The AMERICAN ACADEMY of HIV MEDICINE

HIV SPECIALIST

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

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HIV Testing = PREVENTION 10

TRUVADA® (emtricitabine/tenofovir disoproxil fumarate [DF]) is a once-a-day backbone for combination therapy in adults with HIV-1[1]

#1 prescribed NRTI backbone[2] with Reyataz*[2] Kaletra*[2] Prezista*[2] Lexiva*[2]

Today, Tomorrow, TRUVADA

- **Efficacy: Potent long-term virologic control, even at high viral loads through 3 years in Study 934†[3]**
  - 71% of patients taking TRUVADA achieved <400 copies/mL at 144 weeks versus 58% taking Combivir[3]
  - 73% of patients with high baseline viral loads (>100,000 copies/mL) taking TRUVADA achieved <400 copies/mL at 144 weeks versus 59% taking Combivir[3]
  - HIV RNA <400 copies/mL at 48 weeks (primary endpoint): 84% (n=244) for TRUVADA versus 73% (n=243) for Combivir[3]
- **Safety: Established safety and tolerability profile in Study 934†[1]**
- **Partnership: Proven partner with all leading PIs in long-term clinical trials*[4-12]**
- **Confidence: DHHS preferred for more than 5 years‡[13-18]**

PIs=protease inhibitors; DHHS=Department of Health and Human Services.
*Reyataz® (atazanavir sulfate), Kaletra® (lopinavir/ritonavir), Prezista® (darunavir), Lexiva® (fosamprenavir calcium).[2]
†Study 934 design: A randomized, open-label, active-controlled, multicenter study comparing TDF 300 mg once daily + FTC 200 mg once daily versus AZT 300 mg + 3TC 150 mg fixed-dose combination twice daily, in combination with EFV 600 mg once daily, in 511 antiretroviral-naive patients. From Weeks 96–144, patients received TDF/FTC fixed-dose combination with EFV in place of TDF + FTC + EFV.
‡TRUVADA or its components have been DHHS preferred for initial therapy since 2004.

Truvada®
200 mg emtricitabine-tenofovir disoproxil fumarate 300 mg

Important Safety Information[1]

- Please see **boxed WARNING** information about **lactic acidosis, severe hepatomegaly with steatosis,** and **exacerbations of hepatitis B upon discontinuation of therapy** below
- There are no adequate and well-controlled studies in pregnant women
- Drug interactions have been observed between tenofovir DF and atazanavir or lopinavir/ritonavir. Atazanavir 300 mg should be boosted with ritonavir 100 mg and taken with food when administered with TRUVADA. Atazanavir without ritonavir should not be coadministered with TRUVADA. Patients on atazanavir or lopinavir/ritonavir plus TRUVADA should be monitored for tenofovir-associated adverse reactions. TRUVADA should be discontinued in patients who develop tenofovir-associated adverse reactions

Indication and usage[1]

TRUVADA, a combination of EMTRIVA® (emtricitabine) and VIREAD® (tenofovir disoproxil fumarate), is indicated in combination with other antiretroviral agents (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infection in adults.

The following points should be considered when initiating therapy with TRUVADA for the treatment of HIV-1 infection:

- It is not recommended that TRUVADA be used as a component of a triple nucleoside regimen
- TRUVADA should not be coadministered with ATRIPLA® (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg), EMTRIVA, VIREAD, or lamivudine-containing products[§]
- In treatment-experienced patients, the use of TRUVADA should be guided by laboratory testing and treatment history

WARNINGS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, a component of TRUVADA, in combination with other antiretrovirals.

TRUVADA is not approved for the treatment of chronic hepatitis B virus (HBV) infection, and the safety and efficacy of TRUVADA 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 TRUVADA. 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 TRUVADA. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Dosage and administration

- Recommended dose: one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food
- Dosing interval should be adjusted in patients with baseline CrCl <30 mL/min. Dose recommended in renal impairment: creatinine clearance (CrCl) 30–49 mL/min: 1 tablet every 48 hours. CrCl <30 mL/min or hemodialysis: do not use TRUVADA. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate renal impairment, clinical response to treatment and renal function should be closely monitored in these patients
- No dose adjustment is necessary for patients with mild renal impairment (CrCl 50–80 mL/min)

Warnings and precautions

- New onset or worsening renal impairment
  - Emtricitabine and tenofovir are principally eliminated by the kidney. Renal impairment can include acute renal failure and Fanconi syndrome
  - Assess CrCl before initiating treatment with TRUVADA. Routinely 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)
  - Dosing interval adjustment of TRUVADA and dose monitoring of renal function are recommended in all patients with CrCl 30–49 mL/min. No safety or efficacy data are available in patients with renal impairment who received TRUVADA using these dosing guidelines, so the potential benefit of TRUVADA therapy should be assessed against the potential risk of renal toxicity
  - Avoid administering TRUVADA with concurrent or recent use of nephrotoxic drugs
- Since TRUVADA contains emtricitabine and tenofovir DF, TRUVADA should not be coadministered with EMTRIVA or VIREAD. Due to similarities between emtricitabine and lamivudine, neither ATRIPLA nor TRUVADA should be coadministered with drugs containing lamivudine, including Combivir® (zidovudine/lamivudine), Epivir® or Epivir-HBV® (lamivudine), Epzicom® (abacavir sulfate/lamivudine), or Trizivir® (abacavir sulfate/lamivudine/zidovudine)
- TRUVADA should not be administered with HEPSERA
- Decreases in bone mineral density (BMD): consider monitoring BMD in patients with a history of pathologic fracture or who are at risk for osteopenia. Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of VIREAD
- Redistribution/accumulation of body fat: observed in patients receiving antiretroviral therapy
- Immune reconstitution syndrome: may necessitate further evaluation and treatment
- Triple nucleoside-only regimens: early virologic failure has been reported in HIV-infected subjects. Monitor carefully and consider treatment modification

Adverse reactions

- The most common (incidence ≥10%, any severity) and/or treatment-emergent (Grade 2–4, occurring in ≥5% of subjects) adverse reactions occurring in Study 934 through 144 weeks include diarrhea, nausea, fatigue, sinusitis, upper respiratory tract infections, nasopharyngitis, headache, dizziness, depression, insomnia, abnormal dreams, and rash

Drug interactions

- Didanosine (ddI): tenofovir disoproxil fumarate increases ddI concentrations. Consider dose reductions or discontinuations of ddI if warranted
- Atazanavir (ATV): coadministration decreases ATV concentrations and increases tenofovir concentrations. Use ATV with TRUVADA only with ritonavir; monitor for evidence of tenofovir-associated adverse reactions
- Lopinavir/ritonavir: coadministration increases tenofovir concentrations. Monitor for evidence of tenofovir-associated adverse reactions

[§]Combivir (zidovudine/lamivudine), Epivir or Epivir HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), and Trizivir (abacavir sulfate/lamivudine/zidovudine).

References: 1. TRUVADA Prescribing Information. Gilead Sciences, Inc; November 2009. **2.** Synovate Healthcare Data. US HIV Therapy Monitor. 2009; Q2. **3.** Data on file, Gilead Sciences, Inc. **4.** Sax PE; for A5202 Study Team. ACTG 5202: ABC/3TC vs TDF/FTC in patients with screening HIV RNA ≥100,000 c/mL. Oral presentation presented at: XVII International AIDS Conference; August 3-8, 2008; Mexico City, Mexico. **5.** Reyataz Prescribing Information. Bristol-Myers Squibb; April 2009. **6.** Johnson M, Grinsztejn B, Rodriguez C, et al. 96-week comparison of once-daily atazanavir/ritonavir and twice-daily lopinavir/ritonavir in patients with multiple virologic failures. *AIDS*. 2006;20(5):711-718. **7.** Molina J-M, Podsadecki TJ, Johnson MA, et al. A lopinavir/ritonavir-based once-daily regimen results in better compliance and is non-inferior to a twice-daily regimen through 96 weeks. *AIDS Res Hum Retroviruses*. 2007;23(12):1505-1514. **8.** Riddler SA, Haubrich R, DiRienzo AG, et al; for AIDS Clinical Trials Group Study A5142 Team. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med*. 2008;358(20):2095-2106. **9.** US National Institutes of Health. Clinicaltrials.gov Web site. http://www.clinicaltrials.gov/ct2/show/NCT00262522?term=Abbott+Study+730&rank=1. Accessed June 19, 2009. **10.** US National Institutes of Health. Clinicaltrials.gov Web site. http://www.clinicaltrials.gov/ct2/show/NCT00244712?term=GSK+EPZ104057&rank=1. Accessed June 19, 2009. **11.** US National Institutes of Health. Clinicaltrials.gov Web site. http://www.clinicaltrials.gov/ct2/show/NCT00242216?term=PIQD&rank=1. Accessed June 19, 2009. **12.** US National Institutes of Health. Clinicaltrials.gov Web site. http://www.clinicaltrials.gov/ct2/show/NCT00258557?term=TMC114-C211&rank=1. Accessed November 5, 2009. **13.** Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Dept of Health and Human Services; 2009. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed December 1, 2009. **14.** Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Dept of Health and Human Services; 2008. **15.** Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Dept of Health and Human Services; 2007. **16.** Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Dept of Health and Human Services; 2006. **17.** Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Dept of Health and Human Services; 2005. **18.** Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Dept of Health and Human Services; 2004.

Please see brief summary of full Prescribing Information on following page.

GILEAD

The following is a brief summary for TRUVADA® (emtricitabine/tenofovir disoproxil fumarate (DF)) tablets. Before prescribing, see full Prescribing Information, including boxed WARNINGS.

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 VIREAD® (tenofovir disoproxil fumarate), a component of TRUVADA, in combination with other antiretrovirals *[See Warnings and Precautions]*.

TRUVADA is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of TRUVADA 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 TRUVADA. 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 TRUVADA. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[See Warnings and Precautions]*.

INDICATIONS AND USAGE

TRUVADA, a combination of EMTRIVA® (emtricitabine) and VIREAD, is indicated in combination with other antiretroviral agents (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infection in adults.

The following points should be considered when initiating therapy with TRUVADA for the treatment of HIV-1 infection:

- It is not recommended that TRUVADA be used as a component of a triple nucleoside regimen.
- TRUVADA should not be coadministered with ATRIPLA® (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg), EMTRIVA, VIREAD, or lamivudine-containing products *[See Warnings and Precautions]*.
- In treatment experienced patients, the use of TRUVADA should be guided by laboratory testing and treatment history.

DOSAGE AND ADMINISTRATION

The dose of TRUVADA is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food.

Dose Adjustment for Renal Impairment: Significantly increased drug exposures occurred when EMTRIVA or VIREAD were administered to subjects with moderate to severe renal impairment *[See EMTRIVA or VIREAD Package Insert]*. Therefore, the dosing interval of TRUVADA should be adjusted in patients with baseline creatinine clearance 30–49 mL/min using the recommendations in Table 1. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV-1 infected subjects. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate renal impairment, therefore, clinical response to treatment and renal function should be closely monitored in these patients *[See Warnings and Precautions]*.

No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50–80 mL/min). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients *[See Warnings and Precautions]*.

Table 1.
Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)*		
	≥50	30–49	<30 (Including Patients Requiring Hemodialysis)
Recommended Dosing Interval	Every 24 hours	Every 48 hours	TRUVADA should not be administered.

CONTRAINDICATIONS

None.

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 VIREAD, a component of TRUVADA, 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 TRUVADA 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 HBV before initiating antiretroviral therapy. TRUVADA is not approved for the treatment of chronic HBV infection and the safety and efficacy of TRUVADA 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 TRUVADA. 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 TRUVADA. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

New Onset or Worsening Renal Impairment: Emtricitabine and tenofovir are principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of VIREAD *[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 TRUVADA. 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® (adefovir dipivoxil).

Dosing interval adjustment of TRUVADA and close monitoring of renal function are recommended in all patients with creatinine clearance 30–49 mL/min *[See Dosage and Administration]*. No safety or efficacy data are available in patients with renal impairment who received TRUVADA using these dosing guidelines, so the potential benefit of TRUVADA therapy should be assessed against the potential risk of renal toxicity. TRUVADA should not be administered to patients with creatinine clearance <30 mL/min or patients requiring hemodialysis. TRUVADA should be avoided with concurrent or recent use of a nephrotoxic agent.

Coadministration with Other Products: TRUVADA should not be coadministered with ATRIPLA, EMTRIVA, or VIREAD. Due to similarities between emtricitabine and lamivudine, TRUVADA should not be coadministered with other drugs containing lamivudine, including Combivir® (lamivudine/zidovudine), Epivir® or Epivir-HBV® (lamivudine), Epzicom® (abacavir sulfate/lamivudine), or Trizivir® (abacavir sulfate/lamivudine/zidovudine). TRUVADA should not be administered with HEPSERA.

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 treatment naïve subjects, 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 VIREAD + lamivudine (3TC) + efavirenz (EFV) compared with subjects receiving stavudine + lamivudine + efavirenz. Changes in BMD at the hip were similar between the two treatment groups. 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 VIREAD (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 VIREAD 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 VIREAD. The effects of VIREAD-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]*.

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 currently 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 TRUVADA. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

Early Virologic Failure: Clinical studies in HIV-infected subjects have demonstrated that certain regimens that only contain three nucleoside reverse transcriptase inhibitors (NRTI) are generally less effective than triple drug regimens containing two NRTIs in combination with either a non-nucleoside reverse transcriptase inhibitor or a HIV-1 protease inhibitor. In particular, early virological failure and high rates of resistance substitutions have been reported. Triple nucleoside regimens should therefore be used with caution. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

ADVERSE REACTIONS

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.

The most common adverse reactions (incidence ≥10%, any severity) occurring in Study 934, an active-controlled clinical study of efavirenz, emtricitabine, and tenofovir disoproxil fumarate, include diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. See also full Prescribing Information for the frequency of treatment-emergent adverse reactions (Grade 2–4) occurring in ≥5% of subjects treated with efavirenz, emtricitabine, and tenofovir disoproxil fumarate in this study.

Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

Study 934 - Treatment Emergent Adverse Reactions: In Study 934, 511 antiretroviral-naïve subjects received either VIREAD + EMTRIVA (emtricitabine) administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254). Adverse reactions observed in this study were generally consistent with those seen in other studies in treatment-experienced or treatment-naïve subjects receiving VIREAD and/or EMTRIVA, including diarrhea, nausea, vomiting, fatigue,

sinusitis, upper respiratory tract infections, nasopharyngitis, headache, dizziness, depression, insomnia, and rash event.

Laboratory Abnormalities: Laboratory abnormalities observed in this study were generally consistent with those seen in other studies of VIREAD and/or EMTRIVA.

Postmarketing Experience: The following adverse reactions have been identified during postapproval use of VIREAD: allergic reaction including angioedema, lactic acidosis, hypokalemia, hypophosphatemia, dyspnea, pancreatitis, increased amylase, abdominal pain, hepatic steatosis, hepatitis, increased liver enzymes (most commonly increased AST, ALT, Gamma GT), rash, rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy, 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, asthenia. No additional adverse reactions have been identified during postapproval use of EMTRIVA. 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.

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

DRUG INTERACTIONS

No drug interaction studies have been conducted using TRUVADA tablets. Drug interaction studies have been conducted with emtricitabine and tenofovir disoproxil fumarate, the components of TRUVADA. This section describes clinically relevant drug interactions observed with emtricitabine and tenofovir disoproxil fumarate.

