The AMERICAN ACADEMY of HIV MEDICINE®

HIV SPECIALIST

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

April 2013 Volume 5 No. 1 www.aahivm.org

HIV in the LATINO Community

Now with data through

96 WEEKS

Efficacy

Safety and tolerability profile

Drug interaction profile

INDICATION AND USAGE

COMPLERA (emtricitabine 200mg/rilpivirine 25mg/tenofovir disoproxil fumarate 300mg) is indicated for use as a complete regimen for the treatment of HIV-1 infection in antiretroviral treatment-naïve adult patients with HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy.

This indication is based on safety and efficacy analyses through 96 Weeks from 2 randomized, double-blind, active controlled, Phase 3 trials in treatment-naïve subjects.

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

- More rilpivirine-treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure (HIV-1 RNA ≥ 50 copies/mL) compared to rilpivirine-treated subjects with HIV-1 RNA less than or equal to 100,000 copies/mL
- Regardless of HIV-1 RNA level at the start of therapy, more rilpivirine-treated subjects with CD4+ cell count less than 200 cells/mm^3 at the start of therapy experienced virologic failure compared to subjects with CD4+ cell count greater than or equal to 200 cells/mm^3
- The observed virologic failure rate in rilpivirine-treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz
- More subjects treated with rilpivirine developed tenofovir and lamivudine/emtricitabine associated resistance compared to efavirenz
- COMPLERA is not recommended for patients less than 18 years of age

IMPORTANT SAFETY INFORMATION

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

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate, a component of COMPLERA, in combination with other antiretrovirals**
- **COMPLERA is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of COMPLERA have not been established in patients coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued EMTRIVA® (emtricitabine) or VIREAD® (tenofovir disoproxil fumarate), which are components of COMPLERA. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue COMPLERA. If appropriate, initiation of anti-hepatitis B therapy may be warranted**

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

NNRTI=non-nucleoside reverse transcriptase inhibitor.

GILEAD

For treatment-naïve adult patients with HIV-1 RNA ≤100,000 copies/mL at the start of therapy

One Complete Treatment Option

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

IMPORTANT SAFETY INFORMATION (CONT)

Contraindications

- **Coadministration:** COMPLERA should not be coadministered with drugs that induce CYP3A enzyme or increase gastric pH as loss of virologic response and possible resistance may occur. Use of the following drugs with COMPLERA is contraindicated: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, proton pump inhibitors (such as esomeprazole, lansoprazole, dexlansoprazole, omeprazole, pantoprazole, rabeprazole), dexamethasone (more than a single dose) and *Hypericum perforatum* (St. John's wort)

Warnings and Precautions

- **New onset or worsening renal impairment:** Renal impairment, including cases of acute renal failure and Fanconi syndrome may occur. Assess creatinine clearance (CrCl) before initiating treatment with COMPLERA. Monitor CrCl and serum phosphorus in patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil. Avoid administering COMPLERA with concurrent or recent use of nephrotoxic drugs. Patients with CrCl below 50 mL per minute should not receive COMPLERA
- **Drug interactions:** Use COMPLERA with caution when given with drugs that may reduce the exposure of rilpivirine or when coadministered with a drug with known risk of Torsades de Pointes. Supratherapeutic doses of rilpivirine have been shown to prolong the QTc interval of the electrocardiogram in healthy subjects

  Please see the full Prescribing Information and below for more information about potential drug interactions with COMPLERA.
- **Depressive disorders:** Depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) have been reported with rilpivirine. The incidence of depressive disorders reported through 96 Weeks among rilpivirine (N=686) or efavirenz (N=682) was 9% and 8%, respectively in Phase 3 trials. Most events were mild or moderate in severity. Grade 3 and 4 depressive disorders (regardless of causality) were reported at 1% in both study arms. Suicide attempt was reported in 2 subjects and suicide ideation was reported in 4 subjects treated with rilpivirine. Patients with severe depressive symptoms should seek immediate medical evaluation and the risks of continued therapy should be determined
- **Hepatotoxicity:** Hepatic adverse events have been reported in patients on a rilpivirine regimen. Patients with underlying liver disease and those with marked elevations in serum liver biochemistries may be at increased risk. Appropriate laboratory testing and monitoring should be undertaken for all patients before and during therapy with COMPLERA, as hepatic toxicity has been reported in patients without underlying liver disease or risk factors
- **Decreases in bone mineral density (BMD)** and cases of osteomalacia have been seen in patients treated with tenofovir disoproxil fumarate (DF). Consider monitoring BMD in patients with a history of pathologic fracture or risk factors for osteoporosis or bone loss
- **Coadministration with other antiretroviral products:** Do not administer concurrently with other products containing any of the same active components (emtricitabine, rilpivirine, or tenofovir DF) or with products containing lamivudine or adefovir dipivoxil
- **Fat redistribution/accumulation** has been observed in patients receiving antiretroviral therapy
- **Immune reconstitution syndrome,** including the occurrence of autoimmune disorders with variable times to onset, has been reported

Adverse Reactions

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

Drug Interactions

- COMPLERA is a complete treatment regimen for treating HIV-1 infection and should not be coadministered with other antiretroviral agents
- **Drugs inducing or inhibiting CYP3A:** Drugs which induce CYP3A enzymes should not be coadministered with COMPLERA due to potential for loss of virologic response and/or resistance. **(See CONTRAINDICATIONS).** Coadministration of COMPLERA with drugs that inhibit CYP3A may increase rilpivirine plasma concentrations
  - **Potentially significant drug interactions** may occur with **azole antifungal agents** and **macrolide/ketolide antibiotics** coadministered with rilpivirine by increasing plasma concentrations of rilpivirine (due to inhibition of CYP3A enzymes). Clinical monitoring is recommended when coadministering COMPLERA with **methadone**
- **Drugs increasing gastric pH** may cause significant decreases in rilpivirine plasma concentrations **(See CONTRAINDICATIONS)**
  - Antacids should be administered at least 2 hrs before or 4 hrs after COMPLERA
  - H_2 Receptor antagonists should be administered 12 hrs before or 4 hrs after COMPLERA
- **Drugs affecting renal function:** Caution should be used when coadministering COMPLERA with drugs that reduce renal function or compete for active tubular secretion. Examples include acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, and valganciclovir
- **QT prolonging drugs:** Supratherapeutic doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the EKG in healthy subjects

  Please see full Prescribing Information for more information about potential drug interactions with COMPLERA.

