDC) has issued draft guidance on the use of Truvada for PrEP, but we are awaiting their final guidance.

Studies of awareness of PrEP in communities most at risk in general have shown a low level of awareness, but an interest when the concept is explained. Additionally, the people who have expressed early interest in PrEP are those in serodiscordant relationships. If their partner is on a successful antiretroviral regimen (ART) and has suppressed HIV plasma viremia, their risk in transmitting HIV may already be reduced by as much as 96 percent, as demonstrated in the HPTN 052 study. This raises a question about the cost effectiveness of PrEP in a subset of people who may be at low risk of HIV acquisition.

Surveys of general internists and family practitioners have indicated that they have a preference for experienced HIV providers to prescribe PrEP and follow patients. But many HIV negative at-risk people may not want to go to a clinic that is primarily identified as an HIV care clinic and HIV providers are already over extended.

Few public payers have stepped forward to offer coverage for PrEP, nor have public health departments. It is still to be seen which plans under the Affordable Care Act will offer PrEP as part of their prevention package. So both the distribution and funding systems have yet to be set in place for widespread availability of PrEP. Concerns also remain about the cost of monitoring for side effects, including renal function and bone density.

On the research front there remain many important questions about PrEP. In part due to the concerns about the need for high adherence to maximize the preventative effects of Truvada, other agents and dosing



schedules are being evaluated.

Results are expected soon from the VOICE study, conducted by the Microbicide Trials Network (MTN), of the effectiveness of daily Truvada in women in Africa. (The tenofovir vaginal gel and oral tenofovir arms of the VOICE study were closed early due to lack of efficacy.) Another study that should be reporting results soon is the CDC study of daily tenofovir for PrEP in 2,400 injection drug users in Thailand.

The HIV Prevention Trials Network (HPTN) is conducting the ADAPT Trial (HPTN 067) comparing the following three dosing schedules of Truvada:

> *Daily dosing, time-driven dosing, and event-driven dosing. The time-driven dosing group will be asked to take Truvada twice weekly with a post-exposure boost. The event-driven dosing group will be asked to take Truvada before and after a potential exposure to HIV infection. In all three dosing groups, dosing will not exceed two doses per day or seven doses per week.*

A study jointly conducted by the HPTN and the AIDS Clinical Trials Group (ACTG) is evaluating daily oral maraviroc (MVC) in various combinations with tenofovir (TDF) and emtricitabine (FTC) (NEXT-PREP/HPTN 069/A5305). This is a safety and tolerability study enrolling 400 MSM and soon to add 200 women with the following dosing schedules:

Arm 1: MVC 300 mg + [FTC placebo] + [TDF placebo] orally once daily.

Arm 2: MVC 300 mg + FTC 200 mg + [TDF placebo] orally once daily.

Arm 3: MVC 300 mg + [FTC placebo] + TDF 300 mg orally once daily.

Arm 4: [MVC placebo] + FTC 200 mg + TDF 300 mg orally once daily.

Also ongoing are other topical PrEP studies, including a Phase 2 study of rectal tenofovir gel compared to oral Truvada (MTN 017), a confirmatory study of the effectiveness of coitally-dosed tenofovir gel in South Africa (FACTS trial), and a study of the efficacy of a dapivirine vaginal ring needing replacement only every 28 days (ASPIRE/MTN 020).

Over the next months to years much more clarity will be obtained both on the implementation of daily Truvada for PrEP as well as other dosing options, agents and routes of administration to hopefully realize a significant public health impact of PrEP. HIV

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THINKSTOCK

Feds Recommend Routine HIV Testing

ON NOVEMBER 20, the U.S. Preventive Services Task Force (USPSTF) issued a draft recommendation in support of routine HIV testing for adults and adolescents ages 15 through 65. AAHIVM believes this represents a huge step forward in HIV testing and prevention efforts in the United States.

The USPSTF is an independent panel of experts charged with making evidence-based recommendations to the government regarding clinical preventive services.

These recommendations take the form of grades assigned to a service, along with practice suggestions. The grade of "A" indicates that the USPSTF highly recommends the service as having a substantial net benefit to the patient, and advise practitioners to provide this service.

In this decision, the USPSTF recommended that routine HIV screening for all adolescents and adults ages 15 through 65 now be given a grade of "A"; a significant change from the former "C" grade. Previously, the USPSTF had only recommended HIV Testing for people who are at risk for HIV and pregnant women as a grade "A".

"This decision represents a huge stride forward in efforts to identify HIV infected patients early, and to get them into care and treatment," said James M. Friedman, Executive Director of AAHIVM. "Furthermore, the more routine HIV testing becomes, the more we can help prevent the spread of the disease to others."

"The grade change will play a significant role in coverage of and reimbursement for HIV testing services. USPSTF grades form the basis for coverage of preventative services by government insurers, like Medicare and Medicaid." said Dr. Donna Sweet, Chair of the AAHIVM Board of Directors. "In addition, the Affordable Care Act (ACA) mandates that private insurers must cover all services given a Grade A or B by the USPSTF without cost-sharing. This is a huge victory in the fight against this disease."

The USPSTF is supported by the Agency for Healthcare Research and Quality (AHRQ), an agency of the U.S. Department of Health and Human Services (HHS). The draft recommendation was open for a 30-day public comment period, after which a final determination will be issued.

The USPSTF also proposed testing for adolescents under 15 and adults over 65 who are at increased risk of HIV and reaffirmed its "A" grade for routine testing of pregnant women.

"HIV care providers across the United States join the AAHIVM in showing their support of this decision," noted Friedman. "We also encourage all provider types to make HIV screening routine for all of their patients, in accordance with this decision."

The AAHIVM offers materials and programs to assist providers in implementing routine screening in their practices:

- Together with the CDC, the Academy developed Referral Link, an online provider referral network available on our homepage at www.aahivm.org. Referral Link offers access to AAHIVM-certified HIV Specialists and HIV care providers around the country.
- Visit our online Clinical Topics Library for more educational materials on routine testing, linkage to care, and reimbursement for testing, as well as other clinical information on testing.
- To download the CDC fact sheet on routine testing, please visit: http://www.uspreventiveservicestaskforce.org/uspstf13/hiv/hivfact.pdf

HIV

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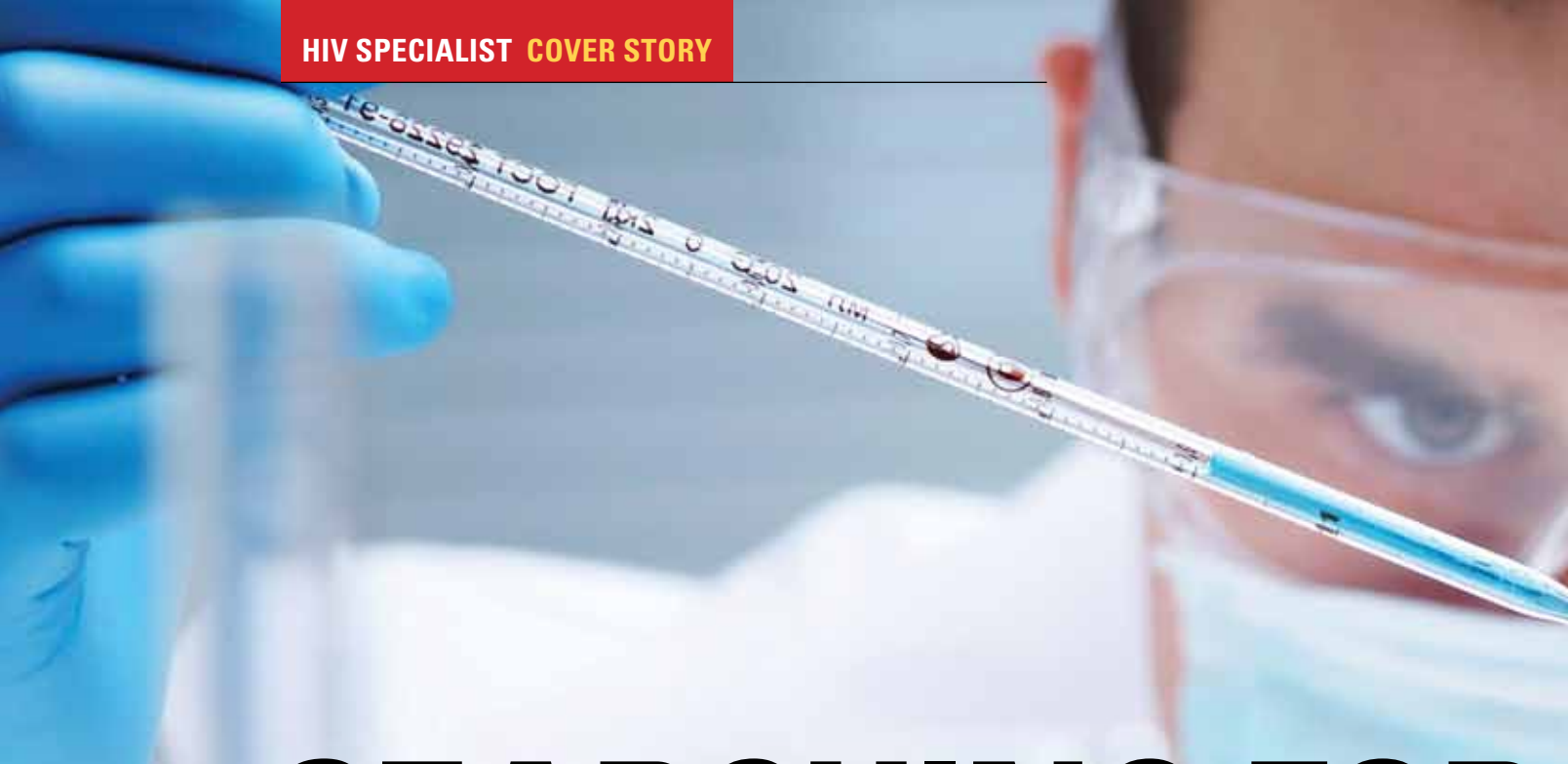