Didanosine: Coadministration of TRUVADA and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions. When tenofovir disoproxil fumarate was administered with didanosine the C_{max} and AUC of didanosine administered as either the buffered or enteric-coated formulation increased significantly. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis, and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving tenofovir DF with didanosine 400 mg daily. In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with TRUVADA. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg. When coadministered, TRUVADA and Videx® EC (didanosine) may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with TRUVADA should be under fasted conditions.

Atazanavir: Atazanavir has been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. **Patients receiving atazanavir and TRUVADA should be monitored for TRUVADA-associated adverse reactions. TRUVADA should be discontinued in patients who develop TRUVADA-associated adverse reactions.** Tenofovir decreases the AUC and C_{min} of atazanavir. When coadministered with TRUVADA, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. **Atazanavir without ritonavir should not be coadministered with TRUVADA.**

Lopinavir/Ritonavir: Lopinavir/ritonavir has been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. **Patients receiving lopinavir/ritonavir and TRUVADA should be monitored for TRUVADA-associated adverse reactions. TRUVADA should be discontinued in patients who develop TRUVADA-associated adverse reactions.**

Drugs Affecting Renal Function: Because emtricitabine and tenofovir are primarily excreted by the kidneys, coadministration of TRUVADA (emtricitabine/tenofovir disoproxil fumarate) with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the coadministered drug. Some examples include, but are not limited to acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, and valganciclovir. Drugs that decrease renal function may increase concentrations of emtricitabine and/or tenofovir.

USE IN SPECIFIC POPULATIONS

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-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose.

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, TRUVADA should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to TRUVADA, 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-1-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1. Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. It is not known whether emtricitabine is excreted in human milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving TRUVADA.**

Pediatric Use: TRUVADA is not recommended for patients less than 18 years of age because it is a fixed-dose combination tablet containing a component, VIREAD (tenofovir disoproxil fumarate), for which safety and efficacy have not been established in this age group.

Geriatric Use: Clinical studies of EMTRIVA (emtricitabine) or VIREAD 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.

Patients with Impaired Renal Function: It is recommended that the dosing interval for TRUVADA be modified in patients with creatinine clearance 30–49 mL/min. TRUVADA should not be used in patients with creatinine clearance <30 mL/min and in patients with end-stage renal disease requiring dialysis *[See Dosage and Administration]*.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Emtricitabine: In long-term oral carcinogenicity studies of emtricitabine, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg/kg/day (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (31 times the human systemic exposure at the therapeutic dose).

Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.

Tenofovir Disoproxil Fumarate: Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

Tenofovir disoproxil fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, tenofovir disoproxil fumarate was negative when administered to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

PATIENT COUNSELING INFORMATION

Patients should be advised that:

- TRUVADA is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using TRUVADA.
- The use of TRUVADA has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination. 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 to never re-use or share needles.
- The long term effects of TRUVADA are unknown.
- TRUVADA tablets are for oral ingestion only.
- It is important to take TRUVADA with combination therapy on a regular dosing schedule to avoid missing doses.
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with TRUVADA 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]*.
- All patients with HIV-1 should be tested for 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 TRUVADA.
- Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported in association with the use of VIREAD. TRUVADA should be avoided with concurrent or recent use of a nephrotoxic agent *[See Warnings and Precautions]*. Dosing interval of TRUVADA may need adjustment in patients with renal impairment *[See Dosage and Administration]*.
- TRUVADA should not be coadministered with ATRIPLA (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg), EMTRIVA, or VIREAD; or with drugs containing lamivudine, including Combivir (lamivudine/zidovudine), Epivir or Epivir-HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), or Trizivir (abacavir sulfate/lamivudine/zidovudine) *[See Warnings and Precautions]*.
- TRUVADA should not be administered with HEPSERA (adefovir dipivoxil) *[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 at risk for osteopenia *[See Warnings and Precautions]*.

*Calculated using ideal (lean) body weight.

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HIV SPECIALIST
PATIENT CARE, PRACTICE MANAGEMENT & PROFESSIONAL DEVELOPMENT INFORMATION for HIV CARE PROVIDERS
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Letter from the DIRECTOR

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

Strategy for The Second Decade

AS I FLY BACK EAST ON THE 'REDEYE,' I am reflecting on our Membership reception and our Board meeting of the last two days in San Francisco. We heard from Jeff Crowley, the director of the Office of National AIDS Policy at the White House, and Michelle Roland, the director of the AIDS Office for the State of California at our reception. The major take away? We've come so far and yet we still have so far to go.

Jeff spoke of the continuing Federal budgetary support in the President's 2011 Budget for HIV/AIDS, though not as much as we all needed—and Michelle spoke of the budgetary crisis in California and the enormous impact it is having on the critical delivery of HIV services in the state. Jeff spoke about the development of a National Strategy for HIV/AIDS, which he hopes to deliver in May/June of this year, and Michelle spoke of the difficulty in implementing a strategic approach to HIV/AIDS when resources are in such short supply.

James Friedman

What was clear from both of their presentations is how fortunate the field is to have such committed individuals in such important positions.

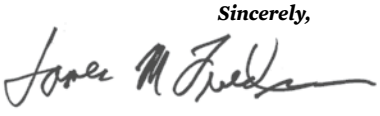
Nearly 30 years ago AIDS was an unknown deadly disease that mostly killed a stigmatized segment of our society. Today the stigma has lessened and our patients live much longer. But now the co-morbidities of aging are further complicating their care, the numbers of newly infected remain constant in spite of our efforts, and one third of our practitioners will leave the field over the next decade. While the yin and yang of success and problems continues, the challenges have evolved and so must we.

At our Board meeting, we began to address the necessary evolution of the Academy. A decade ago Dr. Scott Hitt and several other visionaries founded the American Academy of HIV Medicine—with a mission to improve the quality of care to HIV/AIDS patients. Over the past decade, continuing medical education, the *Fundamentals of HIV Medicine*, and the credentialing of HIV practitioners have become the mainstay of the Academy and central to the practice of quality HIV care. Thousands of copies of *Fundamentals* are in print and nearly 2000 practitioners are currently credentialed as *HIV Specialists*.

Now, as the Academy enters our second decade of supporting HIV care providers, the Board has decided to begin the process of considering how we must adapt to address the set of challenges we now face. Over the next six months, the past and present Board chairpersons, including the current vice chair, will undertake an assessment of our mission, our structure and our strategic direction; and from that assessment, develop a set of recommendations—a Strategy for The Second Decade. As a part of that effort, we will survey you, our members, as to how and what the Academy should do over the next decade to better meet your needs and interests. In addition, I urge you to write to me with your thoughts at jfriedman@aahivm.org. While I can't promise we will implement every suggestion, I will promise that every submission will be read and considered.

It is our expectation that the Academy will adjust to the challenges, further develop our Referral Link (see page 26) to help make routine testing a reality, expand the breadth and depth of our new magazine, replenish the HIV workforce, and find new ways to improve quality of care. In short, increase the "Yin" and diminish the "Yang" of HIV medicine. HIV

Sincerely,



James M. Friedman, MHA
Executive Director
American Academy of HIV Medicine

BY JEFFREY T. KIRCHNER, DO, FAAFP, AAHIVS

Delayed HIV Testing: Missed Opportunities, Missed Prevention

RW IS A 48-YEAR-OLD CAUCASIAN MALE with a history of hypertension, gastroesophageal reflux disease, psoriasis, and sero-negative arthritis. He had been seeing his family physician for about five years, and also had been under the care of a dermatologist and rheumatologist for approximately two years for his skin and rheumatologic conditions.

RW had a history significant for "occasional" IV drug use when he would consume alcohol, but while he had not used any IV drugs since about age 40, he still consumed alcohol every day. He also admitted to having at least 10 lifetime female sexual partners, including several that he "did not know," one of whom, he had been told, was HIV positive. However, RW had never undergone HIV testing — despite noted risk factors and numerous physician encounters. When asked why he was not tested, he said he had generally viewed himself as "healthy" and did not want to have to deal with the possibility of having HIV.

In August 2007, RW presented to his family physician complaining of fatigue, joint pains, frequent bouts of diarrhea over the past four weeks, and an approximately 15 pound weight loss. His physician obtained a CBC, Chemistry panel, thyroid function studies, and stool cultures, all of which were normal or non-diagnostic. At RW's second visit, his physician, based on "prior" risk factors and persistence of recent symptoms, suggested HIV testing. The patient agreed and one week later his ELISA and subsequent Western Blot were both positive, and he was referred to me for HIV consultation. His initial CD4+ count was 237 cells/mm3 and his HIV-RNA level was 69, 325 copies/ml. Also of note, a baseline genotype test revealed a K103N mutation.

The patient had been in an active relationship with a 44-year-old female for the past six months and they had been sexually active for approximately three months. Upon learning of his HIV status, his female partner was subsequently tested and was also positive. Her initial CD4+ count was 978 cells/mm3 and HIV-RNA level was 7,656.

RW was started on a protease inhibitor-based antiretroviral regimen and had an excellent virologic and immunologic response. His partner, whom he subsequently married, has been offered therapy but has decided to wait as her baseline and follow up CD4+ count were both > 800 cells/mm3 and she is otherwise healthy. Not unexpectedly, her baseline genotype also showed a K103N mutation.

MISSED OPPORTUNITIES FOR HIV TESTING

This patient (RW) had multiple visits to his primary care physician and, as noted, saw both a dermatologist and rheumatologist on several occasions. He also had numerous visits to Occupational Medicine for work-related injuries. But RW told me that he was not asked, nor did he request, HIV screening during these medical encounters with four different physicians – even though many of these visits occurred after September 2006 when the CDC began recommending routine opt-out HIV screening.

Ideally, both partners should have been tested at the time they decided to become sexually active as they had been in prior sexual relationships. In addition, RW's wife had seen a nurse practitioner at her primary care practice for a routine PAP/Gyn exam in May 2007 and was not offered HIV screening.

Fortunately, RW remains clinically well on combination ARV therapy, but if one of his physicians had offered HIV testing, a second case could have been easily avoided. Many similar scenarios have been reported or experienced by physicians and patients. Physicians need to do a better job with opt-out testing, and we need to encourage our patients to not be fearful of requesting an HIV test from their healthcare providers – regardless of specialty. HIV

About the Author: Dr. Jeffrey Kirchner is Medical Director–Comprehensive Care Center for HIV at Lancaster (PA) General Hospital. He is on AAHIVM's Board of Directors and is chair of *HIV Specialist*'s Editorial Advisory Group.

BY LEONARD B. JOHNSON, MD & SHARON E. VALENTI, CNP, AAHIVS

Routine Testing: Not So Fast

ST. JOHN HOSPITAL & MEDICAL CENTER in Detroit implemented a pilot program to offer free HIV testing to all internal medicine and adolescent patients, between the ages of 13-64, who attended a hospital-associated, outpatient clinic between August 1 and December 31, 2007.

Our purpose was to evaluate the acceptance of rapid HIV testing among general medical patients when offered to them, free of charge, during their regularly scheduled office appointment. Secondly, we wanted to evaluate how non-HIV physicians, residents and other office staff responded to adding this additional task to the patient's routine office visit.

In 2006, the seroprevalence of HIV among approximately 12,000 of our hospital's inpatients who were tested for HIV was 1.6 percent. Because of this high inpatient seroprevalence, we wanted to determine if our outpatient clinic population had a comparable HIV seroprevalence. Thus, we applied for funding to implement a pilot program in our outpatients clinics.

This project was a non-randomized evaluation of the process, implementation and outcomes of a small group of patients who agreed to be HIV tested during our pilot program. The clinical settings were two general, internal medicine clinics and one adolescent clinic; few such sites are reported in the literature as sites for routine HIV testing. Most outpatient HIV screening is being done through Emergency Departments (EDs), STD and OB/GYN clinics. The results of our program cannot be generalized to these settings.

During the pilot period there were over 6,125 unduplicated outpatient visits; of these, 587 patients (10 percent) were asked if they wanted a free HIV test. Of the 587 patients, 69 percent (n=406) agreed to be tested. Patients who agreed to test were predominantly female (70.7 percent; a rate of 2.5 x that of males); African-American (AA), (73.4 percent); and, of younger age (67.3 percent; between 25 and 44 years). One person (0.0024 percent) was found to have a positive test for HIV using the OraQuick® ADVANCE™ Rapid HIV-1/2 Antibody test and subsequently tested positive on Western Blot.

RESULTS

Non-HIV physicians agreed it is important to screen for HIV infection in primary care; but confusion over reimbursement of HIV screening abounds, leaving many physicians reluctant to implement it routinely. Some residents felt "inadequate" to counsel patients about HIV infection. Despite assurances that pre-HIV counseling was unnecessary before the patient was screened for HIV, the possibility a patient might ask an HIV question – one they were not prepared to answer – deterred some from asking patients to be tested. Finally, on busy office days, nursing/intake assistants and physicians alike were more reluctant to ask patients if they wanted a free HIV test as they felt there was insufficient time to include this extra task.

In conclusion, we agree with CDC's recommendation to implement rapid HIV screening in areas of high HIV prevalence (>0.1 percent of the population). However, routine testing of "all patients" even in areas of high HIV prevalence, should be evaluated carefully and weighed against the cost of testing (test kits; salary costs; training staff in POCT, training residents and non-HIV physicians in HIV 101; and other potential costs of follow-up); and, the rate of return on successfully identifying patients as HIV positive.

In our program, African-Americans and women were more likely to accept testing compared to other groups. Clinicians should be aware, despite their best efforts, certain groups may be more willing than others to accept HIV testing.

Lastly, STD clinics, OB/GYN clinics, EDs, homeless shelters, or neighborhoods with high rates of parolee returns, may be examples of places where individuals are at a higher risk for HIV exposure, and thus, where we should be investing healthcare dollars for routine HIV screening. HIV

About the Authors: Leonard B. Johnson, MD is Program Director for Infectious Disease Fellowship Program at St. John Hospital & Medical Center. Dr. Johnson was Principal Investigator for the pilot study *Rapid HIV Testing in Primary Care* (STJH&MC, 2007).

Sharon E. Valenti, CNP, AACRN, AAHIVS, has been an HIV/AIDS Nurse Practitioner since 2000. She has provided HIV education to nurses in Tanzania, Africa and served on the President's Advisory Council on HIV/AIDS. Ms. Valenti works at St. John Hospital & Medical Center specializing in HIV/AIDS. She was Manager/Coordinator for the pilot study, *Rapid HIV Testing in Primary Care* (SJH&MC, 2007).

Editor's Note: *Marcelo Venegas-Pizarro, MD, AAHIVS, medical director for the Designated AIDS Clinic at Lutheran Hospital in Brooklyn, New York, went to Haiti shortly after the devastating earthquake struck to help treat patients there. For eight days, he worked side-by-side with other medical professionals from the U.S. and Haiti.* **This is his story:**

WE ARRIVED IN PORT-AU-PRINCE AMIDST THE RUINS OF THE EARTHQUAKE OF JANUARY 12 THAT STRUCK HAITI, killed more than 230,000 people, and shocked the world. As if already being the poorest country in the Western hemisphere was not enough, this country was utterly devastated, with thousands of people in the streets afraid of going back inside their homes – if those homes even existed any more.