Pregnancy and Breastfeeding

- **Pregnancy Category B:** There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if potential benefits justifies the potential risk. An Antiretroviral Pregnancy Registry has been established
- **Breastfeeding:** Mothers with HIV should be instructed not to breastfeed due to the potential for HIV transmission. Because emtricitabine and tenofovir have been detected in human milk, the risk to the infant is unknown

Dosing and Administration

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

Renal Impairment: Do not use with patients requiring dose adjustment or with patients with creatinine clearance below 50 mL per minute.

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

GILEAD

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

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

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS
and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate, a component of COMPLERA, in combination with other antiretrovirals *[See Warnings and Precautions].*
COMPLERA is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of COMPLERA have not been established in patients coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued EMTRIVA or VIREAD, which are components of COMPLERA. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue COMPLERA. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[See Warnings and Precautions].*

INDICATIONS AND USAGE

COMPLERA® (emtricitabine/rilpivirine/tenofovir disoproxil fumarate) is indicated for use as a complete regimen for the treatment of HIV-1 infection in antiretroviral treatment-naive adult patients with HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy.

This indication is based on safety and efficacy analyses through 96 weeks from 2 randomized, double blind, active controlled, Phase 3 trials in treatment-naive subjects.

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

- More rilpivirine-treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure (HIV-1 RNA ≥50 copies/mL) compared to rilpivirine-treated subjects with HIV-1 RNA less than or equal to 100,000 copies/mL.
- Regardless of HIV-1 RNA level at the start of therapy, more rilpivirine-treated subjects with CD4+ cell count less than 200 cells/mm^3 experienced virologic failure compared to rilpivirine-treated subjects with CD4+ cell count greater than or equal to 200 cells/mm^3.
- The observed virologic failure rate in rilpivirine-treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz.
- More subjects treated with rilpivirine developed tenofovir and lamivudine/emtricitabine associated resistance compared to efavirenz.

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

DOSAGE AND ADMINISTRATION

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

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

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate (tenofovir DF), a component of COMPLERA, in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with COMPLERA should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

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

New Onset or Worsening Renal Impairment: Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir DF *[See Adverse Reactions]*.

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

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

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

Depressive Disorders: The adverse reaction depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) has been reported with rilpivirine. During the Phase 3 trials (N = 1368) through 96 weeks, the incidence of depressive disorders (regardless of causality, severity) reported among rilpivirine (N = 686) or efavirenz (N = 682) was 9% and 8%, respectively. Most events were mild or moderate in severity. The incidence of Grade 3 and 4 depressive disorders (regardless of causality) was 1% for both rilpivirine and efavirenz. The incidence of discontinuation due to depressive disorders among rilpivirine or efavirenz was 1% in each arm. Suicidal ideation was reported in 4 subjects in each arm while suicide attempt was reported in 2 subjects in the rilpivirine arm. Patients with severe depressive symptoms should seek immediate medical evaluation to assess the possibility that the symptoms are related to COMPLERA, and if so, to determine whether the risks of continued therapy outweigh the benefits.

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

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 or bone loss. Although the effect of supplementation with calcium and Vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

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

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

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

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

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

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

ADVERSE REACTIONS

*See **BOXED WARNINGS** and **WARNINGS AND PRECAUTIONS** sections for additional serious 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.

Studies C209 and C215 – Treatment-Emergent Adverse Drug Reactions: The safety assessment of rilpivirine, used in combination with other antiretroviral drugs, is based on the Week 96 pooled data from 1368 patients in the Phase 3 trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) in antiretroviral treatment-naive HIV-1 infected adult patients. A total of 686 patients received rilpivirine in combination with other antiretroviral drugs as background regimen; most (N=550) received emtricitabine/tenofovir DF as background regimen. The number of subjects randomized to the control arm efavirenz was 682, of which 546 received emtricitabine/tenofovir DF as background regimen. The median duration of exposure for subjects in either treatment arm was 104 weeks.

Adverse drug reactions (ADR) observed at Week 96 in patients who received rilpivirine or efavirenz plus emtricitabine/tenofovir DF as background regimen are shown in Table 1. No new types of adverse reactions were identified between Week 48 and Week 96. The adverse drug reactions observed in this subset of patients were generally consistent with those seen for the overall patient population participating in these studies (refer to the prescribing information for EDURANT).

The proportion of subjects who discontinued treatment with rilpivirine or efavirenz + emtricitabine/tenofovir DF due to ADR, regardless of severity, was 2% and 5%, respectively. The most common ADRs leading to discontinuation were psychiatric disorders: 9 (1.6%) subjects in the rilpivirine + emtricitabine/tenofovir DF arm and 12 (2.2%) subjects in the efavirenz + emtricitabine/tenofovir DF arm. Rash led to discontinuation in 1 (0.2%) subject in the rilpivirine + emtricitabine/tenofovir DF arm and 10 (1.8%) subjects in the efavirenz + emtricitabine/tenofovir DF arm.

Common Adverse Drug Reactions

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

Table 1 Selected Treatment-Emergent Adverse Reactions[a] (Grades 2–4) Reported in ≥2% of Subjects Receiving Rilpivirine or Efavirenz in Combination with Emtricitabine/Tenofovir DF in Studies C209 and C215 (Week 96 analysis)

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

a. Frequencies of adverse reactions are based on all Grades 2-4 treatment-emergent adverse events, assessed to be related to study drug.
b. Includes adverse drug reactions reported as depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicide ideation.