SEARCHING FOR

REMARKABLE PROGRESS HAS BEEN MADE IN TREATING HIV INFECTION as current therapies allow infected individuals to attain near normal lifespans and have dramatically decreased mortality for HIV-1-infected patients. However, antiretroviral therapy (ART) has not cured the disease, and because of the persistence of latent HIV, patients must remain on this costly therapy indefinitely. Moreover, because ART is not readily available in many developing countries, HIV continues to be a major driver of morbidity and mortality worldwide, as well as a significant economic drain.

A persistent viral reservoir in the T cells of HIV-infected patients receiving potent ART is a significant barrier preventing eradication of HIV infection. Because the solution to the HIV pandemic rests on the prevention of new infections, many novel approaches to develop treatments for latent HIV infection are underway. The goal: either complete eradication or induction of a state of stringent control over viral replication without ART.

The challenges are many. For an eradication therapy to be effective and feasible for worldwide use, it must:

- be safe and have manageable side effects;
- not extensively activate the immune system, as activated T cells are more susceptible to HIV infection and are more difficult to protect with ART;
- have a finite duration that will allow the patient to live a healthy life without ongoing treatment;
- be able to access all reservoirs of persistent infection throughout the body;
- be economically and logistically accessible to the developing world.

Despite the demanding task, much progress is being made, in some cases utilizing drugs already pharmacologically characterized and approved for use in humans for treatment of other diseases. This, of course, gives them an advantage over newer approaches because the time from initial testing to implementation is drastically reduced. In addition, researchers are considering many novel approaches that ultimately may prove invaluable in our pursuit of a cure.

The goal of eradication is clearance of all replication-competent virus from the patient, so purging HIV provirus from latent reservoirs is crucial. Important efforts are underway to identify therapeutics that can do so. Current ART does not eradicate HIV infection, as latently infected cells remain persistently infected and unrecognized by the immune system, with minimal expression of HIV genes or proteins.

Most eradication studies have focused on identifying small molecule drugs that elicit proviral expression with the notion that ART will prevent new infections, while the immune system, possibly with the help of other therapeutics, will clear infected cells. Several small molecule drugs de-

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BY DAVID M. MARGOLIS, MD

A CURE

Researchers seek safe and effective approaches to treating and eradicating HIV

veloped for the treatment of HIV latency are in clinical trials. In addition, other options for eradication include gene therapy approaches such as HIV-specific recombinases that destroy proviral DNA or HIV-dependent suicide genes that selectively kill HIV infected cells.

Once replication-competent viral DNA is integrated into the host genome, it can become quiescent and durably suppressed. The goal of induction and clearance strategies, also known as "kick and kill", is to induce transcription of these quiescent, replication-competent HIV proviruses (the "kick"), making them susceptible to immune clearance and the effects of ART (the "kill"). Several compounds that activate transcription of HIV through a variety of mechanisms are currently being studied.

HDAC Inhibitors

Histone deacetylase inhibitors (HDACis) were identified as potential anti-latency drugs following the discovery that their target HDACs were specifically recruited to the HIV promoter and maintained latency.[3,4] HDACi were identified in several screens for compounds that induce transcription from quiescent HIV proviruses.5

Vorinostat (VOR or suberoylanilide hydroxamic acid, SAHA) and valproic acid (VPA) are HDACis that activate HIV transcription in both cell line models of latent HIV and in ex vivo cultured patient cells. Both drugs are currently approved for clinical use; VOR for oncology and VPA for a variety of indications, and many of their pharmacological characteristics are known. HIV-centered clinical trials have been conducted for VPA, and two such clinical trials are ongoing for VOR.[6,7]

Recent work suggests that alternative HDACi, such as VOR, can induce expression from the HIV promoter at lower concentrations than VPA.[9] Initial results are promising.

In a trial being conducted by our group, HIV-positive patients were given a 400 mg dose of VOR and resting CD4+ T cells were isolated to measure viral RNA production and global histone H3 acetylation to determine whether VOR is able to upregulate viral transcription. All patients have demonstrated increased viral RNA production and histone H3 acetylation, indicating that HIV latency was disrupted following a single 400 mg dose of VOR (clinical trial NCT01319383).

Another study is underway at Monash University in Melbourne to assess a multi-dose regimen of VOR administered as 400 mg of VOR daily for 14 days.[10] If the results verify the ability of VOR to activate quiescent HIV in patients, the next step will be to determine if this affects the viral reservoir.

Several additional HDACis that activate transcription of quiescent proviruses including Belinostat, Panobinostat, Givinostat, and Entinostat are in phase II clinical trials for treatment of cancers or juvenile arthritis.[9,11] The trial that administered daily Givinostat included children ranging from six to 17 years of age with only minor adverse events.[12] Therefore, Givinostat could potentially be used to treat youth.

Givinostat and VOR also have been demonstrated to transiently reduce expression of a subset of cytokines at a clinically relevant dose in ex vivo studies.[13,14] Because cytokine production may activate the immune system, making

cells susceptible to HIV infection, suppression of cytokine production may prevent infection of additional cells upon reactivation. Depending upon the safety of these drugs and their pharmacological suitability, they may also be tested in future clinical trials addressing HIV latency.

It is important to note that the most desirable qualities of the ideal HDACi for clinical application in HIV remains to be defined. Such a drug must be clinically well tolerated. Current evidence suggests that inhibitors selective for the Class I HDACs 1, 2, and 3 are the most relevant.[4,15]

Although it is widely assumed a more potent HDAC inhibitor will have a better clinical effect, this is unproven as the optimal duration and schedule is unknown for dosing required to achieve sufficient HIV induction without impairing the immune response or inducing toxicity.

Dilsulfiram

Disulfiram is a zinc-chelating agent with manageable toxicities that has been approved for use in humans to treat alcoholism. Dilsulfiram and its metabolite diethyldithiocarbamate (DDTC) were recently demonstrated to activate HIV transcription from a primary cell model of latent HIV.[16]

A study by Doyon and colleagues suggests disulfiram causes depletion of Phosphatase and tensin homolog (PTEN), an inhibitor of the Akt pathway. Once inhibition of Akt is removed, it phosphorylates HEXIM1 releasing p-TEFb, which is then recruited to the HIV promoter where it can activate transcription. Dilsulfiram-mediated activation of quiescent HIV proviruses was blocked by an inhibitor of the Akt pathway, which indicates disulfiram may modulate HIV expression through its effects on PTEN and the Akt pathway.[17]

A clinical trial (NCT01286259) is underway to determine disulfiram's effect on persistent HIV infection. The pilot study enrolled 14 participants who took 500 mg daily for 14 days. Initial results revealed a modest, but statistically significant, increase in plasma HIV RNA. It is unclear if disulfiram can contribute to clinically significant reductions in the viral reservoir.

PD-1 inhibition

PD-1, a receptor known for its role in immune exhaustion, is the focus of several studies. PD-1 antibodies are being investigated for their ability to activate HIV transcription and/or reverse immune exhaustion caused by HIV infection, while specifically targeting HIV infected cells. To date, a single abstract has been presented, suggesting exposure to PD-1 antibodies induces expression of HIV. However, the relevance and validity of this observation was weakened because cells studied were obtained from viremic patients.[19] A clinical trial to determine the effect of PD-1 antibodies on persistent infection in ART-treated patients is being delayed by unanswered safety concerns arising from toxicities observed in oncology trials.

Vaccination

Several studies have reported increases in viral expression following routine vaccination against other pathogens in HIV-infected individuals, which may be attributable to mild activation of the immune system.[20] However, the increased viral loads and T cell activation after immunization were not associated with better viral control when ART was interrupted[20], indicating that this therapy may need to be performed in the context of ART or other therapeutics. In a provocative study, Persaud and colleagues immunized patients with a poxvirus vaccine engineered to express HIV antigens and observed a significant, albeit transient, decrease in replication-competent HIV in the resting T cell reservoir.[21]

These results suggest such approaches might activate latent virus and/or induce an immune response to low-level antigen production in some cells, thereby resulting in a decline of the number of latently infected T cells. Such vaccines have been studied and well tolerated in HIV infected patients, and so this strategy has potential for use in treating latent HIV.[22]

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While HDACis are the most promising candidates for the "kick and kill" approach, many other cellular pathways are involved in the maintenance of latent HIV, and compounds targeting these pathways may enter clinical trials in the near future.