All around us, buildings were collapsed. Handmade signs that read "We Need Help… food, water, medications," could be seen every couple of blocks. Makeshift tents of sheets strung across wooden poles dotted the streets, providing a semblance of shelter.

As we drove through the dust, we saw the colorful "tap-tap" buses that still, almost miraculously, provided a means of transportation. The presence of US Marines and UN "blue helmets" was evident from the airport to the main hospital.

Edner Boucicoult received us in Port-Au-Prince, as we had flown into Santo Domingo, Dominican Republic and were driven to Haiti by a Dominican colleague. Edner is on the Haitian National AIDS Coordinating Committee (CCM), and works as the communications director for Cecosida, a small Haitian organization that promotes HIV issues in the Haitian media. He would become our guide and liaison to the makeshift clinic of PHAP+, a coalition of Haiti-based AIDS groups led by people

BY MARCELO VENEGAS-PIZARRO, MD, AAHIVS

'Completely Out of Tears'

AN HIV SPECIALIST ON THE GROUND IN HAITI:

living with HIV/AIDS. We would help establish an open air clinic with awnings to cover the waiting areas and consult rooms, as well as house the many medications we carried with us. This is where we would work during our time in Haiti.

HUNGER, TENSIONS, BUT RESILIENCE

I arrived with friend and fellow physician, Jen Kasper, MD, a pediatrician at Massachusetts General Hospital and vice president of Doctors for Global Health. As an internist, I was glad to have her there.

It seemed as if "life went on" with relative ease and calm as people lined up for food rations, water or money or at Western Union offices for money from relatives abroad. However, hunger was growing and tensions rising as it quickly became evident that food and supplies were not getting to the people quickly enough. Still, the resilience and perseverance of the Haitian people was evident as they set up their "homes" in newly formed tent cities alongside roads, in parks, golf courses or plazas, even as earth tremors were felt daily, reminding everyone what had caused the many calamities that had shaken their lives.

We came from New York with a group from Housing Works, the largest AIDS-based community organization in the United States. Housing Works has a long and arduous history of AIDS advocacy and has worked for more than two years with PHAP+. Charles King, Housing Works president, arrived in Haiti four days after the earthquake with Dr. Vaty Poitevien, a Haitian HIV physician, with whom I previously practiced, and

Left — Dr. Venegas-Pizarro, Sourel (admin), Sophie (translator), Saitha, RN, Kerline, RN, Carlton (translator). Bottom: Edner Boucicoult (admin). *Above* — A demolished building in the Delmas area of Port-Au-Prince

'Completely Out of Tears'

AN HIV SPECIALIST ON THE GROUND IN HAITI:

Below — Top row: Dr. Jennifer Kasper, Sophie (translator), Saitha, RN, Bottom row: Sourel (admin.), Kerline, RN, Karina, Madame Marie Rose. *Right* — Dr. Venegas-Pizarro with translator, Clara and patient. *Far Right* — "We Need Help" sign outside Primary Care Clinic in Delmas.

who had lost both of her parents in the earthquake. They had brought suitcases of medications and supplies that helped stock the PHAP+ clinic.

BUILDING A CLINIC, PATIENTS WAITING

The afternoon we arrived, Dr. Kasper and I inventoried all the medications and prepared the outlay of the HIV/AIDS clinic with Haitians from the HIV association, PHAP+. That evening we set up our tent alongside Edner's family in the rear of an HIV/AIDS associated government building. With no electricity or running water, conditions were difficult. But Edner's mother, Simone, made sure we had coffee every morning before leaving to see patients. We arrived at the clinic with over 50 patients waiting, a number that would grow as word of the PHAP+ clinic began to spread.

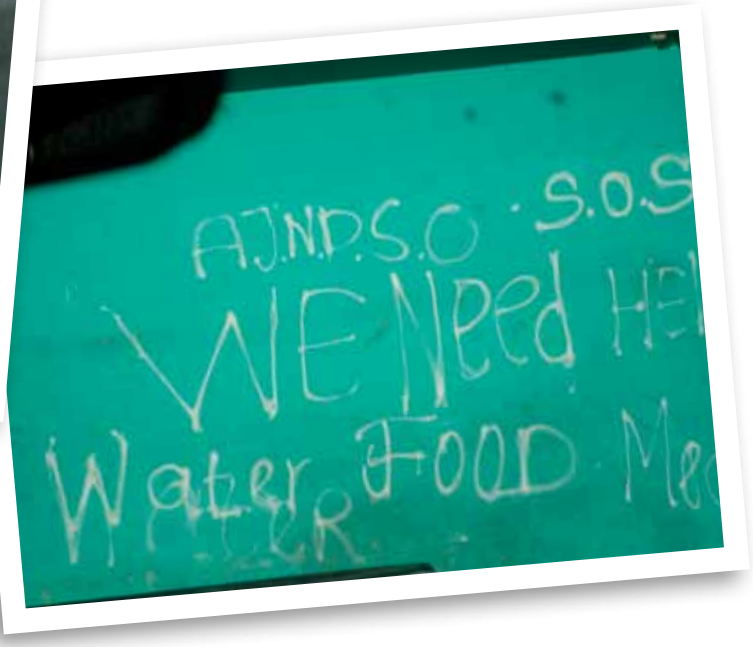
I do not speak Kreyole and so I worked with several interpreters. The first was Carlton, a young man who I later learned was from Miami and who had lost an uncle and a younger nephew in the earthquake. This was his way of giving back. We saw all kinds of patients: children and adults, many with trauma injuries from the first hours of the earthquake that not been attended to, or who had not received follow-up care. We saw many people with fractures, including children who had not received medical attention either because of lack of transportation or because the hospitals were already filled with traumatic injuries and amputations.

Many of the patients we saw had wound infections from lacerations or abrasions from debris falling on them during the earthquake. We also attended to many patients with more common primary care problems, from gastritis to headaches and hypertension. We saw people with diarrhea, upper respiratory infections, vaginitis, urinary tract infections and general malaise. We sent many with trauma injuries to the main hospital with a small note requesting either an x-ray or follow-up care. Often, patients returned the next day, x-rays in hand, wounds bandaged, and dazed from having lost family members and loved ones. The grief was vivid and often overwhelming.

We had patients triaged by the nurses and then we wrote brief notes in makeshift medical records — paper stapled to manila folders. The days went by so quickly. Hunger was real and prevalent; emotions were raw.

I recommended to one young woman that she take an antibiotic with food. As tears rolled down her cheeks, she quietly told me she had not eaten in two days. My translator became emotional, and I had to get up as I felt my own eyes fill with tears. I went to get the antibiotic and my bag for whatever power bars I had left, and gave them to her. I looked into the waiting area and everyone looked thirsty and hungry. How could we feed them all? And the hungry children...? I thought of my own children back in the States.

The next day we brought in some snacks and water to the patients who were waiting, and it was quickly gone – includ-



ing the few power bars and food that Dr. Kasper and I had brought with us. I kept asking: Where is all the foreign aid? Where are all the tents? What will become of our patients once the rainy season starts?

We saw many patients who belonged to the HIV associations who were there for medical reasons other than HIV. They had gone more than a week without anti-retroviral therapy, mostly first line therapy of an NRTI plus NNRTI. We gave what little we had of Lamivudine, AZT, Nevirapine and Efavirenz to hold patients over from two weeks to a month. But when would these patients eventually get their regular supply of medications? And if not, how quickly would resistance mount particularly to the NNRTI's? We dispensed as much Bactrim as we could to patients with CD4's less than 200. Madam Marie Rose, an adherence counselor with the HIV associations, seemed to personally know all the HIV-positive patients and identified all those who had an AIDS diagnosis.

In treating all these patients, we were never alone. We had the support of all the translators: Pierre Paul, Sophie, Carlton and Clara. We relied on the nurses, Saitha and Kerline, and counted on the assistance of Sourel, who helped us take patients to the clinic. Then, there were the other physicians: Dr. Petit Frere, working out of the sister clinic sponsored by Diaspora Community Services, New York, NY, and Dr. Gerson Sergio Jeudi, from Promoteurs Objectif ZeroSIDA. They stayed behind to work at the clinic in Haitia after Dr. Kasper and I eventually left. We were replaced by Dr. Marie Nomil, an internist from Maimonides Hospital in Brooklyn, NY and many other medical providers who answered the call to help those most in need in Haiti.

GET THE SUPPLIES TO THE PEOPLE!

As this is written in February, the PHAP+ clinic is still serving patients and we continue to support it with medications and anti-retrovirals from groups such as AID for AIDS in New York, as well as local HIV pharmacies in New York, NY, that have donated much needed antibiotics and medical supplies.

The issue continues. The aid is there, but it is not getting to the people who are still going hungry. I visited the airport during my stay and walked on the tarmac through rows of containers with supplies that were just not being taken to the people who needed them. The experience I had in Haiti was by far one of my toughest, even though I have worked in many places including Guatemala, El Salvador and Mexico. I am still amazed by the resolve and strength of the Haitian people.

I became good friends with Edner Boucicoult, who described the first minutes after the earthquake as he ran like a "madman" down the street to the house where his baby daughter was staying, and after finding her in safety, broke down in tears. By the time I left, he wrote in a Housing Works blog that he was "completely out of tears" from all the suffering he had seen from his people – from piled up bodies to the devastation of his city. He plans to help in the reconstruction and is currently administering the PHAP+ clinic and coordinating all the relief and support effort.

This article is dedicated to Edner and his beautiful family, along with all the Haitian people who continue the day-to-day struggle for survival and dignity. HIV

About the Author: Marcelo Venegas-Pizarro, MD, AAHIVS, is medical director for the Designated AIDS Clinic at Lutheran Hospital in Brooklyn, New York. He is an HIV Specialist™ and an AAHIVM member. He previously worked for Housing Works as the Chief Medical Officer. ***If you are interested in donating money or volunteering your time in Haiti please sign up at www.housingworks.org.***

HIV Testing = PREVENTION

BACKGROUND

HIV Specialists:

BY BOB GATTY

IN THE STATE OF MASSACHUSETTS, the Department of Public Health estimates 21 percent of the 25,000 to 27,000 people infected with HIV in the state do not know their status, and that 31 percent of recently diagnosed persons are found to have progressed to AIDS within two months of entering care.

That reality in Massachusetts reflects the situation across America. According to the Centers for Disease Control and Prevention (CDC), an estimated 1,106,400 adults and adolescents are living with HIV nationwide, but 21 percent are unaware of their infections.

And so, the disease continues to spread with 53,000 Americans becoming newly infected with HIV each year – one new infection every nine and one-half minutes. Testing and diagnosis is the key to slowing that spread, the experts say.

"The sooner we can get people diagnosed and into care, the more likely we can extend their lives and allow them to live healthy lives," said Carole Hohl, PA-C, AAHIVS, director of HIV services at Boston's Healthcare for the Homeless Program. "We need to get people to know if they are infected. Identifying people infected is shown to decrease their risky behaviors, and getting folks into care will decrease their infectivity if they get treatment."

Hohl was one of more than 100 AAHIVM members who responded to an *HIV Specialist* survey regarding HIV testing and screening. Of those respondents, 43.9 percent estimated that less than 10 percent of patients in their community are being routinely tested for HIV in general practice settings. Only 10.2 percent estimated more than 50 percent of patients were being tested routinely.

By far the majority, 79.8 percent, said rapid tests, now in use in many settings, are helping to increase the percentage of patients tested, but even though the results are available in minutes, many did not see such tests as a cure-all for the testing problem.

Of course, providing a linkage to care for newly diagnosed HIV patients is important to both the frequency of testing and their ultimate outcomes, and 75 percent of respondents said that in their community there was some resource to connect patients to care. But all too often, that linkage appears to be informal at best, often based on the reputation of local HIV healthcare providers.

Positives are Clear. But Impediments Exist.

CATCHING MORE INFECTED PATIENTS CAN HELP SLOW THE SPREAD OF THE DISEASE. BUT THERE ARE REALITIES THAT MUST BE FACED; ANSWERS THAT MUST BE FOUND.

BARRIERS REMAIN

While the CDC is encouraged by the increased numbers of tests that have taken place since its 2006 recommendations were released (see interview with the CDC's Dr. Bernard Branson on pg. 14), major challenges remain in the effort to convince providers in general healthcare settings to include HIV tests routinely for patients.

Such barriers have been identified as insufficient time, complexity of the consent process, lack of knowledge and training, language differences, lack of patient acceptance, pretest counseling requirements, competing priorities, and inadequate reimbursement. Of course, the CDC's recommendations were intended to remove some of those barriers, such as pretest counseling and complexity of the consent process, but the extent of implementation across the nation still remains inconsistent.

Marshall Kubota, MD, AAHIVS, a family practitioner who treats HIV/AIDS patients in Santa Rosa, CA, points out that until 2007 California required written consent forms before a patient could be tested for HIV. But the law changed, and now a written document is not required, except in cases where patients refuse testing.

"It (test frequency) might have improved marginally," Dr. Kubota told *HIV Specialist*. "But I think it is being applied with a great deal of variance in the many different healthcare centers across our state. Local culture and prevalence of HIV/AIDS also affects the frequency of testing."

The issues of cost and time involvement are major factors, according to Dr. Kubota, who believes that the CDC's recommendation for universal screening of patients 13-64 are probably unrealistic, and, he says, the use of rapid tests can play into those problems.

"There is a place for rapid tests, such as in emergency rooms and in-patient settings," he said. "But I consider that test to be a diagnostic test to be used in acute situations. It is expensive compared to regular testing, and it takes up staff time. We are asking outpatient offices to do routine testing and we don't expect a high percentage of positives. We're asking physicians' offices and clinics to do a very large number of tests for very little return. It is not worth the time and the money to test 998 people for two positives."

However, he stressed, "if you're suspicious, that's different. That's not routine testing, that's diagnostic."

Dr. Kubota's practice receives referrals from hospital emergency rooms and other testing sites, so by the time patients reach him for care they are already confirmed positive. "Still, about 40 percent are late diagnoses," he said. "We get referrals because we are well-known in the community. But there is no automatic linkage, and there is no assurance that a referral will end up with a visit. So the loop is not necessarily closed."

Photo Sebastian Czapnik / Dreamstime

HIV Testing = PREVENTION

BACKGROUND

THEN WHY SCREEN?

Sharon E. Valenti, an HIV/AIDS nurse practitioner and HIV Specialist™ at St. John Hospital & Medical Center in Detroit, MI, firmly believes that routine testing should be offered to everyone, but she agrees the problem of reimbursement is a major impediment.

Carole Hohl

"In a nutshell, for non-HIV doctors, the question of offering 'routine' HIV testing to every patient will be difficult to accomplish; rather the decision to offer testing will most likely be highly subjective as to who should be tested. But, still more importantly, the issue of reimbursement looms large," she said. "How many already overworked and understaffed doctors will perform another test if they aren't going to be reimbursed for it?" (See Frontlines by Sharon Valenti & Leonard B. Johnson, MD, page 5)

But, Valenti said, routine testing is "critical" because:

- Individuals need to know their own HIV status to protect themselves and others
- Identifying positives earlier will get them into care and treatment earlier
- We HAVE to decrease the stigma associated with HIV infection, and one way to do it is to be sure everyone is tested without discrimination, which will help avoid 'judgment calls' on who should be tested by physicians and mid-level providers
- The cost: millions of dollars in care and lost wages for HIV treatment will ultimately be reduced by preventing the infection from occurring in the first place. "Research has shown that individuals who know their HIV status are more likely to decrease risk behaviors. "

Marshall Kubota

At Boston's Healthcare for the Homeless Program, while the state of Massachusetts wants every patient to be offered an HIV test, signed consent forms are still required. "It's just another thing for the provider to do, just one more piece of paper that you have to deal with, and just that much more time you have to spend," the program's HIV director, Carole Hohl, observed.