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

Emtricitabine and Tenofovir Disoproxil Fumarate: The following adverse reactions were observed in clinical trials of emtricitabine or tenofovir DF in combination with other antiretroviral agents: The most common adverse drug reactions occurred in at least 10% of treatment-naive subjects in a phase 3 clinical trial of emtricitabine and tenofovir DF in combination with another antiretroviral agent are diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. In addition, adverse drug reactions that occurred in at least 5% of treatment-experienced or treatment-naive subjects receiving emtricitabine or tenofovir DF with other antiretroviral agents in clinical trials include abdominal pain, dyspepsia, vomiting, fever, pain, nasopharyngitis, pneumonia, sinusitis, upper respiratory tract infection, arthralgia, back pain, myalgia, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), anxiety, increased cough, and rhinitis. Skin discoloration has been reported with higher frequency among emtricitabine-treated subjects; it was manifested by hyperpigmentation on the palms and/or soles and was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

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

Table 2 Selected Laboratory Abnormalities (Grades 1-4) Reported in Subjects Who Received Rilpivirine or Efavirenz in Combination with Emtricitabine/Tenofovir DF in Studies C209 and C215 (Week 96 Analysis)

Laboratory Parameter Abnormality, (%)	DAIDS Toxicity Range	Rilpivirine + FTC/TDF N=550	Efavirenz + FTC/TDF N=546
BIOCHEMISTRY			
Increased Creatinine			
Grade 1	1.1-1.3 x ULN[a]	6%	1%
Grade 2	>1.3-1.8 x ULN	1%	1%
Grade 3	>1.8-3.4 x ULN	<1%	0
Grade 4	>3.4 x ULN	0	<1%
Increased AST			
Grade 1	1.25-2.5 x ULN	16%	19%
Grade 2	>2.5-5.0 x ULN	4%	7%
Grade 3	>5.0-10.0 x ULN	2%	3%
Grade 4	>10.0 x ULN	1%	1%
Increased ALT			
Grade 1	1.25-2.5 x ULN	19%	22%
Grade 2	>2.5-5.0 x ULN	5%	7%
Grade 3	>5.0-10.0 x ULN	1%	2%
Grade 4	>10.0 x ULN	1%	1%
Increased Total Bilirubin			
Grade 1	1.1-1.5 x ULN	6%	<1%
Grade 2	>1.5-2.5 x ULN	3%	1%
Grade 3	>2.5-5.0 x ULN	1%	<1%
Increased Total Cholesterol (fasted)			
Grade 1	200-239 mg/dL	14%	31%
Grade 2	240-300 mg/dL	6%	18%
Grade 3	>300 mg/dL	<1%	2%
Increased LDL Cholesterol (fasted)			
Grade 1	130-159 mg/dL	13%	28%
Grade 2	160-190 mg/dL	5%	13%
Grade 3	>190 mg/dL	1%	4%
Increased Triglycerides (fasted)			
Grade 2	500-750 mg/dL	1%	2%
Grade 3	751-1,200 mg/dL	1%	2%
Grade 4	>1,200 mg/dL	0	1%

N = number of subjects per treatment group
a. ULN = Upper limit of normal value.
Note: Percentages were calculated versus the number of subjects in ITT population with emtricitabine + tenofovir DF as background regimen.

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

Adrenal Function: In the pooled Phase 3 trials of C209 and C215, in subjects treated with rilpivirine plus any of the allowed background regimen (N=686), at Week 96, there was an overall mean change from baseline in basal cortisol of -19.1 (95% CI: -30.9; -7.4) nmol/L in the rilpivirine group, and of +0.1 (95% CI: -12.6; 12.8) nmol/L in the efavirenz group. At Week 96, the mean change from baseline in ACTH-stimulated cortisol levels was lower in the rilpivirine group (+18.4± 8.36 nmol/L) than in the efavirenz group (+54.1± 7.24 nmol/L). Mean values for both basal and ACTH-stimulated cortisol values at Week 96 were within the normal range. Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency. Effects on adrenal function were comparable by background N(t)RTIs.

Serum Creatinine: In the pooled Phase 3 trials of C209 and C215 trials in subjects treated with rilpivirine plus any of the allowed background regimen (N=686), there was a small increase in serum creatinine over 96 weeks of treatment with rilpivirine. Most of this increase occurred within the first four weeks of treatment with a mean change of 0.1 mg/dL (range: -0.3 mg/dL to 0.6 mg/dL) observed through Week 96. In subjects who entered the trial with mild or moderate renal impairment, the serum creatinine increase observed was similar to that seen in subjects with normal renal function. These changes are not considered to be clinically relevant and no subject discontinued treatment due to increases in serum creatinine. Creatinine increases were comparable by background N(t)RTIs.

Serum Lipids: In clinical studies, analysis of serum lipids excluded subjects receiving lipid lowering agents during the treatment period. Through Week 96, 1% or fewer subjects receiving rilpivirine + emtricitabine/tenofovir DF were reported as having Grades 3 elevations in fasting cholesterol (> 300 mg/dL), fasting LDL cholesterol (> 190 mg/dL) or Grade 3-4 triglycerides (>751 mg/dL). In subjects in the rilpivirine treatment arm, through Week 96 (N=550), the mean change from baseline in total cholesterol, LDL-cholesterol and triglycerides (pooled data) are as follows: total cholesterol [TC] (fasted) +2 mg/dL (N=430) [mean baseline TC=162 mg/dL]; HDL-cholesterol [HDL] (fasted) +4 mg/dL (N=429) [mean baseline HDL=42 mg/dL]; LDL-cholesterol [LDL] (fasted) -1 mg/dL (N=427) [mean baseline LDL=97 mg/dL], and Triglycerides [TG] (fasted) -14 (mg/dL) (N=430) [mean baseline TG=123 mg/dL]. The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 96 values.

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

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of emtricitabine or tenofovir DF. 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.

Rilpivirine

Renal and Urinary Disorders: nephrotic syndrome

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

Tenofovir Disoproxil Fumarate:

Immune System Disorders: allergic reaction, including angioedema

Metabolism and Nutrition Disorders: lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, and Mediastinal Disorders: dyspnea

Gastrointestinal Disorders: pancreatitis, increased amylase, abdominal pain

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

Skin and Subcutaneous Tissue Disorders: rash

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

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

General Disorders and Administration Site Conditions: asthenia

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

DRUG INTERACTIONS

COMPLERA is a complete regimen for the treatment of HIV-1 infection; therefore, COMPLERA should not be administered with other antiretroviral medications. Information regarding potential drug-drug interactions with other antiretroviral medications is not provided. Please refer to the EDURANT, VIREAD and EMTRIVA prescribing information as needed. There were no drug-drug interaction trials conducted with the fixed-dose combination tablet. Drug interaction studies were conducted with emtricitabine, rilpivirine, or tenofovir DF, the components of COMPLERA. This section describes clinically relevant drug interactions with COMPLERA *[See Contraindications]*.

Drugs Inducing or Inhibiting CYP3A Enzymes: Rilpivirine is primarily metabolized by cytochrome P450 (CYP) 3A, and drugs that induce or inhibit CYP3A may thus affect the clearance of rilpivirine *[See Clinical Pharmacology, Contraindications]*. Coadministration of rilpivirine and drugs that induce CYP3A may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs. Coadministration of rilpivirine and drugs that inhibit CYP3A may result in increased plasma concentrations of rilpivirine. Rilpivirine at a dose of 25 mg once daily is not likely to have a clinically relevant effect on the exposure of drugs metabolized by CYP enzymes.