Other potential targets

While HDACis are the most promising candidates for the "kick and kill" approach, many other cellular pathways are involved in the maintenance of latent HIV, and compounds targeting these pathways may enter clinical trials in the near future.

For example, activation of the protein kinase C (PKC) and NF-κB pathways induces expression of quiescent HIV proviruses. Drugs targeting these pathways, such as tumor necrosis factor-alpha (TNF-α), prostratin, and bryostatin are currently under study for treatment of latent HIV infection.[23-25]

Prostratin activates HIV transcription in several J-lat cell line models of HIV latency.[24] In combination with the HDACis VPA and VOR, prostratin synergistically increases the amount of virus produced from cell line models of HIV latency.[26]

Bryostatin, a macrocyclic lactone, like prostratin, targets the PKC and NF-κB pathways. In addition to modulating the PKC and NF-κB pathways, bryo-1 also downregulates the CD4 receptor on T cells, which limits the ability of HIV to infect these cells.[25] Bryostatin does not activate T-cells and has low cytotoxicity.[27]

Bryostatin has entered a phase II clinical trial for treatment of ovarian cancer,[28] but, despite a partial response of some patients, severe myalgia developed in all study participants.[28] Thus, while studies to advance bryostatin for future treatment of latent HIV are planned, testing must be cautious.

Removal of proviral DNA

The most straightforward solution to eliminating latent reservoirs is simply to remove integrated HIV genomes from infected cells. However, the technological hurdles are enormous.

This would require vectors that identify and act on a specific DNA sequence within the billions of bases of DNA in a cell, where the targets lie predominantly within resting cells that are difficult to transduce, and within less than 0.00001% of the total cell population in all host tissues. This would have to be achieved with exquisite specificity to avoid damaging DNA host sequences.

Toward this goal, HIV-specific recombinase enzymes have been evolved to recognize sequences within the HIV LTRs and to remove the intervening HIV DNA[37], resulting in cells that no longer harbor a functional HIV genome. This should result in a depletion of the patient's viral reservoir following treatment.

While still an evolving technology, encouraging results have been obtained and additional studies performed to improve the therapy and discover more efficient ways to introduce the enzyme into cells.[38] However, this technology presently can benefit only infected cells specifically isolated and purged of proviral genomes; thus, many infected cells will remain in the peripheral blood and other reservoirs.

Elimination of cells expressing HIV proteins

Therapeutics designed to purge latent reservoirs may have varying effectiveness between cells or cell types. The result may be full activation of latent, replication-competent provirus in some cells and minimal activation in others.

Infectious viral particles capable of infecting bystander cells will be produced, increasing the risk of de novo infection events, or infected cells may escape detection by the immune system and return to latency.

The use of HIV-dependent suicide genes addresses both of these problems. Anti-HIV suicide gene constructs encode a toxic or pro-apoptotic protein whose expression is controlled by the HIV LTR, which means the toxin should only be expressed when HIV Tat is expressed. However, early suicide gene constructs either suffered from nonspecific killing of uninfected cells due to basal transcription off of the HIV promoter or conversely failed to kill infected cells rapidly or efficiently enough due to suboptimal suicide gene construction.[39]

Recent constructs have been improved through inclusion of elements that make expression dependent not only on HIV Tat (HIV LTR), but also upon Rev (Rev Response Element [RRE], HIV inhibitory sequences [INS] which increases specificity, while efficacy has been improved through inclusion of more potent pro-apoptotic genes.[39]

However, because expression of the suicide gene and subsequent cell death requires some level of Tat and Rev expression, this approach alone will be ineffective at purging latent provirus. In combination with anti-latency therapeutics, such as the small molecule drugs discussed previously, suicide genes could serve as an adjunctive therapy as they can be used to destroy infected cells prior to virion release, thus reducing viremia and the likelihood of additional infection events. Further, they may allow destruction of infected cells undergoing low level proviral induction sufficiently strong to trigger expression of the toxic proteins, but insufficient to alert the immune system to the presence of the provirus.

Seeking a functional cure

A functional cure either suppresses HIV replication or creates an immune system that can control HIV infection in the presence of active HIV replication. Although replication competent HIV would still be present, patients could discontinue ART without adverse effects. Many HIV gene therapy-based strategies attempt to control HIV by supporting immune function, often through the establishment and expansion of HIV resistant cells.

One way this is being attempted is by inhibiting the expression or activity of cellular proteins required for viral entry, such as CCR5 and CXCR4, the coreceptors for R5- and X4-tropic viruses respectively. Importantly, both CCR5 40,41 CXCR4 42,43 levels can be reduced or eliminated in T cells. Strategies to create such cells include direct modification of coreceptor gene sequences and RNA-based destruction or translational silencing of coreceptor mRNA. Another approach being tested is to reverse the immune exhaustion that occurs during chronic viral infections and to allow the revitalized immune system to control the HIV infection and any secondary infections.

HIV binds to CD4 and uses either the CCR5 or CXCR4 coreceptors to facilitate entry into cells. CCR5 is the predominant coreceptor used by HIV during both initial infection and subsequently.[44,45] Viruses using the CXCR4 coreceptor are more often seen as the disease progresses.[46,47]

Of clinical significance, individuals that are homozygous for the naturally occurring *ccr5 32* mutation are resistant to CCR5-tropic HIV infection [40,48], while some heterozygous individuals exhibit delayed HIV disease progression.[49]

Proof that the homozygous mutation in CCR5 can contribute to an HIV cure is the experience of the "Berlin patient." This HIV-infected patient developed myelogenous leukemia, received a hematopoietic stem cell (HSC) transplant using cells from a *ccr5 32* homozygous donor, and after more than seven years without ART, his HIV viral load remains undetectable.[50,51]

Because this patient underwent a number of procedures associated with his treatment, including radiation therapy, chemotherapy, anti-T cell immunoglobulin treatment and graft-vs.-host disease, it is unclear which components of his treatment and clinical course contributed to his cure.

Nevertheless, this case stimulated the field to reconsider the possibility of eradication of HIV infection, and other groups are attempting to repeat the experience of a transplant-based cure.

In one study conducted by Henrich and colleagues, two patients who underwent an allogeneic stem cell transplant (alloSCT) with homozygous *ccr5 32* donor cells had undetectable levels of HIV in their peripheral blood, as determined by PCR for HIV DNA and an assay for HIV RNA that detects as little as one copy per millileter, between eight and 17 months after the alloSCT52. Further studies are being conducted, but the limited availability of *ccr5 32* homozygous donors and the risks associated with the irradiation and chemotherapy that comprise part of the treatment likely make allogeneic HSC transplant an impractical solution for HIV patients.

An alternative is to engineer a CCR5 deletion within a patient's own cells and then perform an autologous transplant. Using specialized enzymes containing both DNA recognition and endonucleolytic domains, it is possible to introduce these deletions by creating lesions at specific sites within the gene.

These enzymes, known as zinc finger nucleases (ZFNs), bind to DNA through sequence-specific interactions between their zinc finger domains and the DNA. Following binding, the ZFN cleaves the gene, creating double strand breaks that are recognized by the cell's DNA repair machinery and repaired primarily by non-homologous end joining (NHEJ). This type of repair frequently creates an insertion or deletion in the gene, and these mutations often result in translation of a nonfunctional protein.

Ongoing clinical trials (NCT00842634, NCT01044654, NCT01252641) are addressing the safety and efficacy of CCR5-ZFN-treated autologous cells, known as SB-728-T, in humans, including effects on CD4+ T cell counts, viral load, and the ability of the cells to localize to anatomical reservoirs. Preliminary results indicate treatment is generally well tolerated and leads to increased CD4+ T cell levels.55,56 Significantly, SB-728-T cells persist over time and appear to expand and undergo trafficking to the gut-associated lymphoid tissue (GALT).

These results suggest a small initial pool of HIV resistant cells may persist after transplantation. However, whether they exhibit normal immune function and can control HIV replication over time remains to be demonstrated.

Despite these encouraging results, inhibiting CCR5 expression does not protect against CXCR4-tropic viruses and may drive selection for either X4-specific or dual tropic HIV viruses.[57,58]

A potential solution is to inhibit both the CCR5 and CXCR4 coreceptors simultaneously in T cells, preventing viral entry regardless of tropism. ZFNs targeting CXCR4 effectively reduce CXCR4 levels and conveys long-term resistance to X4-tropic HIV infection in cell lines and humanized mice.[59,60]

Not unexpectedly, resistance in mice is limited by selection for R5-tropic viruses.59 However, when homozygous *CCR5Δ32* CD4+ T cells were treated with CXCR4 ZFNs, the cells became resistant to both R5- and X4-tropic HIV 59, supporting the notion that simultaneous reduction of the expression of both coreceptors in patient-derived cells are a therapeutic possibility. If so, these cells could be used as a founder population of HIV resistant cells to help reestablish or preserve immune function and prevent disease progression.