But there, they are aggressively sending counselors to shelters – 25 to 30 of them – to speak with potential patients, and then when someone tests positive, connecting them with care at one of the many clinics in the city or at the program facility itself.

"Having the rapid test is huge so we don't have to track people down to get the results to them," Hohl said. "Still we use the other tests when necessary. And whenever we're giving the results, we want to have a mental health provider or at least a medical practitioner there to provide support for the patient if it's needed. Almost all of our sites do have a clinical person available, so we can do the rapid testing." There, the cost of the tests is covered by a grant from the state health department or Medicaid.

"Our patients are very, very sick people who have a huge number of serious medical problems," Hohl explained. "Plus, the amount of mental illness is huge. It is a challenge."

The Comprehensive Care Medicine (CCM) for HIV program at Lancaster General Health, Lancaster, PA, has been offering free rapid HIV testing with the Ora-Quick™ HIV 1-2 test since July 2008. A grant through the Lancaster General Health Foundation covers the cost of the test, staffing time, and advertising, according to Jeffrey Kirchner, DO, AAHIVS, medical director.

"Anyone who desires a test is able to simply walk in without an appointment," Dr. Kirchner explained. "During the first 18 months, CCM has tested over 400 persons and had six positive results, which is well above the CDC prevalence threshold of 0.1 percent that a community should have to continue routine HIV screening. We hope to eventually offer testing on a daily basis." Originally, tests were offered one-half day per week, but additional grant funding has allowed expansion to two afternoons each week.

SPREAD THE WORD

In Brooklyn, Dr. Alan J. Stein, an infectious disease specialist and solo practitioner, sees upwards of 60 patients each week in a 550-patient practice, about 80 percent of whom have HIV or AIDS. In his community, he estimates that less than 10 percent of patients who visit general health care facilities are tested.

"On the part of practitioners, there isn't any initiative to make them aware of the need to screen patients," he explained. "In New York, we still have to fill out the forms and do the pre-test counseling, and we don't have the opt-out policy as recommended by the CDC. I can't just order an HIV test for a patient."

Dr. Stein says he does not believe that most physicians and

other health care providers are aware of the benefits of early detection in terms of limiting the spread of the infection to others, or that the probability of restoring the immune system to normal with treatment is greater the earlier therapy begins – or that the longer treatment is delayed, more long-term consequences such as cardiovascular, liver and kidney diseases and malignancies can result.

"If doctors don't know what to do if a patient tests positive, then they are less likely to suggest that a patient be tested," Dr. Stein acknowledged. "And a lot of patients may not follow-up if there is no system to link them to care." He receives his patients largely because he is well known in the community.

"But there are a lot of people who just don't perceive themselves to be at risk," he said. "I have female patients who have sex with just one partner, but they are unaware that he is having unprotected sex outside the relationship or using drugs, and that he is positive. So they end up with AIDS. You don't have to be doing anything risky in order to be at risk."

Alan Stein

TESTING IN PREGNANCY

There is much to be said for universal screening and removal of any risk-based requirements, says Judy Levison, MD, AAHIVS, an obstetrician-gynecologist who treats HIV and AIDS patients at the Northwest Health Center at the Baylor College of Medicine in Houston, TX.

Since 2000, Dr. Levison has delivered upwards of 300 babies, and half of the mothers who were tested HIV positive learned of their status because Texas requires universal screening of pregnant women.

"At least they had a reason to get tested," Dr. Levison said. "Many of them have friends who have HIV and don't know it because they don't think they have a reason to be tested. That just emphasizes how important it is to make screening commonplace."

With routine testing in pregnancy and treatment of women known to have HIV, transmission from mother to baby has been slashed from 25% to less than 1%. For pregnant women with limited or no prenatal care, the rapid tests are especially important for proper treatment, Dr. Levison pointed out, noting that delays caused in receiving the results of an ELISA and then the wait for confirmation from the Western Blot can often mean that a woman may deliver before the results are known.

"In those instances we have reduced the opportunity to prevent transmission to the baby," she said. "Had we done a rapid test in labor, we could have found out the results in a couple of hours and the patient could have been started on intravenous AZT in labor and the baby on an AZT syrup within the first 12 hours after birth. By doing that you cut the likelihood of transmission from 25 percent to 10 to 12 percent. So the rapid test is very important to us."

AGE LIMITATIONS

Not only does physician assistant J. Wesley Thompson, AAHIVS, support universal testing and the use of rapid tests, he firmly believes the CDC's recommendations should not be limited to persons 13–64, contending that many people today are sexually active under age 13 and well beyond age 64. He works in a hospital-based outpatient clinic in Charlotte, NC, operated by Carolinas Healthcare System.

"I have a Mrs. Jones who goes to a large Pentacostal church here in Charlotte," Thompson said. "You would not think she would be engaging in any form of risky behavior. But at age 80 she was diagnosed with HIV. She was infected by a younger man, age 70, who apparently was able to show his love to her and others by the miracle of Viagra. You wouldn't think that Mrs. Jones and Mr. Smith would be doing things from which you could contract HIV. But they were."

"Ages 13-64 does not even scratch the surface," Thompson contended. "By 2050, 50 percent of everyone with HIV will be over 50. So the graying of this epidemic is a very real observation based on CDC estimates. Every year I see people coming in who are supposedly monogamous couples and one of them is showing up positive – both straight and gay and every variation in between."

Clearly, the issue of expanding testing, of making screening commonplace in healthcare settings that are routinely visited by patients, is a complex one. The CDC's 2006 recommendations are intended to help achieve that objective, to help prevent the further transmission of the disease.

But there are realities on the frontlines of care that must be faced, and as Dr. Kubota, and nurse practitioner Valenti and others have pointed out, the realities of time and reimbursement must be resolved before that goal will be achieved. HIV

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

HIV Testing = PREVENTION

COVER STORY

The CDC's Dr. Bernard Branson: "Let's Normal

Editor's Note: *Just over three years ago, the U.S. Centers for Disease Control and Prevention (CDC) issued revised testing recommendations to increase HIV testing in health care settings. A major recommendation was that separate written consent not be required for patients to be tested for HIV. Since then, many changes have taken place in physicians' offices, clinics, emergency rooms, and other health care settings across the nation. For an assessment of these developments and the progress that has occurred, HIV Specialist editor Bob Gatty spoke with Dr. Bernard Branson, the CDC's chief architect of the recommendations.* **Here is his report:**

MORE THAN 80 MILLION PEOPLE REPORTED THAT THEY WERE TESTED FOR HIV IN 2009, a dramatic increase from the 71 million in 2006 when the Centers for Disease Control and Prevention (CDC) revised its recommendations with the objective of making the tests about as commonplace as having your blood pressure checked.

Dr. Bernard Branson, who led CDC's effort to update its guidelines for HIV testing that were published in September 2006, says testing levels — as reported in the CDC's National Health Interview Survey — are continuing to increase, a development that will help reduce the impact of HIV on patients' lives if they obtain needed medications, treatment and care.

But the key is HIV testing, which is integral to early diagnosis, prevention, treatment and care. For a patient to be treated and progression to AIDS prevented, the reality of the condition must be known. Knowledge of HIV status is critical if spreading the disease is to be prevented and if risky behaviors are to be modified. With early knowledge of HIV status, HIV positive individuals can be linked to medical care and services that can reduce morbidity and improve quality of life. Helping to assure such linkage to care is a major initiative of the American Academy of HIV Medicine (AAHIVM).

MILESTONES TO SUCCESS

Shortly after the guidelines were published in 2006, a consortium of emergency departments, many of them associated with academic institutions in the inner city, worked together to develop new standards based on the recommendations. "When they were polled last summer, 22 of the 30 had established some sort of HIV screening," Dr. Branson reported. "That's pretty good. I don't want to claim that universal screening is in place, but we are definitely moving in that direction."

Another major positive development occurred in 2008 when Congress allowed the Veterans Administration to change its policies to make HIV testing part of routine care. Previously, Dr. Branson explained, federal law required the VA to obtain a signed informed consent form

Photo Sebastian Czapnik / Dreamstime

Make Testing & Routine”

BY BOB GATTY

before a patient could be tested, and the agency was not permitted to conduct HIV screening programs without specific appropriations by Congress.

But with the change in the law, new implementing regulations became final in July 2009. Then, on August 17, the VA issued a directive stipulating that all of the agency's facilities are now responsible for providing HIV testing as part of routine care. Now, only verbal informed consent by patients is necessary instead of the written permission that had previously been required.

“HIV testing in the VA system is part of routine medical care, as recommended by the U.S. Centers for Disease Control and Prevention,” states the agency's policy on confidential HIV testing. “All patients who do not have documentation of an HIV test in their health record should be tested for HIV at the first reasonable opportunity, provided they consent.”

“Because the VA is one of the nation's largest health care providers, that's a pretty significant development,” observed Dr. Branson.

Meanwhile, at the Centers for Medicare and Medicaid Services (CMS), another important policy change was announced last December when the agency said it will cover HIV screening for women who are pregnant and Medicare beneficiaries of any age who are at increased risk for the infection and voluntarily request the service.

“Today's decision marks an important milestone in the history of the Medicare program,” said U.S. Health and Human Services (HHS) Secretary Kathleen Sebelius. “Beginning with expand-

HIV Testing = PREVENTION

COVER STORY

> "I think with the discussion and the attention that this has received, awareness has been raised and we've seen very steady progress, with all the hallmarks that HIV screening is gaining widespread support."

ing coverage for HIV screening, we can now work proactively as a program to help keep Medicare beneficiaries healthy and take a more active role in evaluating the evidence for preventive services."

"Every adult should know his or her HIV status," said Dr. Howard K. Koh, HHS assistant secretary for health. "This decision by Medicare should help promote screening and save lives."

While Dr. Branson acknowledged that there are not "a huge number" of Medicare patients at risk of HIV, the development is significant because, he explained, "when Medicare takes a step and makes a procedure eligible for reimbursement, it sets the bar for other insurance companies." Approving reimbursement for HIV screening will encourage more providers to offer it and more patients to accept it, he said.

Another big boost for routine HIV testing came when the American College of Obstetricians and Gynecologists, and subsequently the American College of Physicians (ACP), issued guidance to members encouraging them to routinely screen patients for HIV.

"ACP recommends that physicians adopt a routine screening policy for HIV and encourage their patients to get tested, regardless of their risk factors," said Amir Qaseem, MD, PhD, MHA, senior medical associate in ACP's Clinical Programs and Quality Care Department and lead author of the guideline.

"Having these professional organizations on board is pretty significant," Dr. Branson said. "There is no question that this has contributed to the increase in testing that we've experienced. I think with the discussion and the attention that this has received, awareness has been raised and we've seen very steady progress, with all the hallmarks that HIV screening is gaining widespread support."

The response by states across the nation has been encouraging as well, according to Dr. Branson, who noted that 14 of the 20 states that previously required signed separate informed consent forms before an HIV test have enacted legislative changes. The remaining six, Massachusetts, Michigan, Nebraska, New York, Pennsylvania and Wisconsin are all in various stages of considering such changes. (See page 28.)

A BUMP IN THE ROAD

Following the CDC's 2006 recommendations, the U.S. Preventive Services Task Force issued a document stating that there is

continued on page 21

ADVERSE REACTIONS

The safety assessment is based on all safety data from the Phase 2b studies (Studies TMC114-C213, TMC114-C202, TMC114-C215, and TMC114-C208) and Phase 3 studies (TMC114-C211, TMC114-C214, TMC114-C209, DUET-1 (TMC125-C206), and DUET-2 (TMC125-C216)) reported with PREZISTA/ritonavir in a total of 3063 subjects.

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.

Due to the need for co-administration of PREZISTA with ritonavir, please refer to ritonavir prescribing information for ritonavir-associated adverse reactions.

Clinical Trials Experience: Treatment-Naïve Adults

Study TMC114-C211

The safety assessment is based on all safety data from the Phase 3 trial TMC114-C211 comparing PREZISTA/ritonavir 800/100 mg once daily versus lopinavir/ritonavir 800/200 mg per day in 689 antiretroviral treatment-naïve HIV-1-infected adult subjects. The total mean exposure for subjects in the PREZISTA/ritonavir 800/100 mg once daily arm and in the lopinavir/ritonavir 800/200 mg per day arm was 95.0 and 91.4 weeks, respectively.

The majority of the adverse drug reactions (ADRs) reported during treatment with PREZISTA/ritonavir 800/100 mg once daily were mild in severity. The most common clinical ADRs to PREZISTA/ritonavir 800/100 mg once daily (≥ 5%) of at least moderate intensity (≥ Grade 2) were diarrhea, headache, abdominal pain and rash. 2.3% of subjects in the PREZISTA/ritonavir arm discontinued treatment due to ADRs.

ADRs to PREZISTA/ritonavir 800/100 mg once daily of at least moderate intensity (≥ Grade 2) in antiretroviral treatment naïve HIV-1-infected adult subjects are presented in Table 2 and subsequent text below the table.

Table 2: Selected Clinical Adverse Drug Reactions to PREZISTA/ritonavir 800/100 mg Once Daily* of At Least Moderate Intensity (≥ Grade 2) Occurring in ≥ 2% of Antiretroviral Treatment-Naïve HIV-1-Infected Adult Subjects

	Randomized Study TMC114-C211	
System Organ Class, Preferred Term, %	**PREZISTA/ritonavir 800/100 mg once daily + TDF/FTC N = 343**	**lopinavir/ritonavir 800/200 mg per day + TDF/FTC N = 346**
Gastrointestinal Disorders		
Abdominal pain	5%	6%
Diarrhea	8%	15%
Nausea	3%	4%
Vomiting	2%	3%
General Disorders and Administration Site Conditions		
Fatigue	< 1%	3%
Metabolism and Nutrition Disorders		
Anorexia	2%	< 1%
Nervous System Disorders		
Headache	6%	5%
Skin and Subcutaneous Tissue Disorders		
Rash	5%	6%

N=total number of subjects per treatment group
TDF = tenofovir disoproxil fumarate
FTC = emtricitabine
* Excluding laboratory abnormalities reported as ADRs

Less Common Adverse Reactions

Treatment-emergent ADRs of at least moderate intensity (≥ Grade 2) occurring in less than 2% of antiretroviral treatment-naïve subjects receiving PREZISTA/ritonavir 800/100 mg once daily are listed below by body system:

Gastrointestinal Disorders: acute pancreatitis, dyspepsia, flatulence

General Disorders and Administration Site Conditions: asthenia

Hepatobiliary Disorders: acute hepatitis (e.g., acute hepatitis, cytolytic hepatitis, hepatotoxicity)

Immune System Disorders: (drug) hypersensitivity

Metabolism and Nutrition Disorders: diabetes mellitus

Musculoskeletal and Connective Tissue Disorders: myalgia

Psychiatric Disorders: abnormal dreams

Skin and Subcutaneous Tissue Disorders: angioedema, pruritus, Stevens-Johnson Syndrome, urticaria

Laboratory abnormalities:

Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-naïve adult subjects treated with PREZISTA/ritonavir 800/100 mg once daily are presented in Table 3.