Drugs Increasing Gastric pH: Coadministration of rilpivirine with drugs that increase gastric pH may decrease plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs *[see Drug Interactions,Table 4]*.

Drugs Affecting Renal Function: Because emtricitabine and tenofovir are primarily eliminated by the kidneys through a combination of glomerular filtration and active tubular secretion, coadministration of COMPLERA with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated drugs. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, and valganciclovir.

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

Established and Other Potentially Significant Drug Interactions

Important drug interaction information for COMPLERA is summarized in Table 4. The drug interactions described are based on studies conducted with emtricitabine, rilpivirine, or tenofovir DF as individual medications that may occur with COMPLERA or are potential drug interactions; no drug interaction studies have been conducted using COMPLERA. The tables include potentially significant interactions, but are not all inclusive.

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

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

a. This table is not all inclusive.
b. Increase = ↑; Decrease = ↓; No Effect = ↔
c. The interaction was evaluated in a clinical study. All other drug-drug interactions shown are predicted.
d. This interaction study has been performed with a dose higher than the recommended dose for rilpivirine. The dosing recommendation is applicable to the recommended dose of rilpivirine 25 mg once daily.

Drugs with No Observed or Predicted Interactions with COMPLERA

No clinically significant drug interactions have been observed between emtricitabine and famciclovir or tenofovir DF. Similarly, no clinically significant drug interactions have been observed between tenofovir DF and entecavir, methadone, oral contraceptives, ribavirin, or tacrolimus in studies conducted in healthy subjects. No clinically significant drug interactions have been observed between rilpivirine and acetaminophen, atorvastatin, chlorzoxazone, ethinylestradiol, norethindrone, sildenafil, and tenofovir DF. No clinically relevant drug-drug interaction is expected when rilpivirine is coadministered with ribavirin.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

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

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

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

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, COMPLERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.

Emtricitabine: Samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine is secreted in human milk. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine are unknown.

Rilpivirine: Studies in lactating rats and their offspring indicate that rilpivirine was present in rat milk. It is not known whether rilpivirine is secreted in human milk.

Tenofovir Disoproxil Fumarate: Samples of breast milk obtained from five HIV-1 infected mothers in the first post-partum week show that tenofovir is excreted in human milk. The impact of this exposure in breastfed infants is unknown.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving COMPLERA**.

Pediatric Use

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

Geriatric Use

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

Renal Impairment

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

Hepatic Impairment

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

OVERDOSAGE

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

Issued: January 2013

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

Addressing the Unique Needs of a Community

I WOULD BE REMISS to begin this column without acknowledging the recent passing of a hero in the HIV/AIDS community, Dr. C Everett Koop. When I was a senior career policy official in the U.S. Public Health Service, I had the good fortune to work alongside Dr. Koop when he became the Surgeon General of the U.S. I found him to be so unlike the caricature of him the media had created. Yes, he was a stern conservative. He was also warm, friendly, thoughtful, and committed to caring for people—even if they were gay and infected with AIDS. His AIDS pamphlet mailed to every household in the U.S. in 1986 made that abundantly clear and was an important milestone in our HIV/AIDS history. The pamphlet conveyed more than the medical/scientific information in it. It changed the way our society thought about AIDS, and was another step in reducing the stigma associated with being gay in America. His leadership and courage will be his legacy.

It was also recently announced that another HIV champion, Dr. Deborah Parham Hopson, formerly the Director of the HIV/AIDS Bureau (HAB) in the Health Resources and Services Administration (HRSA), will be assuming new responsibilities. The Ryan White Program she headed provided infrastructure, education, resources and services to HIV patients across the United States. And not for just any HIV patients, but those HIV patients who needed it the most—those that did not have access to life saving healthcare. Again while I was in the U.S. Public Health Service, I knew Deborah even before she became a Hopson—before she completed her Ph.D. and before there was a HAB. She has always been a bright, committed caring healthcare professional. A couple of years ago, I had the honor of sitting next to Deborah's mother at a Ryan White event. Her mother was rightfully proud of all that her daughter was achieving. There is no doubt that Deborah's achievements will continue into the future.

James M. Friedman

Our members and the patients we serve owe a lot to these two individuals.

In this issue of *HIV Specialist*, you'll learn the names of other HIV champions, working diligently to raise awareness of the growing epidemic in the Latino community. According to the new 2011 Centers for Disease Control (CDC) Surveillance Report, Latinos represent 21 percent of the new HIV infections while representing 16 percent of the population. In 2011 alone, 10,159 Hispanics were diagnosed with HIV. Far too many. But we know that there are cultural and language barriers that can make their care more challenging. A number of articles in this issue provide some guidance in addressing these challenges.

Working towards reducing the incident rate of HIV in at-risk populations has been the defining factor in the success of fighting the disease. When Dr. Koop began as Surgeon General, the educational and scientific focus was on the gay community. Since then, we have also focused efforts on women, mother-to-child transmission and the African-American community. History has shown that by tailoring outreach to address the unique needs of a population, we can make a bigger difference.

By educating ourselves on the cultural challenges within Latino communities, we can provide better communication, treatment and access to care. HIV

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VOLUME 5 / NUMBER 1 • APRIL 2013

PUBLISHER
THE AMERICAN ACADEMY OF HIV MEDICINE
1705 DeSales St., NW, Suite 700
Washington, D.C. 20036
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Prevention Research Update from CROI 2013

BY JEFFREY T. SCHOUTEN, MD, JD, AAHIVE

MAJOR HIV PREVENTION STUDIES were presented at the 20th Conference on Retroviruses and Opportunistic Infections (CROI). The VOICE study (MTN 003), conducted by the Microbicide Trials Network, enrolled women in a 5-arm, randomized, double-blind, placebo-controlled trial assessing the safety and efficacy of daily use of oral tenofovir (TDF), oral tenofovir/emtricitabine (TDF/FTC) and 1% vaginal tenofovir gel (TFV). Two of the arms had been closed prior to the completion of study for futility (oral TDF and TFV gel, in September and November 2011, respectively).