While the effects of loss of CCR5 on immune function appear modest, the effects of the deletion of CXCR4 on immune function are less well understood, and the effects of simultaneous loss of both receptors remains unexplored.

Reversal of Immune Exhaustion

The pathogen-specific immune response to HIV is determined by the T-cell receptor (TCR)-MHC-peptide complexes formed during antigen presentation and subsequent binding of positive or negative co-stimulatory molecules to their specific receptors or ligands.

Despite clinically successful ART, viral antigenemia persists at low levels, causing T cells to gradually lose their effector functions, including cytotoxicity and cytokine secretion, as well as their proliferative capacity.[62] Progressive functional impairment of T cells, called immune exhaustion, is a hallmark of HIV infection and appears to be multifactorial.[64]

Inhibitory receptors involved in T cell exhaustion are potential targets for immunotherapeutic strategies that could reverse immune exhaustion and allow patients to control HIV without ART.

Among these, PD-1 is one of the best studied and is the most likely to be relevant for near-term immunotherapy. Barber and colleagues demonstrated the potential application of anti-PD-1 antibodies for HIV therapy when they observed improved T cell function after blocking the

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Despite many promising inroads toward a cure for HIV, many challenges exist. Surmounting these challenges will help create a more streamlined avenue toward a cure.

PD-1 receptor in mice.[65] Subsequently, two studies demonstrated restoration of CD4 and CD8-specific responses and cytokine production in vitro upon blocking PD-1.[66,67]

Further, Petrovas and colleagues [68] demonstrated that CTLs expressing PD-1 were more susceptible to apoptosis, although it remains unclear whether blocking PD-1 improves T cell survival. In vivo blockade of PD-1 in chronically SIV-infected rhesus macaques resulted in no changes in SIV-specific T cell function or numbers after a single injection of PD-1 antibody[69], while enhanced SIV-specific immune responses was observed after four repeated injections.[70]

Clinical trials for hematological malignancies using antibodies to block the interaction between the PD-1 receptor and its ligand (PD-L1) have been reported with administration of a humanized anti-PD-1 antibody resulting in a sustained increase in CD4+ T cell counts after a single dose[71] and restoration of T cell responses.[71,72] Further, there have been encouraging results from the use of an anti-PD-1 antibody as an adjuvant in lentiviral vaccines to enhance antigen-specific immune responses.[73] However, concerns about using PD-1 blockade as a therapeutic approach for HIV infection include the possibility that enhancing antiviral responses by blocking PD-1 could also enhance activation in an already pre-activated system. Inhibition of PD-1 may need to be combined with additional therapies for patients to regain full T cell function.

Challenges & Conclusions

Despite many promising inroads toward a cure for HIV, many challenges exist. There is a pressing need for more refined cellular models of HIV latency and standardization of how active and latent HIV is detected. Surmounting these challenges will help create a more streamlined avenue toward a cure.

Many cell-based models of HIV latency have been developed, including cell line and primary cell models. While cell line models offer a preliminary platform for drug discovery and characterization, they have characteristics that make them less attractive as standard latency models.

There is as yet no single, universally employed, standardized method for measuring latent HIV infection that is rapid, accurate, sensitive, and economical. Instead, a variety of methods are employed, including PCR- and protein-based assays. Each method provides valuable information, but because the assays measure disparate aspects of expression and often exhibit variability lab-to-lab, this presents a significant technical roadblock to efficient characterization of therapeutics and hinders understanding of their precise effects on latency.

The current gold-standard method for detecting and quantifying HIV replication is the viral outgrowth assay, which measures p24gag levels by enzyme-linked immunosorbent assay (ELISA) as an endpoint. Although its widespread use is hindered because it is resource intensive and time consuming, it is the most accurate and sensitive measure of HIV replication available.

While HIV infection is generally manageable with life-long HAART, there is a continuing investment of effort and resources aimed at developing an effective and economical treatment strategy to address HIV latency.

Currently, the most promising approach that could possibly be scaled up for treatment of people in resource-limited environments is the concept of "kick and kill." However, if the delivery of gene therapy-based approaches is optimized, it also would be widely distributable to large numbers of people worldwide. The current requirement for immune exhaustion reversal therapies to be administered repeatedly makes them the least likely to be a worldwide solution.

In the meantime, the search continues. Once the effectiveness and safety of these different approaches has been assessed in clinical trials, it will be important to determine whether a single or a combination of these methods will be the most effective and easily distributable way to treat latent HIV infection. **HIV**

Editors Note: This article is a modified and condensed version of *Prospects for treatment of latent HIV*, by Kirston M. Barton, Brandon D. Burch, Natalia Soriano-Sarabia and David M. Margolis, Departments of Microbiology and Immunology, Medicine, and Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599

To view references cited in this article, please visit www.aahivm.org.

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BY JEFFREY T. KIRCHNER, DO, FAAFP, AAHIVS

CURED?

Timothy Brown, "The Berlin Patient"

Most HIV clinicians and many HIV/AIDS patients are aware of "the Berlin patient," who several years ago was noted to be the first person "cured" of AIDS. His case was reported initially in the *New England Journal of Medicine*[1] and later the journal *Blood*[2].

The patient, whose real name is Timothy Ray Brown, is an American who was attending school in Berlin in 1995 when he first tested positive for HIV. Brown continued to live in Germany, where he received early combination antiretroviral therapy. He stayed well during this time with no HIV-related complications. However in 2006, he was diagnosed with acute myeloid leukemia (AML). He initially was treated with several cycles of standard chemotherapy and effectively induced remission, which only lasted for about one year.

In February 2007, Brown had a relapse of his leukemia and a second course of chemotherapy was unsuccessful. Subsequently, his oncologist, Dr. Gero Huetter, recommended that Brown undergo a stem cell transplant (SCT). It had been known since the mid-1990's that the cells of persons homozygous for the chemokine receptor CCR-5 gene variant Δ32 are naturally resistant to infection with CCR5-tropic HIV (R5 HIV) because they lack CCR5 cell-surface expression. More specifically, a 32-base-pair deletion within the coding region results in a frame shift. This genetic shift generates a non-functional receptor that does not support membrane fusion and thus infection by macrophage- and dual-tropic HIV-1 strains.[3] With this in mind, Hutter screened about 70 potential donors before he was able to find one with the CCR5/Δ32 mutation that could be a donor for Brown.

Prior to the stem cell transplant, Brown's pre-transplantation "conditioning" regimen was quite extensive. It included amsacrine,

fludarabine, cytarabine, cyclophosphamide, antithymocyte globuline plus 400 centigray (cGy) total body irradiation (TBI). Antiretroviral therapy was discontinued on the day of transplantation. Although this seemingly went well, he had yet another relapse of his AML 13 months later, and then received a second transplantation with stem cells from the same CCR5/ Δ32 donor. This time his conditioning regimen consisted of cytarabine, gemtuzumab, and 200-cGy TBI.

Post-transplantation procedures

For the purposes of follow-up and close study by Huetter and colleagues, at 6, 24, and 29 months after the first SCT, Brown underwent a colonoscopy. Biopsy specimens were taken due to suspected intestinal graft-versus-host disease (GVHD), which can occur with tapering of immunosuppressive therapy. In addition, 10 to 12 additional colonic biopsy specimens were collected at each time-point for the purpose of the present study. Histologic examination of the colonic biopsies excluded the diagnosis of intestinal graft vs host disease (GVHD). At 12 months after transplantation, Brown underwent a liver biopsy that did confirmed grade 1 GVHD. This was controlled with adaption of additional immunosuppressive therapies (cyclosporine, methylprednisolone, and mycophenolate mofetil).

At 17 months post- transplantation, Brown presented with acute neurologic symptoms and an MRI identified findings compatible with leukoencephalopathy. For further evaluation, several cerebrospinal fluid (CSF) samples were collected and a brain biopsy was performed. Polymerase chain reaction (PCR) detection of JC virus was negative in all samples. Histologic evaluation revealed astrogliosis with microglial activation. The cumulative effect of multiple cycles of chemotherapy after relapse of AML, as well as his pre-transplantation conditioning regimen, (including irradiation) was assumed to contribute to, or collectively cause, his leukoencephalopathy. This neurologic complication fortunately was ultimately self-limiting.

All immunosuppressive treatment was stopped 38 months after the second SCT without any evidence of GVHD.

Testing for the presence of HIV-RNA and HIV-DNA was performed in distinct tissue compartments periodically for 45 months after his second transplant. Viral sequences were not detectable in any of the samples from Brown including plasma, PBMCs, BMMCs, CSF, brain, and colon.

Virus-Free

At approximately 5-years post-transplant he remained (presumably) free of virus. His CD4+ T-cell counts returned to a normal range. Also noted in the report from *Blood* was a progressive decline in HIV-specific antibodies demonstrating a process the authors called "serodeconversion." HIV core-directed antibodies (p17, p24) disappeared completely, the serum level of antibodies against the HIV envelope (gp41, gp120) further decreased and eventually Brown had only HIV envelope-specific antibodies in his serum.