Table 3: Grade 2 to 4 Laboratory Abnormalities Observed in Antiretroviral Treatment-Naïve HIV-1-Infected Adult Subjects*

		Randomized Study TMC114-C211	
Laboratory Parameter Preferred Term, %	**Limit**	**PREZISTA/ritonavir 800/100 mg once daily + TDF/FTC**	**lopinavir/ritonavir 800/200 mg per day + TDF/FTC**
Biochemistry			
Alanine Aminotransferase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	7%	6%
Grade 3	> 5.0 to ≤ 10.0 X ULN	3%	3%
Grade 4	> 10.0 X ULN	< 1%	3%
Aspartate Aminotransferase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	6%	6%
Grade 3	> 5.0 to ≤ 10.0 X ULN	4%	2%
Grade 4	> 10.0 X ULN	1%	2%
Alkaline Phosphatase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	2%	1%
Grade 3	> 5.0 to ≤ 10.0 X ULN	0%	< 1%
Grade 4	> 10.0 X ULN	0%	0%

Table 3: Grade 2 to 4 Laboratory Abnormalities Observed in Antiretroviral Treatment-Naïve HIV-1-Infected Adult Subjects* (continued)

		Randomized Study TMC114-C211	
Laboratory Parameter Preferred Term, %	**Limit**	**PREZISTA/ritonavir 800/100 mg once daily + TDF/FTC**	**lopinavir/ritonavir 800/200 mg per day + TDF/FTC**
Hyperbilirubinemia			
Grade 2	> 1.5 to ≤ 2.5 X ULN	< 1%	4%
Grade 3	> 2.5 to ≤ 5.0 X ULN	< 1%	< 1%
Grade 4	> 5.0 X ULN	0%	0%
Triglycerides			
Grade 2	5.65-8.48 mmol/L 500-750 mg/dL	3%	8%
Grade 3	8.49-13.56 mmol/L 751-1200 mg/dL	1%	5%
Grade 4	> 13.56 mmol/L > 1200 mg/dL	< 1%	< 1%
Total Cholesterol			
Grade 2	6.20-7.77 mmol/L 240-300 mg/dL	16%	23%
Grade 3	> 7.77 mmol/L > 300 mg/dL	1%	5%
Low-Density Lipoprotein Cholesterol			
Grade 2	4.13-4.90 mmol/L 160-190 mg/dL	14%	10%
Grade 3	≥ 4.91 mmol/L ≥ 191 mg/dL	5%	5%
Elevated Glucose Levels			
Grade 2	6.95-13.88 mmol/L 126-250 mg/dL	7%	8%
Grade 3	13.89-27.75 mmol/L 251-500 mg/dL	< 1%	0%
Grade 4	> 27.75 mmol/L	0% > 500 mg/dL	0%
Pancreatic Lipase			
Grade 2	> 1.5 to ≤ 3.0 X ULN	2%	1%
Grade 3	> 3.0 to ≤ 5.0 X ULN	< 1%	< 1%
Grade 4	> 5.0 X ULN	0%	< 1%
Pancreatic Amylase			
Grade 2	> 1.5 to ≤ 2.0 X ULN	5%	2%
Grade 3	> 2.0 to ≤ 5.0 X ULN	3%	3%
Grade 4	> 5.0 X ULN	0%	< 1%

N=total number of subjects per treatment group
TDF = tenofovir disoproxil fumarate
FTC = emtricitabine
* Grade 4 data not applicable in Division of AIDS grading scale.

Clinical Trials Experience: Treatment-Experienced Adults

Study TMC114-C214

The safety assessment is based on all safety data from the Phase 3 trial TMC114-C214 comparing PREZISTA/ritonavir 600/100 mg twice daily versus lopinavir/ritonavir 400/100 mg twice daily in 595 antiretroviral treatment-experienced HIV-1-infected adult subjects. The total mean exposure for subjects in the PREZISTA/ritonavir 600/100 mg twice daily arm and in the lopinavir/ritonavir 400/100 mg twice daily arm was 80.7 and 76.4 weeks, respectively.

The majority of the ADRs reported during treatment with PREZISTA/ritonavir 600/100 mg twice daily were mild in severity. The most common clinical ADRs to PREZISTA/ritonavir 600/100 mg twice daily (≥ 5%) of at least moderate intensity (≥ Grade 2) were diarrhea, nausea, rash, abdominal pain and vomiting. 4.7% of subjects in the PREZISTA/ritonavir arm discontinued treatment due to ADRs.

ADRs to PREZISTA/ritonavir 600/100 mg twice daily of at least moderate intensity (≥ Grade 2) in antiretroviral treatment-experienced HIV-1-infected adult subjects are presented in Table 4 and subsequent text below the table.

Table 4: Selected Clinical Adverse Drug Reactions to PREZISTA/ritonavir 600/100 mg Twice Daily* of At Least Moderate Intensity (≥ Grade 2) Occurring in ≥ 2% of Antiretroviral Treatment-Experienced HIV-1-Infected Adult Subjects

	Randomized Study TMC114-C214	
System Organ Class, Preferred Term, %	**PREZISTA/ritonavir 600/100 mg twice daily + OBR N = 298**	**lopinavir/ritonavir 400/100 mg twice daily + OBR N = 297**
Gastrointestinal Disorders		
Abdominal distension	2%	< 1%
Abdominal pain	6%	3%
Diarrhea	14%	20%
Dyspepsia	2%	1%
Nausea	7%	6%
Vomiting	5%	3%
General Disorders and Administration Site Conditions		
Asthenia	3%	1%
Fatigue	2%	1%
Metabolism and Nutrition Disorders		
Anorexia	2%	2%
Diabetes mellitus	2%	< 1%
Nervous System Disorders		
Headache	3%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	7%	3%

N=total number of subjects per treatment group
OBR = optimized background regimen
* Excluding laboratory abnormalities reported as ADRs

Less Common Adverse Reactions
Treatment-emergent ADRs of at least moderate intensity (≥ Grade 2) occurring in less than 2% of antiretroviral treatment-experienced subjects receiving PREZISTA/ritonavir 600/100 mg twice daily are listed below by body system:
Gastrointestinal Disorders: acute pancreatitis, flatulence
Musculoskeletal and Connective Tissue Disorders: myalgia
Psychiatric Disorders: abnormal dreams
Skin and Subcutaneous Tissue Disorders: pruritus, urticaria

Laboratory abnormalities:
Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-experienced adult subjects treated with PREZISTA/ritonavir 600/100 mg twice daily are presented in Table 5.

Table 5: Grade 2 to 4 Laboratory Abnormalities Observed in Antiretroviral Treatment-Experienced HIV-1-Infected Adult Subjects*

		Randomized Study TMC114-C214	
Laboratory Parameter Preferred Term, %	**Limit**	**PREZISTA/ritonavir 600/100 mg twice daily + OBR**	**lopinavir/ritonavir 400/100 mg twice daily + OBR**
Biochemistry			
Alanine Aminotransferase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	7%	5%
Grade 3	> 5.0 to ≤ 10.0 X ULN	2%	2%
Grade 4	> 10.0 X ULN	1%	2%
Aspartate Aminotransferase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	6%	6%
Grade 3	> 5.0 to ≤ 10.0 X ULN	2%	2%
Grade 4	> 10.0 X ULN	< 1%	2%
	Alkaline Phosphatase		
Grade 2	> 2.5 to ≤ 5.0 X ULN	< 1%	0%
Grade 3	> 5.0 to ≤ 10.0 X ULN	< 1%	< 1%
Grade 4	> 10.0 X ULN	0%	0%
Hyperbilirubinemia			
Grade 2	> 1.5 to ≤ 2.5 X ULN	< 1%	2%
Grade 3	> 2.5 to ≤ 5.0 X ULN	< 1%	< 1%
Grade 4	> 5.0 X ULN	< 1%	0%
Triglycerides			
Grade 2	5.65-8.48 mmol/L 500-750 mg/dL	10%	11%
Grade 3	8.49-13.56 mmol/L 751-1200 mg/dL	7%	10%
Grade 4	> 13.56 mmol/L > 1200 mg/dL	3%	6%
Total Cholesterol			
Grade 2	6.20-7.77 mmol/L 240-300 mg/dL	25%	23%
Grade 3	> 7.77 mmol/L > 300 mg/dL	10%	14%
Low-Density Lipoprotein Cholesterol			
Grade 2	4.13-4.90 mmol/L 160-190 mg/dL	14%	14%
Grade 3	≥ 4.91 mmol/L ≥ 191 mg/dL	8%	9%
Elevated Glucose Levels			
Grade 2	6.95-13.88 mmol/L 126-250 mg/dL	10%	11%
Grade 3	13.89-27.75 mmol/L 251-500 mg/dL	1%	< 1%
Grade 4	> 27.75 mmol/L > 500 mg/dL	< 1%	0%
Pancreatic Lipase			
Grade 2	> 1.5 to ≤ 3.0 X ULN	3%	4%
Grade 3	> 3.0 to ≤ 5.0 X ULN	2%	< 1%
Grade 4	> 5.0 X ULN	< 1%	0%
Pancreatic Amylase			
Grade 2	> 1.5 to ≤ 2.0 X ULN	6%	7%
Grade 3	> 2.0 to ≤ 5.0 X ULN	7%	3%
Grade 4	> 5.0 X ULN	0%	0%

N=total number of subjects per treatment group
OBR = optimized background regimen
* Grade 4 data not applicable in Division of AIDS grading scale.

Serious ADRs
The following serious ADRs of at least moderate intensity (≥ Grade 2) occurred in the Phase 2b studies (Studies TMC114-C213, TMC114-C202, TMC114-C215, and TMC114-C208) and Phase 3 studies (TMC114-C211, TMC114-C214, TMC114-C209, DUET-1 (TMC125-C206), and DUET-2 (TMC125-C216)) with PREZISTA/ritonavir: abdominal pain, acute hepatitis, acute pancreatitis, anorexia, asthenia, diabetes mellitus, diarrhea, fatigue, headache, hepatic enzyme increased, hypercholesterolemia, hyperglycemia, hypertriglyceridemia, immune reconstitution syndrome, low density lipoprotein increased, nausea, pancreatic enzyme increased, rash, Stevens-Johnson Syndrome, and vomiting.

Additional ADRs to PREZISTA/ritonavir identified in adult subjects in other clinical trials
The additional ADR of interest identified from other clinical trials was osteonecrosis.

Patients co-infected with hepatitis B and/or hepatitis C virus
In subjects co-infected with hepatitis B or C virus receiving PREZISTA/ritonavir, the incidence of adverse events and clinical chemistry abnormalities was not higher than in subjects receiving PREZISTA/ritonavir who were not co-infected, except for increased hepatic enzymes [*see Warnings and Precautions*]. The pharmacokinetic exposure in co-infected subjects was comparable to that in subjects without co-infection.

Postmarketing Experience
The following events have been identified during postmarketing use of PREZISTA. Because these events are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Redistribution of body fat has been reported.
Rarely, rhabdomyolysis (associated with co-administration with HMG-CoA reductase inhibitors and PREZISTA/ritonavir) and toxic epidermal necrolysis have been reported *[see Warnings and Precautions].*

DRUG INTERACTIONS
See also *Contraindications* and *Clinical Pharmacology (12.3)* in Full Prescribing Information.

Potential for PREZISTA/ritonavir to Affect Other Drugs
PREZISTA co-administered with ritonavir is an inhibitor of CYP3A and CYP2D6. Co-administration of PREZISTA and ritonavir with drugs that are primarily metabolized by CYP3A and CYP2D6 may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events (see Table 6).

Potential for Other Drugs to Affect Darunavir
Darunavir and ritonavir are metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of darunavir and ritonavir. Co-administration of darunavir and ritonavir and other drugs that inhibit CYP3A may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir (see Table 6).

Established and Other Potentially Significant Drug Interactions
Table 6 provides dosing recommendations as a result of drug interactions with PREZISTA/ritonavir. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

Table 6: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction [*See Clinical Pharmacology (12.3)* in Full Prescribing Information for Magnitude of Interaction, Tables 10 and 11]

Concomitant Drug Class: Drug Name	**Effect on Concentration of Darunavir or Concomitant Drug**	**Clinical Comment**
HIV-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
didanosine	↔ darunavir ↔ didanosine	Didanosine should be administered one hour before or two hours after PREZISTA/ritonavir (which are administered with food).
HIV-Antiviral Agents: HIV-Protease Inhibitors (PIs)		
indinavir (The reference regimen for indinavir was indinavir/ritonavir 800/100 mg twice daily.)	↑ darunavir ↑ indinavir	The appropriate dose of indinavir in combination with PREZISTA/ritonavir has not been established.
lopinavir/ritonavir	↓ darunavir ↔ lopinavir	Appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer lopinavir/ritonavir and PREZISTA, with or without ritonavir.
saquinavir	↓ darunavir ↔ saquinavir	Appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer saquinavir and PREZISTA, with or without ritonavir.
HIV-Antiviral Agents: CCR5 co-receptor antagonists		
Maraviroc	↑ maraviroc	Maraviroc concentrations are increased when co-administered with PREZISTA/rtv. When used in combination with PREZISTA/rtv, the dose of maraviroc should be 150 mg twice daily.
Other Agents		
Antiarrhythmics: bepridil, lidocaine (systemic), quinidine, amiodarone, flecainide, propafenone	↑ antiarrhythmics	Concentrations of these drugs may be increased when co-administered with PREZISTA/ritonavir. Caution is warranted and therapeutic concentration monitoring, if available, is recommended for anti-arrhythmics when co-administered with PREZISTA/ritonavir.
digoxin	↑ digoxin	The lowest dose of digoxin should initially be prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.
Anticoagulant: warfarin	↓ warfarin ↔ darunavir	Warfarin concentrations are decreased when co-administered with PREZISTA/ritonavir. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with PREZISTA/ritonavir.
Anticonvulsant: carbamazepine	↔ darunavir ↑ carbamazepine	The dose of either darunavir/ritonavir or carbamazepine does not need to be adjusted when initiating co-administration with darunavir/ritonavir and carbamazepine. Clinical monitoring of carbamazepine concentrations and its dose titration is recommended to achieve the desired clinical response.