A total of 5,029 women were enrolled at 15 sites in South Africa, Uganda, and Zimbabwe. Broad eligibility criteria included report of vaginal intercourse in the prior 3 months, negative pregnancy test, and willingness to use effective contraception throughout study. HIV testing was done monthly and plasma TDF levels were measured quarterly. The mean age was 25.3 years and 79 percent of the women were unmarried.

Over follow-up of 5511 person-years, 334 HIV infections occurred, including 22 infections defined as acute HIV with RNA present at enrollment. Excluding these 22 participants, HIV incidence was 5.7 per 100 person-years, and ranged from 0.8 to 9.9 per 100 person-years by site. This was higher than projected in the study design. None of the interventions were effective at reducing HIV acquisition. Effectiveness was –48.8 percent for TDF (hazard ratio [HR] 1.49; 95% confidence interval [CI] 0.97, 2.29), –4.2 percent for TDF/FTC (hazard ratio [HR] 1.04; 95%CI 0.73, 1.49), and 14.7 percent for TFV gel (HR 0.85; 95%CI 0.6, 1.2).

In a case-cohort subset, TFV was detected on average in only 28 percent of available quarterly plasma samples among participants randomized to TDF, 29 percent to TDF/FTC, and 22 percent to TFV gel. The drug assay sensitivity was very low so should have detected recent or intermittent use. Most women self-reported high rates of adherence, in the range of 90 percent. Product use was so low that the study could not even measure the effectiveness in the subset of regular users determined by drug levels. No safety concerns were identified.

The VOICE results are consistent with the FemPrEP study in a population of women in southern Africa at high risk for HIV acquisition. Qualitative research is forthcoming from the VOICE study to attempt to understand the discordance with self-report and product use determined by objective measure, as well as perception of risk. In contrast, the Partners PrEP study, which showed high efficacy of TDF and TDF/FTC, was conducted in serodiscordant couples.

Another major prevention study presented was Project Accept (HPTN 043) conducted by the HIV Prevention Trials Network. It was a large community randomized trial testing whether HIV incidence can be reduced in communities receiving community-based voluntary counseling and testing (CBVCT) relative to communities receiving standard clinic-based voluntary counseling and testing (SVCT). Included in the study were 16 communities in South Africa, 10 in Tanzania, 8 in Zimbabwe, and 14 in Thailand randomized in matched pairs to either CBVCT or SVCT.

CBVCT was designed to: make VCT more available in community settings; engage the community through outreach; and provide post-test support. These strategies targeted change in community norms to reduce the risk for HIV infection among all community members, regardless of direct participation in the intervention. The post-intervention assessment was conducted using a single cross-sectional random survey of 18- to 32-year-old community residents who provided blood samples (N = 54,327) for HIV incidence analysis. HIV incidence was estimated using a multi-assay algorithm developed by the HPTN Network Laboratory that included the BED assay, an avidity assay, CD4+ cell count, and HIV viral load. This incidence assay and algorithm is a major contribution of this study.

During the 36-month intervention phase of the study, 15,603 units of community mobilization, 71,842 units of voluntary counseling and testing, and 51,787 units of post-test support services were delivered. The estimated reduction in incidence in intervention vs. control communities was 13.9 percent (relative risk [RR] = 0.861, 95% confidence intervals [CI] 0.725–1.023; p = 0.08). HIV incidence was reduced by 1.5 percent among the 18- to 24-year-olds and by 25.4 percent (RR = 0.75; 95%CI 0.54-1.04, p = 0.08) in 25- to 32-year-olds.

Incidence was reduced by 11.6 percent in women (95%CI 0.73-1.07, p = 0.17) and by 19.3 percent in men (95%CI 0.57-1.15, p = 0.19). Women older than 24 years had a 30.2 percent reduction in incidence (95%CI: 0.54-0.90, p = 0.009). Younger men, older men, and younger women did not have enough incident cases to evaluate the intervention effect reliably. These results suggest a modest reduction in incidence in the intervention versus control communities and support new studies adding enhanced linkage to care and treatment as prevention to reduce community viral load and transmission. HIV

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SHUTTERSTOCK

New US Report Suggests New Steps for Anti-AIDS Program

The U.S. initiative to fight AIDS should increase its programs, better target resources and focus more on prevention, says a new report from the Institute of Medicine (IOM) released in late February.

The report praised the President's Emergency Plan for AIDS Relief (PEPFAR), citing the "millions of lives worldwide" that have been saved and improved by U.S. investments against AIDS. It also laid out a path for PEPFAR to build on its progress and increase effectiveness as countries seek to "sustainably manage the response to HIV."

"PEPFAR has achieved—and in some cases surpassed— its initial ambitious aims," the report said. "That success has in effect 'reset' the baseline and shifted global expectations for what can be achieved in partner countries."

The IOM said PEPFAR should take the long view in its efforts to fight HIV and AIDS, fostering delivery systems and best practices that will serve AIDS-ridden countries in the future. It also recommended that new policies tighten the links between diagnosis and treatment for HIV/AIDS patients and encourage treatment adherence. PEPFAR must also encourage a greater focus on prevention, targeted services and program monitoring in partner countries, the report said.

"As it moves forward, PEPFAR must continue to be bold in its vision, implementation, and global leadership," said international health expert Robert Black, who led the study.

PEPFAR was launched by President George W. Bush in 2003 with $15 billion to spend against AIDS worldwide. It was subsequently reauthorized in 2008 with up to $39 billion through this year. HIV

The HIV/AIDS Community Pays Tribute to the Surgeon General That Changed the Face of AIDS

BY VERONICA MILLER, PHD, EXECUTIVE DIRECTOR, THE FORUM FOR COLLABORATIVE HIV RESEARCH

As the nation and indeed the world says goodbye to Dr. C. Everett Koop, the 13th Surgeon General of the U.S., and one of the greatest public health leaders of all time, it is a good time to reflect on Dr. Koop's leadership from the first days of the AIDS crisis to the end of Dr. Koop's life when he advocated for accelerated HIV testing.

During to the 2010 National Summit on HIV Diagnosis, Prevention and Access to Care in Washington, Dr. Koop gave an hour-long and very candid address to the HIV/AIDS community reflecting his lessons learned over 25 years in combating HIV/AIDS. He talked about June 1981, when he first learned that five homosexual men in Los Angeles who were dying from Pneumocystis Carinii pneumonia, which he called "a disease so rare that a handful of cases in a single year is like an epidemic." He then recounted learning a month later of 26 cases of homosexual men who were diagnosed with Kaposi's sarcoma, an equally rare form of skin cancer.