Timothy Brown now lives in California and is followed by clinicians at San Francisco General Hospital, including Drs. Steve Deeks and Steve Yukl. Worth noting, Yukl presented date in June 2012 at a meeting in Spain suggesting the presence of low levels of HIV in Brown. Using polymerase chain reaction (PCR) testing on Brown's lymphocytes, plasma, and rectal tissue, they were able to detect small amounts of HIV-RNA and pro-viral DNA.[4]

However, another researcher, Dr. Douglas Richman from San Diego, found no evidence of HIV in their tissue samples from Brown and suspects his colleagues had found contaminants. Dr. Yukl noted the challenges that he and several collaborating labs have had determining if Brown had eradicated HIV from his body.

"There are some signals of the virus and we don't know if they are real or contamination, and, at this point, we can't say for sure whether there's been complete eradication of HIV," says Yukl. "The point of the presentation of our data was to raise the question of how do we define a cure and, at this level of detection, how do we know the signal (suggesting presence of virus) is real? Hutter and others believe these "traces of HIV" are remnants of the disease that can't replicate or cause a recurrence.[5]

However, as Hutter and colleagues note in their paper in ***Blood,*** *"... the unfeasibility to analyze every single cell in living humans rules out the possibility to positively prove viral eradication in this patient".*

What purged the virus?

If Timothy Brown is truly "virus-free," what allowed the virus to be purged from his body? Was it the removal of all HIV-infected cells, which does not seem likely? The SCT did indeed repopulate his immune system. Dr. Steve Deeks believes there may have been additional therapeutic benefit from his multiple "conditioning" regimens and subsequent immunosuppressive therapies.[6] He also believes there was possible benefit from the graft versus host response that occurs with SCT.

It is obvious that the approach used to cure Brown of HIV is not realistic for patients infected with the virus for both practical and cost reasons. Worth noting is a paper from this year's International AIDS conference that reported similar results with two other patients.[7] The principles by which Brown was apparently cured have definitely stimulated new lines of genetic research and the hope for subsequent therapeutic interventions. Moreover, his case provides optimism in looking for treatment beyond antiviral therapies or therapeutic vaccines. HIV

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U.S. MILITARY ATTACKS HIV

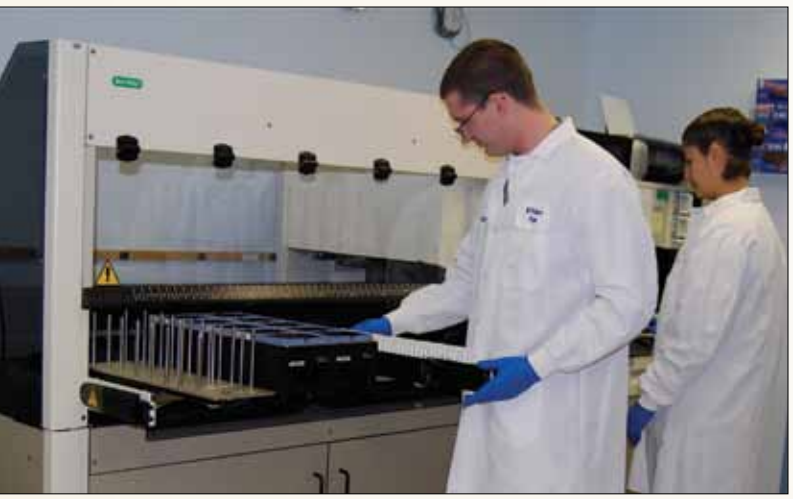
A Promising Time in HIV Vaccine Research

BY LISA REILLY

FOR THE FIRST TIME in history, scientists and global leaders alike are talking about the end of AIDS. Progress has been made, but it needs to continue against this disease on all fronts, including a vaccine and also new treatment options to help improve the lives of those living with HIV.

Historically, the U.S. military medical community has made significant contributions towards solving many international health problems, particularly in the area of infectious diseases. HIV/AIDS is no exception.

No one agency, company, or group of people will end this epidemic or advance HIV vaccine and treatment options alone. The U.S. military will continue to work collaboratively towards a safe, globally effective vaccine, so that we may one day achieve an AIDS-free generation.



Efforts by the U.S. military medical community have been ongoing in this battle.

In 2009, the U.S. Military HIV Research Program (MHRP) at the Walter Reed Army Institute of Research announced results of an Army-sponsored clinical trial in Thailand that demonstrated, for the first time, a modest ability to protect against HIV infection, reducing the number of infections by 31.2 percent. The Thai HIV vaccine clinical trial, also known as RV144, tested the "prime-boost" combination of two vaccines: ALVAC® HIV vaccine (the prime), and AIDSVAX® B/E vaccine (the boost).

This study offered the vaccine research field renewed hope and, more importantly, it provided scientific direction to help guide future vaccine development. In 2012, military researchers—with the support of partners worldwide—made substantive progress in understanding what it will take to develop a more efficacious HIV vaccine.

How the Vaccine Reduced Risk

In April, the *New England Journal of Medicine* published a paper co-authored by MHRP scientists that detailed clues to why the vaccine tested in the landmark RV144 trial protected some volunteers.

This unprecedented collaboration, led by researchers at Duke University and MHRP, brought together investigators from around the world to study those who became infected compared to those who did not. One finding was that immunoglobulin G antibodies that bind to the V1/V2 region of HIV's Envelope protein correlated with lower infection rates among those who were vaccinated.

Next, scientists examined whether those vaccine-induced antibody responses selectively blocked certain HIV variants. They examined HIV genome sequences from 110 volunteers who participated in RV144, and who subsequently became infected with HIV.

The findings, published in September in *Nature*, reinforced that antibodies directed at the V1V2 region reduced the risk of infection. "Taken together the work suggests that the Env-V2 region could be a critical target for future HIV vaccines," noted Col. Jerome Kim, MHRP Principal Deputy Director and senior author on the study.

RV144 Follow up

In the May issue of *The Lancet Infectious Diseases*, researchers reported that vaccine efficacy seemed to peak early—cumulative vaccine efficacy was estimated to be 60.5 percent (95 percent CI 22–80)—through the 12 months after initial vaccination, after which it declined quickly. This early, high protective immune response suggests an additional boost or other augmentation of immune response would improve efficacy.

A public-private collaborative team is planning follow-up clinical studies using a similar vaccine regimen in Southern Africa as well as Thailand. Researchers are working to improve and prolong the level of protection by using an extra vaccine boost and better adjuvants in these studies, which are slated to begin in 2015.

Next Generation Vaccines

Military scientists continue to work closely with partners across the world to develop and test novel vaccine strategies. In collaboration

TRICKZY, KEITH BISHOP / ISTOCK, BONOTOM STUDIO

with the NIH, MHRP has developed a promising next-generation MVA vaccine that is currently in clinical testing in Africa and Sweden in combination with two investigational DNA vaccines.

Collaborative work with Harvard University, Crucell Corporation and MHRP, published in January in the journal *Nature*, point the way to other novel vaccine combinations that will soon be evaluated in clinical studies.

One combination—an Ad26 and MVA heterologous prime boost vaccine regimen—provided partial protection against infection by Simian Immunodeficiency Virus (SIV) in rhesus monkeys. In addition, in the animals that became infected, the optimal vaccine combinations also substantially reduced the amount of virus in the blood.

Further analysis also provided insights into the immune responses that might have provided protection in the rigorous SIV model, called "immune correlates." The results show that antibodies to Env correlated with protection against acquisition, whereas both T cell and antibody responses correlated with post-infection virologic control.

"These distinct immunologic correlates likely reflect fundamentally different requirements to block establishment of infection compared with controlling viral replication after infection," said Col. Nelson Michael, Director of MHRP and senior author on the paper.

Interestingly, these study results also point to the V2 region of the HIV surface that may play a key role in protection from HIV. HIV

The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the Department of Defense.

ABOUT THE AUTHOR: **Lisa Reilly** is communications director at the U.S. Military HIV Research Program. She is based in Bethesda, MD and supports research and PEPFAr-funded activities at MHRP research sites in Africa and Thailand.

The US Military and HIV

The Military HIV Research Program (MHRP) at the Walter Reed Army Institute of Research was established in 1986. The program began to provide of the first descriptions of the natural history of HIV/AIDS, and its large observational cohort study continues today.

The DoD initiated HIV screening of all applicants for military service beginning in August of 1985, only months after the first screening test for the newly identified virus was developed. It began "force wide" HIV screening for active duty members two months later.

In 1986, MHRP published evidence of the then-controversial notion that HIV could be transmitted heterosexually. In 1987, MHRP scientists developed the criteria for Western blot positivity—the fist supplemental confirmatory test for HIV. Fast-forward to 2009; the U.S. Army announced the results of the RV144 Thai study, the first HIV vaccine trial to show some ability to protect people against this disease.