Table 6: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction [*See Clinical Pharmacology (12.3)* in Full Prescribing Information for Magnitude of Interaction, Tables 10 and 11] **(continued)**

Anticonvulsant: phenobarbital, phenytoin	↔ darunavir ↓ phenytoin ↓ phenobarbital	Co-administration of PREZISTA/ritonavir may cause decrease in the steady-state concentrations of phenytoin and phenobarbital. Phenytoin and phenobarbital levels should be monitored when co-administering with PREZISTA/ritonavir.
Antidepressant: trazodone, desipramine	↑ trazodone ↑ desipramine	Concomitant use of trazodone or desipramine and PREZISTA/ ritonavir may increase plasma concentrations of trazodone or desipramine which may lead to adverse events such as nausea, dizziness, hypotension and syncope. If trazodone or desipramine is used with PREZISTA/ritonavir, the combination should be used with caution and a lower dose of trazodone or desipramine should be considered.
Anti-infective: clarithromycin	↔ darunavir ↑ clarithromycin	No dose adjustment of the combination is required for patients with normal renal function. For patients with renal impairment, the following dose adjustments should be considered: • For subjects with CLcr of 30-60 mL/min, the dose of clarithromycin should be reduced by 50%. • For subjects with CLcr of < 30 mL/min, the dose of clarithromycin should be reduced by 75%.
Antifungals: ketoconazole, itraconazole, voriconazole	↑ ketoconazole ↑ darunavir ↑ itraconazole (not studied) ↓ voriconazole (not studied)	Ketoconazole and itraconazole are potent inhibitors as well as substrates of CYP3A. Concomitant systemic use of ketoconazole, itraconazole, and darunavir/ritonavir may increase plasma concentration of darunavir. Plasma concentrations of ketoconazole or itraconazole may be increased in the presence of darunavir/ritonavir. When co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg. Plasma concentrations of voriconazole may be decreased in the presence of darunavir/ritonavir. Voriconazole should not be administered to patients receiving darunavir/ritonavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.
Antimycobacterial: rifabutin The reference regimen for rifabutin was 300 mg once daily	↑ darunavir ↑ rifabutin ↑ 25-*O*-desacetylrifabutin	Dose reduction of rifabutin by at least 75% of the usual dose (300 mg once daily) is recommended (i.e., a maximum dose of 150 mg every other day). Increased monitoring for adverse events is warranted in patients receiving this combination and further dose reduction of rifabutin may be necessary.
ß-Blockers: metoprolol, timolol	↑ beta-blockers	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with PREZISTA/ritonavir.
Benzodiazepines: parenterally administered midazolam	↑ midazolam	Concomitant use of parenteral midazolam with PREZISTA/ritonavir may increase plasma concentrations of midazolam. Co-administration should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Co-administration of oral midazolam with PREZISTA/ritonavir is CONTRAINDICATED.
Calcium Channel Blockers: felodipine, nifedipine, nicardipine	↑ calcium channel blockers	Plasma concentrations of calcium channel blockers (e.g., felodipine, nifedipine, nicardipine) may increase when PREZISTA/ritonavir are co-administered. Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Systemic: dexamethasone	↓ darunavir	Systemic dexamethasone induces CYP3A and can thereby decrease darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA.
Corticosteroid: Inhaled/Nasal: fluticasone	↑ fluticasone	Concomitant use of inhaled fluticasone and PREZISTA/ritonavir may increase plasma concentrations of fluticasone. Alternatives should be considered, particularly for long term use.

Table 6: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction [*See Clinical Pharmacology (12.3)* in Full Prescribing Information for Magnitude of Interaction, Tables 10 and 11] **(continued)**

HMG-CoA Reductase Inhibitors: pravastatin, atorvastatin, rosuvastatin	↑ pravastatin ↑ atorvastatin ↑ rosuvastatin	Use the lowest possible dose of atorvastatin, pravastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as fluvastatin in combination with PREZISTA/ritonavir.
Immunosuppressants: cyclosporine, tacrolimus, sirolimus	↑ immunosuppressants	Plasma concentrations of cyclosporine, tacrolimus or sirolimus may be increased when co-administered with PREZISTA/ritonavir. Therapeutic concentration monitoring of the immunosuppressive agent is recommended when co-administered with PREZISTA/ritonavir.
Narcotic Analgesic/ Treatment of Opioid Dependence: methadone, buprenorphine, buprenorphine/ naloxone	↓ methadone ↔ buprenorphine, naloxone ↑ norbuprenorphine (metabolite)	No adjustment of methadone dosage is required when initiating co-administration of PREZISTA/ritonavir. However, clinical monitoring is recommended as the dose of methadone during maintenance therapy may need to be adjusted in some patients. No dose adjustment for buprenorphine or buprenorphine/naloxone is required with concurrent administration of PREZISTA/ritonavir. Clinical monitoring is recommended if PREZISTA/ritonavir and buprenorphine or buprenorphine/naloxone are coadministered.
Neuroleptics: risperidone, thioridazine	↑ neuroleptics	A dose decrease may be needed for these drugs when co-administered with PREZISTA/ritonavir.
Oral Contraceptives/ estrogen: ethinyl estradiol, norethindrone	↓ ethinyl estradiol ↓ norethindrone	Plasma concentrations of ethinyl estradiol are decreased due to induction of its metabolism by ritonavir. Alternative methods of nonhormonal contraception are recommended.
PDE-5 inhibitors: sildenafil, vardenafil, tadalafil	↑ PDE-5 inhibitors	Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours can be used with increased monitoring for PDE-5 inhibitor-associated adverse events.
Selective Serotonin Reuptake Inhibitors (SSRIs): sertraline, paroxetine	↔ darunavir ↓ sertraline ↓ paroxetine	If sertraline or paroxetine is co-administered with PREZISTA/ ritonavir, the recommended approach is a careful dose titration of the SSRI based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with PREZISTA/ritonavir should be monitored for antidepressant response.

In addition to the drugs included in Table 6, the interaction between PREZISTA/ritonavir and the following drugs were evaluated in clinical studies and no dose adjustments are needed for either drug [see *Clinical Pharmacology (12.3)* in Full Prescribing Information]: atazanavir, efavirenz, etravirine, nevirapine, omeprazole, ranitidine, and tenofovir disoproxil fumarate.

Other nucleoside reverse transcriptase inhibitors (NRTIs):

Based on the different elimination pathways of the other NRTIs (zidovudine, zalcitabine, emtricitabine, stavudine, lamivudine and abacavir) that are primarily renally excreted, no drug interactions are expected for these drugs and PREZISTA/ritonavir.

Other PIs:

The co-administration of PREZISTA/ritonavir and PIs other than lopinavir/ritonavir, saquinavir, atazanavir, and indinavir has not been studied. Therefore, such co-administration is not recommended.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C: PREZISTA should be used during pregnancy only if the potential benefit justifies the potential risk.

No adequate and well-controlled studies have been conducted in pregnant women. Reproduction studies conducted with darunavir showed no embryotoxicity or teratogenicity in mice, rats and rabbits. However, due to limited bioavailability and/or dosing limitations, animal exposures (based on AUC) were only 50% (mice and rats) and 5% (rabbit) of those obtained in humans at the recommended clinical dose boosted with ritonavir.

In the rat pre- and postnatal development study, a reduction in pup body weight gain was observed with darunavir alone or in combination with ritonavir during lactation. This was due to exposure of pups to drug substances via the milk. Sexual development, fertility and mating performance of offspring were not affected by maternal treatment with darunavir alone or in combination with ritonavir. The maximal plasma exposures achieved in rats were approximately 50% of those obtained in humans at the recommended clinical dose boosted with ritonavir.

In the juvenile toxicity study where rats were directly dosed with darunavir, deaths occurred from post-natal day 5 through 11 at plasma exposure levels ranging from 0.1 to 1.0 of the human exposure levels. In a 4-week rat toxicology study, when dosing was initiated on post-natal day 23 (the human equivalent of 2 to 3 years of age), no deaths were observed with a plasma exposure (in combination with ritonavir) of 0.1 of the human plasma exposure levels.

Antiretroviral Pregnancy Registry: *To monitor maternal-fetal outcomes of pregnant women exposed to PREZISTA, an Antiretroviral Pregnancy Registry has been established. Physicians 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 in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV. Although it is not known whether darunavir is secreted in human milk, darunavir is secreted into the milk of lactating rats. 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 PREZISTA.**

Geriatric Use

Clinical studies of PREZISTA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, caution should be exercised in the administration and monitoring of PREZISTA in elderly patients reflecting the greater frequency of decreased hepatic function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)* in Full Prescribing Information*].*

Hepatic Impairment

No dose adjustment of PREZISTA/ritonavir is necessary for patients with either mild or moderate hepatic impairment. No pharmacokinetic or safety data are available regarding the use of PREZISTA/ritonavir in subjects with severe hepatic impairment, therefore, PREZISTA/ritonavir is not recommended for use in patients with severe hepatic impairment [*see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)* in Full Prescribing Information].

Renal Impairment

Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV-infected subjects with moderate renal impairment (CrCL between 30-60 mL/min, n=20). No pharmacokinetic data are available in HIV-1-infected patients with severe renal impairment or end stage renal disease; however, because the renal clearance of darunavir is limited, a decrease in total body clearance is not expected in patients with renal impairment. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis [*see Clinical Pharmacology (12.3)* in Full Prescribing Information*].*

OVERDOSAGE

Human experience of acute overdose with PREZISTA/ritonavir is limited. Single doses up to 3200 mg of the oral solution of darunavir alone and up to 1600 mg of the tablet formulation of darunavir in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

No specific antidote is available for overdose with PREZISTA. Treatment of overdose with PREZISTA consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since PREZISTA is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling (17.5) in Full Prescribing 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 PREZISTA.** A Patient Package Insert for PREZISTA is available for patient information.

General

Patients should be informed that PREZISTA is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. Patients should be told that there are currently no data demonstrating that therapy with PREZISTA can reduce the risk of transmitting HIV to others.

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 remain under the care of a physician while using PREZISTA.

Instructions for Use

General

Patients should be advised to take PREZISTA and ritonavir (NORVIR®) with food every day as prescribed. Patients should be instructed to swallow whole tablets with a drink such as water or milk. PREZISTA must always be used with ritonavir (NORVIR®) in combination with other antiretroviral drugs. Patients should not alter the dose of either PREZISTA or ritonavir (NORVIR®), discontinue ritonavir (NORVIR®), or discontinue therapy with PREZISTA without consulting their physician.

Patients Taking PREZISTA Once Daily

If a patient misses a dose of PREZISTA or ritonavir (NORVIR®) by more than 12 hours, the patient should be told to wait and then take the next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time. If the patient misses a dose of PREZISTA or ritonavir (NORVIR®) by less than 12 hours, the patient should be told to take PREZISTA and ritonavir (NORVIR®) immediately, and then take the next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time. If a dose of PREZISTA or ritonavir (NORVIR®) is skipped, the patient should not double the next dose. Inform the patient that he or she should not take more or less than the prescribed dose of PREZISTA or ritonavir (NORVIR®).

Patients Taking PREZISTA Twice Daily

If a patient misses a dose of PREZISTA or ritonavir (NORVIR®) by more than 6 hours, the patient should be told to wait and then take the next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time. If the patient misses a dose of PREZISTA or ritonavir (NORVIR®) by less than 6 hours, the patient should be told to take PREZISTA and ritonavir (NORVIR®) immediately, and then take the next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time. If a dose of PREZISTA or ritonavir (NORVIR®) is skipped, the patient should not double the next dose. Inform the patient that he or she should not take more or less than the prescribed dose of PREZISTA or ritonavir (NORVIR®).

Drug Interactions

PREZISTA/ritonavir 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.

Patients receiving estrogen-based contraceptives should be instructed to use alternate contraceptive measures during therapy with PREZISTA/ritonavir because hormonal levels may decrease.

Fat Redistribution

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including PREZISTA/ritonavir, and that the cause and long-term health effects of these conditions are not known at this time.

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 Revised: January 2010 10101710B

References: 1. US Department of Health and Human Services. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed December 9, 2009. **2.** Data on file. Tibotec Therapeutics, Division of Centocor Ortho Biotech Products, L.P.

HIV Testing = PREVENTION

Written Consent: A Barrier to Testing?

BY BONNIE PROKESCH, MD

HAVE YOU EVER BEEN TESTED FOR HIV? Do you mind if I check your blood for HIV when I check all of the other lab tests, like your cholesterol levels and blood count? Okay, then can you sign here?"

This is a common discussion that I hold with patients I see in my weekly clinic at Grady Memorial Hospital in Atlanta, many who are unable to read at a level needed to make sense of the consent form they must sign for HIV testing. By explaining to my patients that I check HIV in everyone, just like I check cholesterol, I try to remove the awkwardness and stigma inherent in having to ask for consent prior to testing. However, after the discussion is over and the patient is willing to be tested, I must review the written consent with them, almost instantly bringing the stigma back.

Then the hesitancy begins. It is as if signing a piece of paper adds another level of weight to the discussion, a level that does not exist when patients are tested for other sexually transmitted infections. In fact, some patients who are eager to be tested when we initially discuss the plan shy away from the idea and decide against it once they see the piece of paper. I know I am not the only clinician to experience such an occurrence.

Recently, I spent a month on the medicine wards of a Veterans Administration (VA) hospital, where written consent is no longer required for HIV testing. As I went from room to room to ask my patients if they would mind having their blood tested for HIV, not needing a written, signed consent was a huge relief. Not only did I not need to bring all the materials required for a signed consent (which involves a computer at the VA), I could have an open and honest discussion with my patients — without the formalities of consent forms, red tape, and the stigma of HIV perpetuated by both.

Never once did I have a patient refuse testing. Never once did I have a patient ask if he needed to sign a form. The process was perfectly natural.

Moreover, the lack of needing written consent became crucial in caring for some of my inpatients. I am writing mainly of those who were unstable, nonverbal, or, after having devastating stays in the intensive care unit, were unable to write. Some of these patients were extremely ill with low albumin levels and symptoms that could have been due to opportunistic infections, so being able to determine if HIV was playing a role in their illness was crucial.

Instead of needing to obtain consent from their loved ones, who often become overly concerned with the need for HIV testing, I was able to ask them directly and get consent even by head nod or hand grip. In a world in which family members need not consent on behalf of their loved ones for syphilis, HPV, or even hepatitis testing, what a relief it is for patients who can discover if they are HIV positive in a confidential way — without their loved ones having to know.

Why, especially in the era of ARVs, when individuals with HIV are living long, healthy lives, are we often required to obtain written consent for HIV testing? Not only does testing protect our patients, it protects their partners and loved ones as well.

As more states and healthcare systems adopt policies that no longer require written consent for testing, hopefully the taboo nature of HIV testing discussions will dissolve and every patient will be aware of his HIV status just as he knows that his cholesterol level may be elevated. HIV

About the Author: Dr. Bonnie Prokesch is a first year resident in Internal Medicine at Emory University in Atlanta, GA.

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"no direct evidence on benefits of screening for HIV infection in the general population," although it acknowledged that other evidence "indicates that testing is extremely accurate, a high proportion of patients receive a diagnosis at immunologically advanced stages of disease, and interventions (particularly HAART) are effective in reducing morbidity and mortality in patients with immunologically advanced disease." But the Task Force said additional studies are needed before it can endorse testing of persons not at increased risk for infection.

"They definitely recommend screening for persons at increased risk, either those with individual risk factors, or persons who receive health care in a high prevalence facility," Dr. Branson said. "The Task Force acknowledged that most providers don't know what the HIV prevalence is in their facilities, so that recommendation may be difficult to implement. They pointed out that one approach to determining prevalence would be to initiate screening unless local prevalence data were available – the strategy advocated by the 2006 CDC recommendations."

But Dr. Branson explained that the Task Force has strict evidentiary criteria on which it bases its decisions. "Their model was predicated on preventing clinical progression or

HIV Testing = PREVENTION

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> "We have to make sure that not only are patients linked to care, but that they remain in care, and while they are in care, that they continue to receive assistance with preventing further transmission."

death within three years. But the CDC perspective in dealing with HIV, where we may not get clinical progression for 10 years, is that we would like to see people diagnosed earlier," he explained.