Dr. Koop called these first cases "ground zero in the fight against HIV/AIDS" and recounted the rapid progression of this disease during the 1980s. By 1985, 12,000 cases had been reported; by 1986, the number had jumped to 16,000. A year later, there were 30,000 cases. He likened the contagion to the arrival and spread of small pox and the bubonic plague in Europe in the Middle Ages.

But what makes Dr. Koop so remarkable is how he responded to this escalating crisis. Even though the virus remained a mystery for many years, Dr. Koop focused on the science, which showed that HIV is not contagious but rather, transmitted via blood or semen. And he used this understanding and his compassion as a physician to respond to politicians who called for a quarantine of AIDS patients and to overcome public fear at a time when Americans worried about contagion through casual contact in schools, restaurants and public restrooms.

In the face of a deadly epidemic, Dr. Koop was also bold. In 1986, he issued the famous Surgeon General's report to the American people on just what the AIDS threat was all about. And long before there was the Internet , he turned the report into an eight-page pamphlet and sent it to all American households – 107 million at the time. He said that as Surgeon General, his job was to wage all-out war against disease, not people – which he did by giving Americans the facts in plain English, dispelling rumors and educating the public about how the disease is transmitted, who is at risk and what people could do to protect themselves.

After antiretroviral therapy changed the course of AIDS from a deadly disease to a chronic condition, Dr. Koop continued to press for research and became a vocal advocate for accelerated routine testing. And late in his life, he spoke out about against ignorance and complacency, which he called the "new front in the war against HIV/AIDS." His takeaway observation was that the nation must remain aware and knowledgeable about HIV and the public health community must always be vigilant in its prevention and early detection efforts.

From this first days as Surgeon General to his last years of life, Dr. Koop was the Surgeon General that changed the face of AIDS. And he did it with candor, compassion and a respect for all people—gay and straight, married and unmarried, regardless of their race or creed. In every way, he was the "nation's doctor" and the straight talk he gave to the American public combined with the care he gave to people with HIV/AIDS must always be what we in the HIV/AIDS community must aspire to. HIV

'Intensified' Antiretroviral Regimen Reduces Viral Shedding in Semen

The addition of Selzentry (maraviroc) and Isentress (raltegravir) to a standard triple drug antiretroviral cocktail rapidly suppresses HIV viral load in semen and significantly reduces the likelihood of intermittent, low level shedding of the virus in seminal fluid, aidsmap reports.

Researchers published their findings in the online edition of The Journal of Infectious Diseases of this study of 13 gay men who began this intensified therapy and 25 controls who took a standard triple-drug regimen of antiretrovirals (ARVs). None of the participants had a sexually transmitted infection (STI), which has been shown to cause viral shedding in semen.

After recent studies have shown that suppressing viral load drastically reduces the likelihood of transmissions, other research has identified individuals who maintain an undetectable viral load in their blood, but who still experience isolated HIV shedding (IHS) in their semen, raising the possibility that they still may be intermittently infectious. There have indeed been isolated reports of such transmissions.

Those taking the intensive therapy experienced more rapid viral suppression in their semen. IHS was found in more than one clinic visit in two participants (15 percent) on intensive therapy compared with 12 of the controls (48 percent). After one of the participants maintained an undetectable viral load in his blood but a detectable seminal viral load for 14 months after beginning intensified treatment, the investigators observed another cohort to find if there was viral shedding in men taking long-term therapy. They examined blood and semen samples from 26 men who had been on long-term standard ARVs, all of whom had no STIs and an undetectable viral load in the blood.

Among those in this group taking ARVs for less than six months, about half had intermittently detectable virus in their semen. Meanwhile, only 20 percent of those taking therapy for one to three years had detectable seminal virus; and none of those on treatment for more than three years did. HIV

STUDIES

Real World Benefits of HIV Treatment

The journal, *Science,* reports on two studies that demonstrate the real life benefits of HIV treatment, including reduced likelihood of HIV transmission in communities and increasing overall life expectancy.

For "High Coverage of ART Associated with Decline in Risk of HIV Acquisition in Rural KwaZulu-Natal, South Africa," (22 Feb 2013: 966-971), researchers looked at rates of HIV acquisition in a subdistrict that was seeing a rapid scale-up of antiretroviral treatment.

They found "a steep and highly significant decline in an individual's adjusted HIV acquisition hazard with increasing ART coverage." They found that a person who did not have HIV living in an area where 30 to 40 percent HIV-positive people were receiving treatment was, on average, 38 percent less likely to contract the virus than someone living in an area where less than 10 percent of HIV-infected people were receiving treatment.

"Increases in Adult LIfe Expectancy in Rural South Africa: Valuing the Scale-Up of HIV Treatment" (22 Feb 2013: 961-965) notes that during the last century, until the impact of the global HIV epidemic in the late 1980s, life expectancy was on the rise through most of the world. Looking at a group of 101,000 in KwaZulu-Natal, researchers compared life expectancies before and after the availability of antiretroviral treatment in the public health system in 2003. The societal value of the additional 11 years of life expectancy that followed the arrival of treatment, they said "far outweigh the costs of providing treatment," with real world savings of uninterrupted lives, fewer orphans and better returns on educational investments—numbers they said that policymakers and donors can factor into their decisions. HIV

SHUTTERSTOCK

Discovery in HIV May Solve Efficiency Problems for Gene Therapy

A RESEARCH TEAM from Case Western Reserve University School of Medicine has discovered an approach that could make gene therapy dramatically more effective for patients.

Led by professor Eric Arts, PhD, the scientists discovered that the process of gene therapy is missing essential elements thereby reducing the effectiveness of this treatment. Re-introducing this element into their model system suggests that improvements for gene therapy are on the horizon.

The findings are detailed in the article, "A new genomic RNA packaging element in retroviruses and the interplay with ribosomal frameshifting," published February 15 in the journal *Cell Host & Microbe*.

Failure to distribute enough modified genetic information to the patient's body has prohibited gene therapy from being more widely used, the article points out. Gene therapy relies mainly on viruses—which transport genomes inside the cells they infect—to deliver genetic material into a patient's cells.