ACCELERATING PROGRESS

Q & A with COL Nelson Michael, MD PhD, director of the U.S. Military HIV Research Program at Walter Reed Army Institute of Research

Why is an HIV vaccine so important?
There have been great strides in the use of antiretrovirals as preventive measures for microbicides or taken orally. I think these are very powerful tools, but there are substantial challenges to deploy these worldwide as public health countermeasures. All of our proven preventive measures need to be used together, and I think that in some parts of the world, they may help control the epidemic, but they will never defeat it without a vaccine. That's pretty clear from a historical precedent of similar epidemics.

What is the status of HIV Vaccine Research?
The HIV vaccine field is the most vibrant since the endeavor began nearly two decades ago. The scientific basis for developing vaccines has never been better, in terms of understanding the immune system and protective immune responses, and there is much more consistency across animal models. On the clinical trials side, trials are not proceeding at the pace many would like to see. But I am excited because the major groups that are developing approaches for vaccines for HIV have never worked more collaboratively than these days.

How will the introduction of PrEP affect how AIDS vaccine trials are conducted?
It is already impacting how we design vaccine clinical trials. It might drop the incidence to such a low level that the power of the study is diminished, leaving you with two options: You can make the trials bigger or you could follow them out for longer, and both can add considerable costs. This is a small price to pay for a potential drop in HIV transmission rates in a community by the effective use of PrEP. In the long run, if you can reduce community incidence with PrEP, and other non-vaccine countermeasures, then the subsequent introduction of a partially-effective vaccine could have a tremendous impact on controlling the HIV pandemic.

"The pace of research success in HIV vaccines is accelerating; it's the most exciting time I have ever seen in the field."

—COL Nelson Michael, MD, PhD

Does MHRP conduct any therapeutic studies?
Yes. Our program expanded into therapeutics research several years ago at two clinical research sites in Kenya when MHRP was designated an NIAID Clinical Trials Unit partnered with the AIDS Clinical Treatment Group. Our local partners there have co-authored several papers including one on use of nevirapine for PMTCT and another on initiating early TB treatment for HIV positive patients. We will soon be submitting an application to the NIH in the hopes of expanding our ability to conduct HIV therapeutics research with a particular emphasis on interventions in the very earliest days of HIV infection with the intent to seek a cure.

Is there potential for a therapeutic vaccine?
Yes. This has been a topic upon which the HIV/AIDS field has had variable interest in over 30 years. I believe that a perfect storm of discovery science, clinical trial results, and product availability has led the field, including MHRP, to become excited about exploring HIV therapeutic vaccines again. We believe that our ability to identify HIV infected subjects literally in the first few days after infection will put us in a unique position to study the therapeutic use of HIV vaccines that can, along with potent and highly suppressive antiretroviral therapy and medications to cull out the latent HIV reservoir, offer the hope of more effective viral clearance—the first step toward cure.

Do you provide care to research participants in Africa?
One unique aspect of our program is that we provide prevention, care and treatment services in each of the communities in which research is conducted. Funded through the President's Emergency Plan for AIDS Relief (PEPFAR), this provides an ethical, non-coercive environment to conduct clinical research. The integration with research sites has created vibrant synergy that enhances clinical research and improves the public health infrastructure in Africa.

Why is the military pursuing an HIV vaccine?
HIV is a global threat, and we are part of an international effort to reduce the impact of HIV infection worldwide. HIV continues to pose a threat to Service Members, and it can also compromise the stability of a nation where the disease is prevalent and endanger worldwide security. HIV is a war starter. The U.S. military medical research establishment is continuing in its long tradition of developing countermeasures for infectious diseases that affect our troops, those of other nations, and the global community in which we all live as diseases like HIV tear at the very fabric of the world's ability to peacefully and productively co-exist.

BY THERESA N. MACK, MD, MPH, AAHIVS

Early HIV Treatment Is Prevention

THE RISK OF SEXUAL TRANSMISSION OF HIV is directly related to the plasma HIV viral load and HIV-infected persons who maintain high levels of HIV RNA load can transmit virus at high rates.

The results of observational studies and clinical trials show that anti-retroviral therapy (ART) not only can reduce the plasma viral load of HIV-infected persons to undetectable levels, but also that HIV-infected persons with undetectable viral load are less infectious and may be less likely than those with detectable viral load to transmit HIV through sexual contact.

Although it is now well accepted that reducing the viral load to undetectable levels with ART substantially decreases the risk of sexual HIV transmission in serodiscordant couples, the risk is not completely eliminated. This is because undetectable plasma levels of HIV do not ensure that HIV will not be present in semen or vaginal secretions, particularly in persons with genital tract inflammation due to a sexually transmitted disease. Sexual transmission may also occur when adherence is less than ideal or when the preventive benefits of ART are offset by risky behaviors. Accordingly, all people living with HIV should use condoms to prevent acquisition of STDs as well as transmission of HIV.

Study HPTN 052: HIV Treatment Is Prevention

The HIV Prevention Trials Network Study 052 was conducted to determine whether immediate versus delayed ART in HIV-infected persons can reduce transmission of HIV to their uninfected spouses or partners. The trial began in 2005 and enrolled 1763 HIV serodiscordant couples, 97 percent of whom were heterosexual.

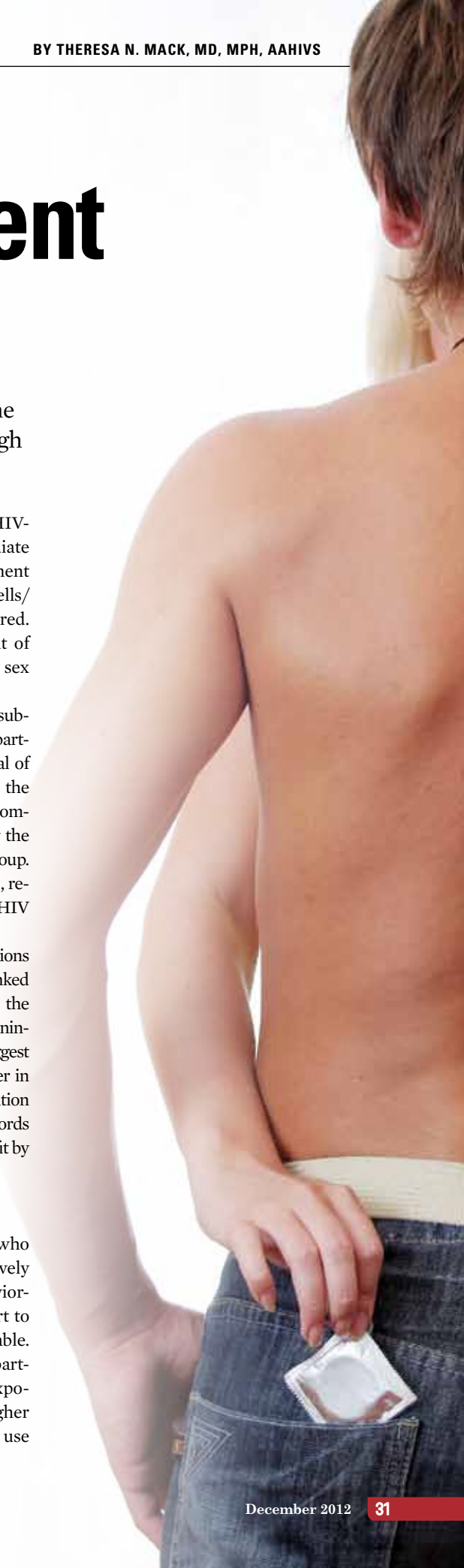
At enrollment, the HIV-positive partner was required to have a CD4 count between 350 and 550 cells/mm^3; the median CD4 count at enrollment was 436 cells/mm^3. Couples were randomized so that the HIV-positive partner received either immediate antiretroviral therapy or delayed treatment until the CD4 count fell below 250 cells/mm^3 or an AIDS-related event occurred. Both groups received the same amount of HIV-related care, counseling on safer sex practices, and free condoms.

The results showed that early ART substantially protected HIV-negative sexual partners from acquiring HIV infection. A total of one HIV transmission occurred among the 886 couples in the early treatment group compared with 27 HIV transmissions among the 877 couples in the delayed treatment group. This difference was significant ($P<0.0001$), reflecting a 96 percent reduction in risk of HIV infection in the early treatment group.

Furthermore, in all cases the new infections were confirmed as being genetically linked to the HIV-positive partners, confirming the source of the new infection in previously uninfected partners. These results strongly suggest that initiating ART sooner rather than later in HIV-positive persons provides a prevention benefit for their uninfected partners and affords a potentially enormous public health benefit by slowing the spread of HIV infection.

Clinical Applicability of HPTN 052

The rate of HIV transmission in men who have sex with men has remained relatively high in spite of expanded ART and behavioral interventions. This may be due in part to the fact that ART is not universally available. In serodiscordant male homosexual partnerships, where there are repeated exposures, the risk of HIV transmission is higher than in heterosexual couples. Condom use



THINKSTOCK

reduces HIV transmission dramatically, but because of incorrect or inconsistent use, condoms are about 95 percent effective.