"The Task Force's recommendation had to do with benefits for the particular individual," he added. "The CDC's perspective is that earlier diagnosis will result both in treatment being started earlier and in less transmission, so the basis for our recommendation is slightly different. It will take some time to develop sufficient evidence to meet the Task Force criteria, just as it did with prenatal screening."

While the Task Force's reaction to universal testing has not been a fatal blow to widespread acceptance and implementation of CDC's 2006 guidelines, endorsement likely would result in even greater acceptance – particularly by some health insurers, including the federal employees' health benefit plan, which establish their reimbursement criteria based on the Task Force's recommendations.

However, Dr. Branson noted that CDC's recommendation for prenatal screening for HIV was widely adopted and widely reimbursed, even though, until 2005, the Task Force recommended screening only for high-risk pregnant women.

THE HIV SPECIALISTS' ROLE

Dr. Branson was asked what role HIV specialists can play to help encourage more testing, including testing in other health care settings.

"The role they've been playing in terms of advocacy is crucial and needs to be continued," he said. "Second, they need to make sure that people understand how beneficial treatment is in terms of relative changes in life expectancy and that treatment regimens are a lot easier with fewer side effects. Too few people realize the benefits are so substantial."

Clearly, such information can be part of the message provided to HIV patients by HIV providers who are treating them as they counsel and encourage their patients to be sure that their sex partners are tested as well.

In addition, Dr. Branson emphasized the importance of the Academy's effort to establish linkages to care for patients who have tested positive. "From the CDC perspective, that is the next major area where we have to concentrate," he said. "We have to make sure that not only are patients linked to care, but that they remain in care, and while they are in care, that

Bio Brief: Bernard M. Branson, MD

BERNARD BRANSON is currently Associate Director for Laboratory Diagnostics in the Division of HIV/AIDS Prevention at the CDC, where he also conducts research into HIV prevention strategies. Dr. Branson has been the chief architect for CDC's activities surrounding new technologies for HIV testing, including rapid HIV tests and tests for HIV incidence. Most recently, Dr. Branson was the lead author for CDC's Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health Care Settings. Dr. Branson has been involved in HIV counseling and testing for more than 20 years. In 1985, Dr. Branson also initiated the State AIDS Hotline and Maryland's program for anonymous HIV counseling and testing.

they continue to receive assistance with preventing further transmission."

Many health care professionals, if they are not familiar with HIV care, are concerned about what steps they should take if they screen and find that a person is infected with HIV, Dr. Branson noted.

"I think if people were secure that they could have a referral resource to make it easy, that would facilitate more screening and help achieve the ultimate goal, which is to make sure that people receive the appropriate care that they need," he said.

(For more on the Academy's efforts on Linkage to Care, please see the article on page 26)

The more that HIV testing becomes a routine component of patients' visits to their doctors for checkups and other services, as well as to emergency rooms – and even dental offices – the easier it will be to remove some common and persistent roadblocks to testing, Dr Branson said.

Certainly HIV specialists should encourage such testing in their encounters with general practitioners and other medical specialists as well, he said.

LEARNING FROM PREGNANCY TESTING SUCCESS

The 2006 CDC recommendations point out that prevention strategies that incorporate universal HIV screening have been highly effective, noting that screening blood donors for HIV has nearly eliminated transfusion-associated HIV infection in the United States.

In addition, the document states, "incidence of pediatric HIV/AIDS in the United States has declined substantially since the 1990s, when prevention strategies began to include specific recommendations for routine HIV testing of pregnant women."

The recommendations also state "Perinatal transmission rates can be reduced to <2% with universal screening of pregnant women in combination with prophylactic administration of antiretroviral drugs, scheduled cesarean delivery when indicated, and avoidance of breast feeding."

"What we learned was that by making (HIV testing) more routine, it increased acceptance rates. That was partly the basis for the emphasis on 'opt-out', where it became normal to get tested instead of not to get tested," Dr. Branson

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> "When people perceive the benefit that HIV testing is straightforward and effective and relatively simple, it will help them to understand that, like other conditions, early detection makes a difference."

explained. "People like to be successful. In terms of prenatal screening, what they saw was dramatically reduced numbers of HIV-infected babies being born. When they see success, it changes their mind."

Clearly, he said, the lesson to be learned is that expanding the opt-out approach to HIV testing generally, making it a routine part of health care unless specifically declined, will help to identify HIV-infected patients at an earlier stage, dramatically improving outcomes and helping to prevent the disease from spreading.

Moreover, as tests become more routine in medical practices across the nation, the stigma associated with them will also be reduced, Dr. Branson predicted. "In the early days of HIV infection, especially with the concept of risk-based screening, you had to be sort of 'eligible' for HIV to be tested." But now, he said, "when the idea is that anybody can and should get tested as a routine, it has a big tendency to reduce stigma associated with the testing process."

THE TESTS

"Like everything else, you have to choose the right tool for the right circumstance," Dr. Branson said.

Rapid tests "make a lot of sense" in instances where a patient may not be coming back for the results, such as when visiting emergency departments. But, he pointed out, such tests can be more expensive and sometimes less reliable than conventional tests, especially very early after infection.

However, because at least four rapid tests are in the "waived" category under the Clinical Laboratory Improvement Amendments (CLIA) administered by CMS, they can be performed in many more health care settings than tests that are categorized as either "moderate" or "high complexity."

"In many offices, to do more complicated tests really is not possible. The fact that rapid HIV tests are waived makes them feasible, because many (health care providers) only do waived tests in their offices. So that greatly expands the number of places that can actually do HIV testing," he explained.

Dr. Branson also said that new assays that will test for both the HIV antigen and the HIV antibody at the same time will be coming out soon. "In groups that have high rates of new HIV infection, they may be preferable," he said.

"But I think that rapid tests have made a lot of this expansion (of testing) possible, because of the concern that people had before, and frankly, the cost of trying to track people down to inform them of their test results."

FOCUSING ON 'COMMUNITIES'

In 2007, the CDC launched an initiative to expand testing in 25 jurisdictions across the nation with the highest burden of AIDS among African Americans. In that initiative, the states were eligible to apply for funding to support testing.

That three-year funding cycle has run its course, Dr. Branson explained, and now CDC is preparing for the next cycle, which will expand the effort to include Hispanics and men who have sex with men (MSM) of any race "because the incidence is highest in these three groups; that's where most new infections are occurring."

Among racial/ethnic groups, African Americans face the most severe burden of HIV and AIDS in the nation. While blacks represent approximately 12 percent of the U.S. population, they account for almost half of people living with HIV in the U.S. (46 percent), as well as nearly half of new HIV infections each year (45 percent). Latinos are also disproportionately impacted; Hispanics represent 13 percent of the population, but account for an estimated 18 percent of people living with HIV and 17 percent of new infections. By risk group, gay and bisexual men of all races remain the population most severely impacted by HIV. Men who have sex with men account for more than half of all new HIV infections in the U.S. each year (53 percent) as well as nearly half of people living with HIV (48 percent).

What about older Americans? "We don't discourage testing people 65 and older, but given the rates and number of cases in that age group at the time the recommendations came out, it was not shown to be cost-effective to test everyone," Dr. Branson explained. "We still recommend testing for people 65 and older who are not in a monogamous relationship and who continue to have sex with more than one partner."

The bottom line, said Dr. Branson, is that testing must become normalized and routine, in whatever setting is appropriate.

"When people perceive the benefit that HIV testing is straightforward and effective and relatively simple, it will help them to understand that, like other conditions, early detection makes a difference." HIV

Major CDC HIV Testing Guideline Revisions

- **HIV screening is recommended** for all patients ages 13-64 in all health care settings after the patient is notified that testing will be done unless the patient declines (opt-out screening).
- **Persons at high-risk for HIV infection** should be screened for HIV at least annually.
- **Separate written consent for HIV testing is not recommended;** general consent for medical care should be sufficient to encompass consent for HIV testing.
- **Prevention counseling should not be required** with HIV diagnostic testing or as part of routine HIV screening programs in health care settings.
- **HIV screening should be included** in the routine panel of prenatal screening tests for all pregnant women, and HIV screening is recommended after the patient is notified that testing will be done unless the patient declines (opt-out screening).

CDC is also in the process of updating recommendations for HIV testing in non-health care settings, with publication expected in 2010.

Resources:

- VA Policy on HIV Testing: http://www.hiv.va.gov/vahiv?page=prtop02-ov-02
- Revised CDC Recommendations for HIV Testing: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm
- Medicare Expands List of Covered Preventive Services to Include HIV Tests: http://www.hhs.gov/news/press/2009pres/12/20091208a.html
- American Congress of Obstetricians and Gynecologists HIV Testing Policy: http://www.acog.org/departments/dept_notice.cfm?recno=39&bulletin=4619
- American College of Physicians Recommends Routine HIV Testing: http://www.acponline.org/pressroom/hiv_screen.htm
- US Preventive Services Task Force: Screening for HIV: http://www.ahrq.gov/clinic/uspstf05/hiv/hivreview.htm
- CDC HIV/AIDS Initiatives in the African American Community: http://www.cdc.gov/hiv/topics/aa/resources/factsheets/aa.htm
- HIV and AIDS in America: A Snapshot :http://www.cdc.gov/nchhstp/newsroom/docs/AAAFastFacts-FINAL508COMP.pdf

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

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REFERRAL LINK:

Helping Doctors Link HIV Patients to Care

EVEN THOUGH THE CENTERS FOR DISEASE Control & Prevention (CDC) in 2006 recommended voluntary routine HIV screening of adults, adolescents, and pregnant women ages 13-64 in U.S. health care settings, some medical providers, particularly general practitioners, have not widely adopted and implemented the recommendations partly because of concern that they will be unable to link an HIV-infected individual to HIV primary care services.

To address this issue with linkage to care, the American Academy of HIV Medicine (AAHIVM), with the help of Centers for Disease Control & Prevention (CDC) funding, has launched a pilot referral resource for health providers that routinely offer HIV testing as a normal part of medical practice. Housed through the AAHIVM Web site (www.aahivm.org), Referral Link is designed to provide referral information for all HIV medical care providers in each of the six pilot cities — Baton Rouge, LA; Cochise County, AZ; Cleveland, OH; Columbia, SC; Sacramento, CA; and Tampa, FL. The contact information, provider Web site, referral, and practice information for each provider is listed.

Referral Link seeks to target allied health professionals who identify an HIV case among their patient population and need to refer that patient to another practice. It is also useful for HIV providers and patients seeking referrals to other areas of HIV-related care or supportive services, or to other providers in a given region.

"This resource will give those providers that are following the CDC's HIV testing recommendations the tool they need to ensure that their newly-diagnosed patients will be linked to care with a quality HIV care provider," said Donna Sweet, MD, MACP, AAHIVS, chair of the Board of Directors for AAHIVM.

The information is truncated and searchable by patient type and services provided. Referral Link also allows for narrowing of search functions by all categories, such as case management, Medicaid availability and confirmatory testing services.

"Ultimately, we would like to geographically expand this service and offer it as a resource to healthcare providers across the country," said James M. Friedman, Executive Director of AAHIVM. "We believe this tool will boost the HIV-testing rate and, at the end of the day, save lives." HIV

If you are interested in helping the Academy expand Referral Link to your area, please contact Amber McCracken, AAHIVM Communications Director, at amber@aahivm.org.

HIV Testing = PREVENTION

It is an all too common scenario, where a patient is referred "urgently" with what turns out to be a false positive HIV assay.

Navigating False Positive Testing

BY RICHARD PROKESCH, MD, AAHIVS

"FAITH" WAS REFERRED TO ME as a "must see today" patient from a family practitioner who frequently sends patients to our practice. Her HIV test had come back "positive," and after hearing the results, she understandably was distraught and inconsolable. She was 16 years old and "most of the time" practiced "safe sex" and only had had unprotected sex "a few times."

The test result had been faxed over to me and showed a positive ELISA, but only 1 band positive on the Western Blot confirmatory test. It was a false positive test! After taking a full history, including a sexual history and examining her, I felt comfortable that the test was indeed a false positive, and used the opportunity to stress the importance of "safe sex." In this case, it was a shocking wake-up call hopefully worth the relatively brief trauma for her to learn a valuable lesson.

It is an all too common scenario, where a patient is referred "urgently" with what turns out to be a false positive HIV assay. Unfortunately, many of the primary care physicians (and their extenders) who do not routinely care for persons infected with HIV are not adept at interpreting the screening tests. I have seen "positive" people with no positive Western blot bands, and even those with only a positive ELISA and without Western blot being ordered.

The HIV ELISA test is very sensitive, meaning that it will detect a high (99% +) number of people who are infected with HIV, but not as specific, meaning that some of the "positive" tests will not be detecting the HIV but reacting to some other antigen. There are a number of known reasons for a false positive HIV ELISA such as a second or higher pregnancy, prior or current syphilis infection, an autoimmune disease such as diabetes or Graves disease, etc. However more often there is no obvious reason for a false positive test.

We also see patients who have a positive HIV ELISA and an "indeterminate" Western blot meaning that some Western blot bands are positive, but not enough to fulfill the criteria for a true positive. The history is crucial. If the patient has risk factors for HIV contraction, then he or she may be in the "window period" where the full antibody response hasn't had time to develop and a repeat test needs to be run in six weeks and then again (if still not positive) in three months. However if the patient has no risk factors for HIV infection, there is a very low probability that it will turn out to be a true positive test. In that case follow up testing is not necessary.

Last week I saw "Julie" — again an urgent referral. She was sobbing incessantly as I introduced myself to her and was ready to explain to her the great results and markedly improved survivals with HAART. "My fiancée died of AIDS," she tearfully confessed "and now I'm next."

When I asked how long ago it was that her fiancée had died, she replied "six years ago." She had had several negative HIV tests during those years, but her new primary care provider "assumed" she was positive and told her so, and referred her to the "specialist."

I reassured her that if she had not had another exposure to the virus that she is not HIV infected, and when another HIV ELISA was again negative she cried once again — this time with joy. Sometimes even a definitively negative test can be interpreted as positive by both a patient and their provider. HIV

About the Author: Richard Prokesch, MD, FACP, FIDSA, AAHIVS is in private practice in Riverdale, GA. He is chair of AAHIVM's Georgia chapter and is on AAHIVM's Board of Directors.

HIV Testing = PREVENTION

BY HOLLY KILNESS

CDC Testing Recommendations: The States Respond

THE CENTERS FOR DISEASE CONTROL and Prevention (CDC) released its "Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings" in 2006, advising routine screening of all patients ages 13-64 in all health care settings, with annual tests for persons at high risk for HIV infection.

The medical community and lawmakers in most states largely support the recommendations, and, 44 states (including the District of Columbia) have enacted fully compatible laws.

Since September 2006, 21 states have passed legislation to specifically bring their laws on HIV testing more in line with CDC's recommendations. For example, New Hampshire lawmakers passed legislation stating that healthcare providers "...may test when the patient has consented for the presence of an antibody or antigen to a human immunodeficiency virus in accordance with the most current testing and consent recommendations of the Centers for Disease Control and Prevention."