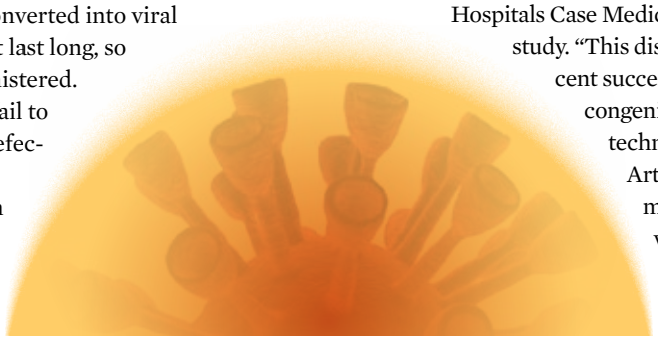
Unfortunately, the success rate of viral vectors is uneven. For instance, adenoviruses, a cause for the common cold, and lentiviruses, such as HIV-1, are routinely converted into viral vectors. But adenovirus vectors don't last long, so therapy must be frequently re-administered. And lentiviral vectors, while stable, fail to deliver genetic material to enough defective human cells.

Dr. Arts, a professor of medicine in the Division of Infectious Diseases and HIV Medicine, learned that lentiviral carriers lack sufficient genetic material necessary for treatment. HIV-1, when converted from virus to lentiviral vector, loses a specific RNA element required to pack its "container" with its own genetic material to be effective. After identifying the problem, researchers introduced the element into a lentiviral vector, successfully and significantly improving the quality and quantity of the gene therapy.

Dr. Arts and colleagues named the genetic element, Genomic RNA Packaging Enhancer element (or GRPE). During virus production, GRPE coordinates the production and filling of the container with the genetic material of HIV-1, or the desired human gene.

Delivery and success of gene therapy for human cells has the potential of increasing five to ten times with the introduction of the GRPE into the lentiviral vector, according to the article.

"Using lentivirus for gene transfer appears to be a safe option," said Stanton L. Gerson, MD, director of the Case Comprehensive Cancer Center and the Asa and Patricia Shiverick- Jane Shiverick (Tripp) Professor of Hematological Oncology at Case Western Reserve School of Medicine and director of the Seidman Cancer Center at University Hospitals Case Medical Center, who is not involved in the study. "This discovery could greatly advance the recent successes ongoing in cancer and childhood congenital diseases. Improvements in the technology of gene delivery identified by Arts and his colleagues could lead to many more effective studies that help patients with many different diseases, including cancer. Its impact could be felt in a few short years." HIV



SHUTTERSTOCK

ViiV Healthcare announces FDA priority review designation for dolutegravir as a potential treatment for HIV infection

ViiV Healthcare announced February 15 that the U.S. Food and Drug Administration (FDA) has granted a priority review designation to dolutegravir submitted for the treatment of HIV infection, in combination with other antiretroviral agents, in adults and adolescents. A priority review designation is granted to drugs that, if approved, have the potential to offer significant improvement compared to marketed products or provide a treatment where no adequate therapy exists. The FDA has assigned dolutegravir a Prescription Drug User Fee Act (PDUFA) target date of 17 August, 2013.

The new drug application (NDA) for dolutegravir was received by the FDA on 17 December 2012, and includes the results of four pivotal phase III clinical trials that treated a total of 2553 patients with HIV/AIDS across the treatment spectrum, from therapy naïve to salvage patients. Dolutegravir is in development and subject to evaluation of the benefits and risks by the regulatory authorities before it can be approved and made available on prescription.

ViiV Healthcare submitted a Marketing Authorisation Application (MAA) for dolutegravir to the European Medicines Agency (EMA) on 17 December, 2012. HIV

HIV Prevention in Practice: Teachable Moments

SOME HIV-INFECTED PERSONS continue to engage in high-risk sexual behaviors, particularly unprotected anal or vaginal; sex with multiple partners; and sex with anonymous partners. Some HIV-infected persons continue to participate in these unsafe behaviors even when they are knowledgeable about modes of HIV transmission and STD acquisition risks.

Among the reasons for persistent high-risk behavior in HIV-infected persons are a lack of critical information or motivation, inadequate skills needed to practice safer sex behaviors, uncertainty about specific behavior prevention, uncertainty about factors that may affect the risk of transmission with different sexual partners, and alcohol, drug use, or mental health issues. More effective prevention messages are needed to educate and motivate HIV-infected persons who engage in high-risk sexual behaviors to modify these behaviors.

Sexual Risk Modification

Sexual risk modification begins with a sexual history, which is taken at the initial visit and then at routine HIV medical care visits. A more recent sexual history should be obtained when patients present with STDs or are at risk for an STD. Our clinic participated in a study to improve understanding of the increasing incidence of bacterial STDs and to determine the potential effect of STDs on increased risk of HIV transmission in HIV-discordant partnerships among MSM.[1] The results showed that STDs were diagnosed in a similar proportion of HIV-infected and HIV-negative MSM, and the rates did not differ between men with HIV-concordant and HIV-discordant partnerships.

These findings emphasize the need for interventions to foster serostatus discussion, condom use, fewer anonymous partners, and STD screening. STD testing itself can be a behavior education maneuver. For example, HIV-negative patients who present with gonorrheal or chlamydial urethritis should be told that HIV is transmitted in exactly the same way as these STDs are acquired, and that the event that transmitted this infection could transmit HIV in the future. So the clinical setting of STD diagnosis provides an opportunity to talk about the mode of HIV transmission and prevention.

Many HIV providers do not provide protracted risk reduction discussions because they assume that most MSM already know the mantra about condom use and other risk reduction strategies. Most conversations about risk reduction actually take place as the sexual history is elicited, asking patients: 1) whether they use condoms, 2) about the number of sexual contacts, 3) if they know the people with whom they are having sex, and 4) how they encounter partners. Risk screening can actually serve as the intervention, as patients realize that their behaviors put them at risk.

Brief HIV Prevention Messages Can Reduce High-Risk Behaviors

Studies have indicated that even brief interventions by HIV providers during routine clinical care can modify sexual risk behaviors.

Fisher et al showed that a clinician-delivered "behavioral prescription" using the information-motivation-behavioral skills model of HIV prevention significantly ($P<0.05$) reduced unprotected sex among HIV-infected persons during 18 months of follow-up.[2]

Gardner et al screened HIV-infected persons for behavioral risks and delivered targeted prevention messages at all routine visits. They found a significant ($P<0.001$) decline in unprotected intercourse that was directly related to the frequency of receipt of safer sex discussions.[3]

Rose et al determined the effectiveness of assessing sexual risk behavior and delivering risk-reduction-oriented prevention messages over 6 months of follow-up to patients who reported risk behaviors with HIV-uninfected or unknown-status partners.[4] Patients who received the risk-reduction intervention reported a significant (OR = 0.49; 95% CI = 0.26 to 0.92) decrease in the number of sexual partners.