HIV transmission is highest when neither early ART nor condoms are used and lowest when both are used. In one study the transmission rate exceeded 60 percent when neither ART nor condoms were used, compared with essentially zero when both were used. This suggests that, when counseling and advising patients about the risks of HIV transmission, clinicians should provide a balanced estimate of the risk over the course of many sex acts, because it is not realistic to assume that the risk of transmission can be reduced to zero even with ART plus other protective interventions such as condom use. If a man has sex without a condom, his partner is at risk for HIV. This is not insignificant and remains a life or death situation despite the availability of effective ART.

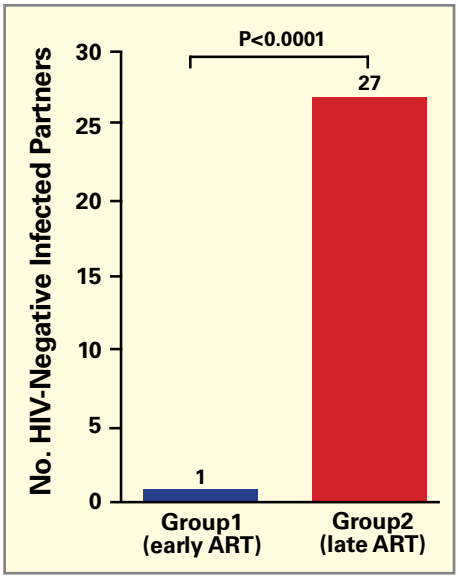
A person who intends to engage in sexual acts also must know whether his or her partner is HIV infected. This is particularly important for women, who often are not only afraid to ask men about their HIV status, but also are reluctant to insist that men use condoms for fear of damaging the relationship or even being abused.

This is not an insignificant issue, because women, who comprised 2 percent to 3 percent of the HIV-infected population when the epidemic began, now comprise 25 percent. Especially troubling is the number of newly infected young men who have unprotected sex with men. Younger patients who are HIV-infected or at high risk for HIV acquisition have become complacent. They misperceive HIV to be a curable disease or a disease that can be treated with one pill daily and not as an infection that necessarily should be prevented.

How Can Treatment-For-Prevention be Implemented?

How realistic is it to assume that HIV-infected patients who are currently not on ART will accept early initiation of treatment primarily to reduce the risk of viral transmission? Some of these patients have no place to live, are substance abusers, or have mental health issues. For many of them, the lifetime commitment of taking medication daily to prevent viral transmission is not a priority.

At the very least, they must be educated about what they will be taking, why they will be taking it, and what happens if they miss a dose. When the HIV treatment guidelines were recently revised and I told my patients that the new guidelines recommended ART



The study results show that antiretroviral therapy substantially protected HIV-negative sexual partners from acquiring HIV infection in the early treatment group. One HIV transmission occurred among the 886 couples in the early treatment group compared with 27 HIV transmissions among the 877 couples in the delayed treatment group, as shown in the graph. This difference was statistically significant (P<0.0001), reflecting a 96 percent reduction in risk of HIV infection in the early treatment group.

with a CD4 count above 500 cells/mm^3, we had discussions about initiating treatment, and two points of view became clear: 1) "I'm not broken and I don't want to fix it," or 2) "I'll wait and bide my time because right now I'm doing OK."

These points of view are understandable if patients are doing well, but if they come back and complain that they don't feel well, they're tired at work, or they can't do some of things they did previously, then that would be a reason to begin the discussion again about ART--even though the CD4 count remains high. These issues have always been subjects for discussion, but now the benefits and risks of earlier treatment of HIV at higher CD4 counts must be considered. Earlier initiation also may prevent HIV- associated nephropathy (HIVAN), HIV associated dementia (HAD), peripheral neuropathy, and opportunistic infections. Now there are more effective medications with fewer side effects and better tolerability, but if a patient is not ready to take them they will not work. So, unless a patient is ready, willing, and able to begin ART at a higher CD4 count, the new recommendations will not be implemented universally. These are the challenges we face in practice on a daily basis.

Summary and Conclusion

Effective ART has been shown to prevent transmission of HIV from an infected person to a sexual partner. Therefore, ART should be offered to patients who are at risk of transmitting HIV to sexual partners. HIV

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BY DENNIS HARTIGAN-O'CONNOR, MD, PHD, BS

In Search of an Effective Vaccine

THE SEARCH FOR AN EFFECTIVE VACCINE AGAINST HIV has long been frustrated by uncertainty about which specific immune responses contribute to protection against disease. However, the past two years have seen considerable progress, with new focus placed on both binding and neutralizing antibodies, as well as CD4$^+$ helper T cell responses that are critical to generation of those antibodies.

The RV144 trial tested efficacy of two vaccines in combination, ALVAC HIV vaccine (the prime) and AIDSVAX B/E vaccine (the boost), and demonstrated a 31 percent reduction in the rate of HIV infection based on the modified intent-to-treat population.[1]

Although the trial results were released in 2009, this year saw publication of a sophisticated analysis of possible immunologic correlates of protection.[2] Six primary variables reflecting different immune responses were chosen to evaluate the roles of T-cell, IgG antibody, and IgA antibody responses in modulation of infection risk. Two of these variables correlated significantly with protection: IgG binding to two different envelope (Env) variable regions correlated inversely with HIV infection, while IgA binding to Env correlated directly with infection.

One surprising aspect of this result is the suggestion that vaccine-induced antibodies that bind but do not neutralize HIV (i.e., that do not prevent the virus from infecting CD4$^+$ cells) can contribute to protection. It was also fascinating to learn that vaccine-induced responses may work against one another, with a consequent need to carefully focus the design of future vaccines to avoid unhelpful responses.

HIV-infected individuals commonly generate binding antibodies, but only occasionally generate *neutralizing* antibodies that access the virus' conserved receptor-binding regions and thereby prevent infection. In intact virus particles, these critical regions are normally surrounded by variable, heavily-glycosylated core and loop structures.

Six primary variables reflecting different immune responses were chosen to evaluate the roles of T-cell, IgG antibody, and IgA antibody responses in modulation of infection risk.

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Despite this barrier, however, some individuals living with HIV do generate neutralizing antibodies, and a number of specific antibodies have now been identified that display both potent neutralization and broad reactivity to different viral strains. Sophisticated screening techniques allowed identification of the antibody VRC01 in 2010[3] and purified preparations of this antibody were more recently shown to provide sterilizing protection to non human primates from mucosal SHIV challenges.[4]

More intensive screening techniques resulted in isolation of new monoclonal antibodies (the so-called "PGT" antibodies) that are almost 10-fold more potent than those resulting from earlier screens.[5] Some of these antibodies bind to select Env monomers, as opposed to assembled trimeric Env, and these monomers are candidate vaccine immunogens.

These exciting results in the area of antibody responses to HIV have spawned renewed interest in the $CD4^+$ T cells that are thought to be critical to their generation. Follicular helper T cells, in particular, are memory cells found in the B cell follicles of secondary lymphoid organs. It was recently shown that for live attenuated SIV vaccines, which remain the most efficacious of all vaccines in nonhuman primate models of HIV, the degree of protection achieved correlates strongly with the magnitude and function of SIV-specific, effector-differentiated T cells in the lymph node, but not with the responses of such T cells in the blood or with other immune parameters.[6]

Maintenance of these responses depends on replication of the attenuated vaccine in follicular helper T cells. Although these findings do not clearly delineate a mechanism of protection, they are strongly suggestive of a model in which persistent replication of attenuated virus maintains antiviral effector memory T cells in tissues that, if present at a sufficient frequency, can control SIV infection in the first days after challenge.

Perhaps the most compelling evidence in support of the T cell protection model of attenutated vaccine efficacy is the analogous control of SIV infection that is stimulated in some cases by SIV-protein–expressing cytomegalovirus (RhCMV) vectors.[7]

It was recently shown that about half of macaques receiving either RhCMV vectors alone or RhCMV vectors followed by adenovirus 5 vectors manifested early complete control of SIV. The rationale behind such vaccines is to stimulate development of effector-memory T cells that are pre-positioned at sites of viral entry, where they might be effective against the smaller and less diverse viral populations present at infection.

Such results have given new direction to the field and new hope for success.

Strikingly, although virus replication is evident in all protected animals, the level of virus wanes over time until it barely detectable by sensitive assays. These results suggest the possibility that, as in the case of attenuated SIV vaccines, persistent stimulation of antiviral T cell responses provides for continuous surveillance for SIV-infected cells.

Such results have given new direction to the field and new hope for success. Results from experiments with live attenuated and RhCMV vaccines suggest that antiviral T cells can indeed contribute to protection against disease, if those responses are of the right type and are correctly situated in tissue sites. Identification of highly-potent, broadly-neutralizing antibodies has spurred development of alternative forms of Env that maximize exposure of the CD4 binding site to the immune system and mask irrelevant regions of the protein. HIV

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Highly Sensitive HIV RNA Assays - Clinical Practice and Perspectives

BY JOHNNIE A. LEE, MD, MPH, FACP

This communication provides an update on low-level ("residual") viremia and highly sensitive viral load assays as we explore the possibility of HIV eradication.