Other states have tried, but not succeeded in bringing their laws in line. HIV testing laws are under the jurisdiction of each state, and can be incongruent with national recommendations, presenting conflicting information to clinicians.

Some important components of the 2006 recommendations, such as the advent of "opt-out" screening (an HIV test will be performed unless the patient declines), and elimination of separate consent and pre-test counseling provisions, caused legislative headaches in some states. In Massachusetts, the law states that "No health care facility ... and no physician or health care provider shall (1) test any person for the presence of the HTLV-III antibody or antigen without first obtaining his written informed consent."

For the purpose of this section "written informed consent" means a written consent form for each requested release of the results of an individual's HTLV-III antibody or antigen test "... and shall be distinguished from written consent for the release of any other medical information..." However, as of early February, the Massachusetts legislature was considering language more compatible with CDC's recommendations.

Patient-focused and civil liberties groups and individuals in some states saw patient rights as paramount, spawning complex arguments suggesting that routine testing could impede these rights and potentially curb counseling opportunities as well as generate privacy concerns. There also were questions about the availability of counseling and the lack of linkage to quality care and necessary support services for the newly diagnosed.

One example of effective compromise legislation was enacted in Illinois in 2008, where the state Health Department invited community, legal, and medical groups to help create a sound state HIV testing policy. That cooperative effort ultimately led to legislation that fully followed the CDC recommendations, while protecting patient rights by including specific requirements for brief pretest information, informed consent ("opt-out"), patient anonymity, and opportunities for the patient to ask questions related to the test.

As of January 2010, seven states still have some aspect of law that does not fully comply with the CDC recommendations, according to the National HIV/AIDS Clinicians' Consultation Center (NCCC). They are Massachusetts, Minnesota, Nebraska, New York, Pennsylvania, Rhode Island, and Wisconsin. Six of those states are not compatible with the recommendations on consent, while two are not compatible with the recommendations on counseling.

In some states, the law may not conflict with the CDC recommendations, but also may not be fully supportive. For example, the testing laws in New York prescribe, "... no person shall order ... an HIV ... test without first having received the written, informed consent of the subject. ... Where a written consent to HIV related testing is included in a signed general consent to medical care ... the consent form shall have a clearly marked place adjacent to the signature where the subject of the test ... shall be given an opportunity to specifically decline in writing HIV related testing on such general consent."

In other cases, a state may not have laws on the books addressing specific aspects of testing. According to the National HIV/AIDS Clinicians' Consultation Center (NCCC), 30 states have HIV testing laws that do not specifically address opt-in or opt-out requirements for testing. Although some state laws may not be fully compatible with all aspects of the CDC 2006 recommendations, that does not necessarily preclude routine testing. It may just make the goal of routine testing in all health care settings slightly more difficult to accomplish. HIV

About the Author: Holly Kilness is Director of Public Policy at AAHIVM.

BY STEVEN F. WAKEFIELD AND SARAH B. ALEXANDER

Wait, Wait, Don't Test Me!

IF YOUR PATIENT REFUSES AN HIV TEST, could there be a legitimate reason? When a person says "no" to the test because of participation in an HIV vaccine clinical trial, pay attention.

The CDC recommends opt-out HIV testing as a valuable tool to identify HIV positive individuals and interrupt the transmission of HIV. All available tools to identify and counsel HIV-infected individuals should be pursued. However, one important population of persons must be considered in any such policy: participants in HIV vaccine trials.

By 2008, more than 30,000 individuals worldwide had participated voluntarily in experimental HIV vaccine trials. The CDC recommendations pose some complex issues for these individuals, as many will test positive in antibody-based screening assays. In the last five years, almost all HIV vaccines have elicited some reactivity in commercially based assays. All of these vaccine study participants are HIV-negative by RNA/DNA assays.

We don't know how long experimental vaccine recipients will retain these antibodies; some have demonstrated seropositivity for more than 15 years after their trial concluded. With HIV tests, including EIA, Western Blot and rapid tests detecting antibodies, not the virus, HIV vaccine trial participants risk being falsely labeled as HIV positive as a result of HIV testing.

Not only does an incorrect HIV diagnosis cause unwarranted distress to the patient, false diagnoses impact HIV reporting to government and health organizations, potentially calling those statistics into question. Revealing the presence of antibodies to the patient, even if it is not in the form of a false diagnosis, can compromise his or her "blind" participation in the study. This is important because "blinded" participation is necessary for accurate conclusions about the vaccine's efficacy.

During the informed consent process, HIV vaccine trial participants are asked to have all HIV testing performed at their trial sites. The vaccine trial study design requires that sites regularly test participants and provide testing to any participant or former participant on request. Validated algorithms to define HIV infection for vaccination are available at all HIV Vaccine Trials Network sites. Physicians may encounter patients who decline HIV tests because of study participation, and their requests should be respected.

Using the CDC database of HIV testing sites, (available at www.hivtest.org) every HIV testing site within 25 miles of each HIV Vaccine Trials Network study site was sent information about vaccine-induced seropositivity to raise awareness of the importance of HIV testing only at the study site.

You can decrease the risk of an incorrect diagnosis in HIV vaccine trial participants by learning if there are HIV vaccine trials in your area and by asking patients if they are participating in such a trial. If a patient who is a trial participant needs an HIV test, coordinate the test with the participant's trial site.

Apply these best practices to avoid the potential for incorrect diagnosis.

- Inform the patient of his or her legal rights surrounding HIV testing. He or she must consent to–and has the right to refuse–an HIV test (trial participants are advised not to be tested outside the trial site).
- Ask patients if they are participating in an HIV vaccine trial—even if they don't fit your perceptions of study participants.
- Familiarize yourself with HIV vaccine trials happening in your area. Visit www.hvtn.org for information.
- If you need HIV test results on a patient who is an HIV vaccine trial participant, contact the participant's trial site. Coordinate the HIV test through the trial site. The site can perform RNA or DNA HIV testing that provides accurate results to you and the participant. HIV

About the Authors: Steven F. Wakefield is Director of Community Relations and Education at the HIV Vaccine Trials Network (HVTN), located at Fred Hutchinson Cancer Research Center, Seattle, WA.

Sarah B. Alexander is Director of Communications and External Relations at the HVTN. The Network is supported through a cooperative agreement with the National Institute of Allergy and Infectious Diseases, part of the U.S. National Institutes of Health. To learn more about the HVTN, visit www.hvtn.org.

FEDERAL POLICY UPDATE:

Reason for Hope Despite Fiscal Crisis

DURING HIS TIME IN OFFICE, President Bush created an innovative new program to target global HIV/AIDS: the President's Emergency Plan for AIDS Relief (PEPFAR), which required countries receiving funding to develop and implement a national strategy to coordinate efforts to combat the disease. Ironically, it was quickly noted that the United States itself did not have such a strategy, and President Obama promised to change that.

Indeed, many officials in the various departments responsible for tackling the domestic HIV epidemic agree that a national U.S. strategy on HIV/AIDS is long overdue. The U.S. National Strategy for Pandemic Influenza was created in 2005 to address a scientifically theorized emerging threat, yet the HIV/AIDS epidemic has been present in America for almost 30 years and no such program exists.

In concept, the national strategy should both set ambitious national goals for combating the disease and seek better coordination among the programs targeted at monitoring and prevention, as well as programs for treating and caring for those already infected.

Currently, federal funding for, and administration of, HIV/AIDS programs is split among the Centers for Disease Control and Prevention (CDC), the Department of Health and Human Services (HHS), the Health Resources and Services Administration (HRSA), the National Institutes of Health (NIH), the Substance and Mental Health Services Administration (SAMHSA), the Centers for Medicare and Medicaid Services (CMS), the Department of Housing and Urban Development (HUD), and the Veterans Administration (VA).

The Obama White House laid out three goals for the national strategy: reduce HIV incidence, increase access to care and optimize health-related outcomes, and reduce HIV-related health disparities. The White House spent much of last year soliciting public comment through town-hall style events around the country, and requested information from interested groups through an online web-portal.

The American Academy of HIV Medicine (AAHIVM) developed a set of policy recommendations for the strategy, with guidance and input from its Policy Committee. In those recommendations, the Academy sought to focus on the three goals outlined by the White House as well as on steps that could be taken to improve public policies that affect HIV care providers, the care they provide, and the patients they serve.

Jeff Crowley, President Obama's Director of National AIDS Policy, is a strong advocate within the White House for an aggressive initiative to combat HIV/AIDS.

Photo Bob Gatty

The Academy's first recommendation dealt with increasing the U.S. HIV workforce and shoring up the pipeline of future HIV care providers. Another recommendation was to include provider representation on all HIV-related governing bodies. AAHIVM believes that experience from the front lines of battling the disease, and the perspective of those charged with treating the infected, will be invaluable to any HIV related policy discussion.

Reimbursement that adequately reflects the costs of evaluation and disease management, along with the true costs of procedure, labs, and treatment, was also addressed. Another section concerned the topic of coordination of care across medical specialties, and the need for interdisciplinary care to adequately manage the disease. The recommendations were sent to the White House and to the Office of National AIDS Policy (ONAP) last December and can be accessed at the AAHIVM Web site.

Since the start of 2010, an inter-agency committee to develop

President Barack Obama signs the Ryan White HIV/AIDS Treatment Extension Act of 2009, Friday, Oct. 30, 2009, in the Diplomatic Reception Room of the White House in Washington. Behind him are various lawmakers and Jeanne White-Ginder, mother of Ryan White, second right. House Speaker Nancy Pelosi of Calif. is at right.

Photo Gerald Herbert / AP Photo

the National HIV/AIDS Strategy (NHAS), led by Jeffrey S. Crowley, White House Director of National AIDS Policy, has held a series of closed meetings, and the Administration has indicated a draft version of the strategy may be made available for public comment. The timeframe for completion is still uncertain, and HIV/AIDS interest groups (including AAHIVM) are actively and vigorously monitoring progress.

One of the best indicators of how federal policy will emerge in the coming year is the federal budget process, which will provide program funds. The President released his proposed budget for all federal agencies on February 1, but shortly before that the White House announced plans to freeze all discretionary spending programs for three years to reduce the federal budget deficit. Despite that, most HIV/AIDS programs received continued funding at previous levels or modest increases.

The President's budget included a $31 million increase for HIV prevention programs at CDC, including new program collaboration and service integration efforts among HIV, tuberculosis, hepatitis, and sexually transmitted infection (STI) program areas. Another $21 million will go to viral hepatitis efforts. CDC will also launch a new prevention initiative targeted at men who have sex with men (MSM) and transgender populations. The CDC budget also included funding for enhanced surveillance among ethnic and racial minority groups.

Federal Ryan White care and treatment program funding was also increased by $40 million, with a $5.1 million increase for Part C programs at Ryan White HIV clinics nationwide to support Early Intervention Services programs. Ryan White funding for programs in states was also increased moderately, by $10 million, while funding for eligible metropolitan areas was kept at previous levels. Funding for the AIDS Drug Assistance Programs (ADAPs) in the states received a $20 million increase. Other Ryan White programs received continued funding at previous levels, or modest increases.

NIH received increases of $98.7 million for HIV/AIDS related research. Housing programs for people living with HIV/AIDS, and programs targeted at reducing health disparities in minority communities also received increases, as did global HIV programs.

In a season of deep cuts, continued funding of a program at previous levels is a vote of confidence. An increase in funding is a major victory. Still, the response of much of the HIV/AIDS advocacy community to the President's budget was less than positive. Many argued that the President had not done enough in his budget to support the fight against HIV/AIDS. Even more measured responses noted that the funding levels in the President's budget are lower than the estimated need-numbers put forth by advocates for the various federal programs in question, including all parts of Ryan White. Others worried about the lack of specified funding for the NHAS.

However, in a statement from ONAP, White House officials reaffirmed their commitment to developing a national strategy that focuses on "reducing HIV incidence, increasing access to care and optimizing health outcomes, and reducing HIV-related health disparities."

While the President's budget is a powerful indication of White House goals for the coming fiscal year, it is not the final word as Congress will use it as a starting point to hammer out appropriations for specific programs to the various federal agencies. Small changes to funding levels of the programs can occur at any point along that process. Additionally, any sort of health care reform efforts that Congress may still manage to pass could affect available resources for some HIV/AIDS programs.

Despite a relatively slow start in moving forward HIV/AIDS policymaking, year two of the President's term has started out with several reasons for optimism. The President's budget provided security for HIV/AIDS programs in the midst of a harsh budgetary climate, and ONAP has provided assurances that it is moving forward with development of the National HIV/AIDS Strategy. President Obama made the fight against HIV/AIDS one of his top domestic agenda priorities during his campaign, and there seems to be reason to hope it remains a top priority. HIV

About the Author: Holly Kilness is Director of Public Policy at AAHIVM.

Letters to THE EDITOR

A PATIENT'S PERSPECTIVE:

Better Understanding of the Concerns of Female Patients by Physicians is Needed

MY NAME IS DENA GRAY and I am writing to you from Houston, TX. I accessed your magazine online through your website. It is an excellent publication. Thank you for designing the tool for HIV specialists to access. I hope it continues to grow and add value to the relationship between the patient and the client.

Thank you as well for allowing me the opportunity to make some commentary, particularly on the issue regarding HIV and Women.

I have been HIV positive since 1991, diagnosed at the age of 21. I am 40 years old now and am grateful for every moment that I have had.

In the first few years of my "new" life, I lived very silently. However, as a journalism and communications major in college, I found the role of silent sufferer hard to maintain. So, with the assistance of other HIV positive advocates, I channeled the energy and education into a new role of advocate, for myself and for the community, especially women.

One of the challenges that women face in trying to live and thrive with HIV is the feeling of inferiority, not only within their families and communities, but primarily with their doctors and the organizations that provide services to them. Fear of being "kicked out" or not receiving services is a fundamental reason why so many women choose not to seek services or do not advocate for their own healthcare.

Over the past 20 years, I have received hundreds of calls from men and women who seek assistance in challenging their doctor's wisdom or the agency's practices. We feel like we must do what someone else says ... we don't trust our own opinions anymore ... like we don't know how to manage our lives. (Of course if we did, we wouldn't have the disease.)

Some attention needs to be paid to understanding these concerns of women and their roles as self-advocates. We need to encourage more women to seek partnerships with their doctors and providers so they feel like an active participant in their care.

For providers ... I have a friend who is a director of a standardized patient program at a major university, her second such job. At both positions, HIV/AIDS was never a disease that resident physicians learned how to manage with clients through the educational process.

I would be interested to know how many and where the schools are that encourage HIV/AIDS study in the standardized patient programs. I pose the thought/questions because if we are to encourage routine testing of HIV/AIDS and make it a part of normal screenings, then doctors implementing the tests should have some background regarding how to handle their patients. I am very impressed with standardized patient programs, but it seems like an effort is needed to increase HIV/AIDS as a study curriculum. HIV

— Dena Gray

Editor's Note: Dena Gray will be a frequent contributor to *HIV Specialist* in the future.

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Editor-in-chief

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Assistant editors

Anthony Amoroso, MD
Institute of Human Virology, University of Maryland School of Medicine, Baltimore Veterans Hospital, USA

Bruce Gilliam, MD, AAHIVS
AIDS Education and Training Center (AETC), Maryland General Hospital, University of Maryland School of Medicine, USA

Eric P Goosby, MD
United States Global AIDS Coordinator

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