Virological Failure and Residual Viremia

Virologic end points are evolving as more sensitive viral load assays are introduced. Combination antiretroviral (ART) regimens can suppress viral replication in most people with HIV, but low-level viremia (LLV) may be detected periodically in patients with so-called "undetectable" viral load. Recent treatment guidelines define optimal virologic suppression as a viral load persistently below the level of detection (<20– 75 copies/mL), depending on the assay used.[1] Also, the guidelines clarify the significance of residual viremia, noting that there is no definitive evidence that patients with viral loads <200 copies/mL using these assays are at increased risk for virologic failure.[1]

Residual viremia is detected in most HIV-1-infected patients on antiretroviral therapy despite suppression of plasma RNA to <50 copies per ml, but the source and duration of this viremia is currently unknown. Palmer analyzed longitudinal plasma samples from 40 patients pretherapy and weeks 60-384 using an HIV-1 RNA assay with single-copy sensitivity.[2] All patients were on therapy with plasma HIV RNA <50 copies/ml by week 96. Single-copy assay results revealed that 77 percent of patient samples had detectable LLV (≥1 copy/mL), and all patients had at least one sample with detectable viremia. They reported a biphasic decline in plasma RNA levels occurring over weeks 60-384: an initial phase of decay with a half-life of 39 weeks and a subsequent phase with no perceptible decay. These data suggest that low-level persistent viremia arises from at least two cell compartments, one in which viral production decays over time and a second in which viral production remains stable for at least seven years.

In a review of the link between LLV and HIV treatment in the Swiss HIV Cohort, Boillat-Blanco reported that the majority of patients with low levels of plasma HIV RNA did not experience treatment failure.[3] This case control study included 179 case subjects enrolled from January 2000-December 2010 with undetectable HIV RNA for at least 24 weeks on stable antiretroviral therapy who presented with persistent low-level viremia (21-400 copies/mL) in at least 3 consecutive plasma samples. They were compared with 5389 control patients without LLV (i.e. with at least 3 consecutive viral load values ≤20 copies/mL for at least 32 weeks).

They reported further that, although not statistically significant, individuals with LLV, had poorer adherence on average compared with controls. Two-thirds of case patients still had LLV at week 48 of the study. Only 12 percent of case patients experienced virological failure (i.e. viral load rising to >400 copies/mL by week 48, while none of the 26 case patients with very low-level viremia (21-49 copies/mL) experienced virological failure. Treatment intensification did not affect outcome and virologic failure occurred with equal frequency patients who intensified treatment (9 percent), compared with those who did not (12 percent).

The Role of Highly Sensitive Viral Load Assays in Eradication Efforts

Highly sensitive viral load assays may prove useful in other areas of contemporary HIV medicine, especially in our understanding of HIV eradication.[4, 5]

Using a highly sensitive single copy assay, McMahon et al speculate that sources of this viremia include virus production from long-lived cells containing integrated proviruses or from ongoing cycles of viral replication in sanctuary sites.[4]

This is chiefly because the pool of latently infected CD4 T cells is established during the earliest stages of acute HIV infection and persists with a long half-life, despite prolonged suppression of plasma viremia.[3]

To identify potential sources of LLV, they studied whether residual viremia is affected by antiretroviral intensification. Using raltegravir (Isentress; Merck), neither individual participant results nor aggregate data showed significant changes in median HIV-1 RNA before, during, or after intensification. All subjects had therapeutic raltegravir levels by day 14 of intensification. These data suggest that HIV-1 was not derived from rapidly cycling short-lived cells (e.g. CD4 cells; half-life, 1–10 days) that are responsible for the viremia observed in untreated individuals.

Guidance for Clinicians

These data provide a clearer understanding of newer, more sensitive viral load assays and very low-level viremia for both clinicians and patients. These "detectable" viral loads, while not uncommon with more sensitive assays,[1] have not been shown to be predictive of the emergence of resistance to therapy or treatment failure. Treatment intensification does not appear to play a role in reducing residual viremia, even when newer antiretroviral classes are used (e.g. integrase inhibitors).

Clinicians should be confident in their discussions with patients offering reassurance to them that low level viremia does not necessarily require a change of regimen or treatment intensification. Accumulating evidence indicates that treatment in the presence of very low level "detectable" viral loads is, in fact, working, and that continued adherence to treatment along with regular patient follow-up are the cornerstones of managing HIV as a chronic, manageable, medical condition. HIV

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Advancing New Strategies for HIV Prevention

BY LAUREN TEMME, PHARMD, BCPS AND M. KEITH RAWLINGS, MD

THE NUMBER OF NEW HIV INFECTIONS IN THE U.S. each year has remained largely unchanged for the last 20 years, with approximately 50,000 new infections annually.[1] Although the incidence of HIV infections has been stable, rates of infection continue to rise in some patient populations, such as young black men who have sex with men (MSM).

Treatment as prevention and expanded HIV testing have helped to reduce new infections. Department of Health and Human Services (DHHS) and International Antiviral Society-USA (IAS-USA) HIV treatment guidelines now recommend treatment for all HIV-infected individuals,[2,3] and the U.S. Preventive Services Task Force recently recommended opt-out HIV testing for adults.[4] However, data suggest that these strategies alone will not halt the HIV epidemic.

On July 16, 2012, Truvada (emtricitabine/tenofovir disoproxil fumarate [FTC/TDF]) was approved by the Food and Drug Administration (FDA) in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.[5] This indication is based on the iPrEx trial in MSM at high risk for HIV-1 infection and the Partners PrEP trial in heterosexual serodiscordant couples. Data from these studies and other Phase 3 PrEP clinical trials are summarized below.

Studies Evaluating FTC/TDF for PrEP[6]

Study	Population	mITT[a] % Reduction in HIV Incidence (95% CI)			Combined Self-Report and Pill-Count Medication Adherence (95% CI)	Pill-Count Medication Adherence (95% CI)	TFV Blood Detection[b] (95% CI)
iPrEx	MSM	44% (15-63%)			>50%:[c] 50% (18-70%) >90%:[c] 73% (41-88%)	NR	92% (40-99%)
Partners PrEP	Heterosexual discordant couples	Overall	Men	Women	NR	100%[d] (87-100%)	90% (58-98%)
		75% (55-87%)	84% (54-95%)	66% (28-84%)			
TDF2	Heterosexual men and women	62% (22-83%)	80% (25-97%)	49% (-21 to 81%, NS)	NR	NR	84% (-62 to 98%, NS)
FEM-PrEP	Heterosexual women	NS	NS	NS	NR	NR	NS

Abbreviations: FTC/TDF, emtricitabine/tenofovir disoproxil fumarate; mITT, modified intent-to-treat; MSM, men who have sex with men; NR, not reported; NS, not significant; TFV, tenofovir

[a] Excluded only those enrolled patients later found to be infected at randomization and those with no follow-up visit or HIV test

[b] The percentage of reduction in HIV incidence among those with TFV detected in blood, compared with those without detectable TFV

[c] The percentage of reduction in HIV incidence, compared with the placebo group, is presented for 2 groups: those with 50% medication adherence and those with 90% medication adherence

[d] In a substudy of participants who provided counts via home-based unannounced pill counts with supplementary adherence counseling if the counts were <80%

The Centers for Disease Control and Prevention (CDC) has issued interim guidance on the use of FTC/TDF for PrEP in both high-risk MSM and heterosexually active adults at very high risk of sexual HIV acquisition, which are available at http://www.cdc.gov/hiv/prep/.[6,7] or (dependent on publication of formal guidelines)

The U.S. Public Health Service has recently issued comprehensive guidelines on the use of FTC/TDF for PrEP, which are available at: (insert website).[7]

In order to educate prescribers and individuals on the appropriate use of PrEP, a Risk Evaluation and Mitigation Strategy (REMS) was developed. In addition, Gilead has several assistance programs in place to help uninsured or financially needy individuals access Truvada for PrEP. These programs include free male and female condoms as well as free HIV testing and drug assistance for qualified individuals. The REMS educational materials and assistance programs can be accessed at www.truvada.com.

Gilead has committed to five post-marketing studies to better understand the safety, efficacy, and resistance profile of Truvada for PrEP in the U.S., which will report:

- Pregnancy outcomes for women who become pregnant while taking Truvada for PrEP
- Resistance analyses in individuals participating in PrEP demonstration projects who seroconvert while taking Truvada
- Drug adherence and its relationship to adverse events, risk of seroconversion, and resistance development in seroconverters in at least 7,000 participants in demonstration projects
- National drug utilization data in order to better characterize PrEP users
- U.S. CDC Demonstration Project of Truvada for PrEP in MSM and heterosexual men and women

PrEP implementation at the community level is currently underway at many sites across the country. As part of a comprehensive strategy to prevent HIV infection, PrEP is an additional option for individuals who are at high risk for sexually acquired HIV infection. Truvada for PrEP is a new tool that, along with other prevention strategies, can help us move towards an AIDS-free generation. HIV

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