Finally, Patel et al showed that routine brief risk-reduction messages by medical providers with biannual STD testing significantly reduced the incidence of STDs (including syphilis, chlamydia, and gonorrhea).[5]

STD Acquisition Is Related to Behavioral Risk

Because many STDs are asymptomatic, routine screening for STDs—especially syphilis, gonorrhea, and chlamydia—should be performed at baseline and at least annually for all sexually active HIV-infected persons. Diagnosis of an STD in an HIV-infected person indicates ongoing or recurrent high-risk behavior and should prompt prevention discussions or referral for counseling.

The majority of persons who acquire STDs, however, continue to become infected with new STDs, while a smaller percentage acquire only one STD. Persons in the former group are in the high-risk category and may be somewhat refractory to provider messages, while those in the latter group may simply have "slipped up" and are candidates for refresher discussions and debriefing about what led to the exposure despite generally practicing safe sex.

A new STD in an HIV-positive person has serious clinical implications, particularly because STDs can facilitate HIV transmission, increase viral load, and reduce the CD4 count. HCV can be a sexually transmitted infection. There has been a recent rapid and significant rise in the incidence of HCV

in HIV-infected populations of MSM, particularly in some localities, and some data suggest transmucosal HCV transmission as a result of high-risk sexual behaviors.[6] This is important, because HCV infection complicates the treatment of HIV. For example, HCV coinfection in patients with HIV infection may impair CD4-cell reconstitution in those who receive antiretroviral therapy.[7]

Teachable Moments

The doctor-patient relationship is a key factor in reducing the risk of HIV transmission by HIV-infected persons. Long-standing, trusting professional relationships related to HIV treatment offer a particular opportunity to integrate prevention into care, but HIV-infected patients rarely initiate prevention discussions with their HIV care providers.

For this reason, it is imperative that medical providers make time during appointments to build this relationship and initiate prevention discussions. Prevention messages can be brief, and shorter messages are often better than longer ones. Although—as noted above—HIV-infected patients rarely initiate discussion of prevention, providers can take advantage of opportunities that may arise during clinical interviews.

To initiate a prevention discussion with an HIV-infected patient, clinicians must be alert for "teachable moments," which can be defined as an opportunity to stimulate patient action, particularly with regard to health behavior change.[8]

But physicians caring for HIV-positive patients often miss opportunities to deliver routine HIV prevention messages. For example, clinicians may be less likely to discuss prevention during ongoing care than during initial visits, and the delivery of prevention messages often drops off over time. Prevention messages should be given at every visit, and it should be considered a missed opportunity if prevention is not discussed. Prevention of HIV transmission is pertinent at all stages of HIV infection, so, please, listen for opportunities to deliver routine HIV prevention messages during all patient visits. Prevention topics can include condom negotiation, how to practice safer sexual behavior, limiting sex partners, and how to talk to partners about safer sex and HIV status.

Disclosure of HIV status is important because it allows partners to be included in the decision-making process by either allowing or not allowing potentially unsafe sex to occur. Tieu et al conducted a study to assess factors associated with serodiscordant or serostatus-unknown, unprotected intercourse among MSM, including disclosure of HIV status.[9] A substantial proportion of the study participants did not reveal their HIV status, highlighting the need for interventions to encourage communication between HIV-infected patients and their partners.

Conclusions

HIV providers can help prevent HIV transmission by talking to their patients about HIV risk reduction, discussing the risky behaviors associated with HIV transmission and STD acquisition, and sharing the facts with patients so they can make informed and safer decisions about sexual behaviors. HIV

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Latinos and HIV

POLITICIANS IN WASHINGTON and business executives across the nation have come to learn that the Latino population in the United States is growing and is rapidly becoming a powerful force in both the political arena and the marketplace.

One major political candidate learned that the hard way last November, and businesses that fail to respond are losing share to those that recognize the importance of this growing economic powerhouse.

But there is another side to that story as Washington struggles with immigration reform and the corporate world tries to adapt and appeal to this expanding and diverse market, one with unique traditions, desires, and needs.

That is the story of millions of men and women who are disproportionately affected by HIV and whose unique traditions and needs must be recognized, understood, and effectively addressed by the HIV specialists who treat them—many of whom are not of their culture and may not speak their language.

On February 28, the Centers for Disease Control and Prevention (CDC) issued its 2011 HIV Surveillance Report, which details the state of HIV/AIDS in the United States through 2011. The report includes these conclusions and, thus, illustrates the challenges that confront HIV specialists every day:

- Latinos are disproportionately affected by HIV, and the rate of new infections among Latino men was two-and-one-half times as high as that of white men.
- In 2009, Latino MSM accounted for 81 percent (6,000) of new HIV infections among all Latino men and 20 percent among all MSM. Among Latino MSM, 45 percent of new HIV infections occurred in those under age 30.
- While Latina women accounted for 21 percent (2,000) of new infections among Latinos in 2009, their rate of HIV infection was more than four times that of white women.
- At some point in life, one in 36 Latino men will be diagnosed with HIV, as will one in 106 Latina women.
- In 2009, Latinos accounted for 19 percent of the 42,959 new diagnoses of HIV infection in the 40 states and five U.S. territories with long-term confidential name-based HIV infection reporting.
- By the end of 2008, an estimated 111,438 Latinos with an AIDS diagnosis had died in the U.S. and dependent areas. in 2007, HIV was the fourth leading cause of death among Latinos aged 35-44 and the sixth leading cause of death among Latinos aged 25-34 in the U.S.

Prevention Challenges

The report cites several factors that contribute to the HIV epidemic in Latino communities.

Behavioral risk factors for HIV infection differ by country of birth. Data suggest that the highest percentages of diagnosed HIV infections among Latino men are attributed to sexual contact with other men, regardless of place of birth, but men born in Puerto Rico have a substantially larger percentage of diagnosed HIV infections attributed to injection drug use than Latino men born in other countries.

Latino men and women are most likely to be infected with HIV as a result of sexual contact with men. Latina women may be unaware of their male partner's risk factors.

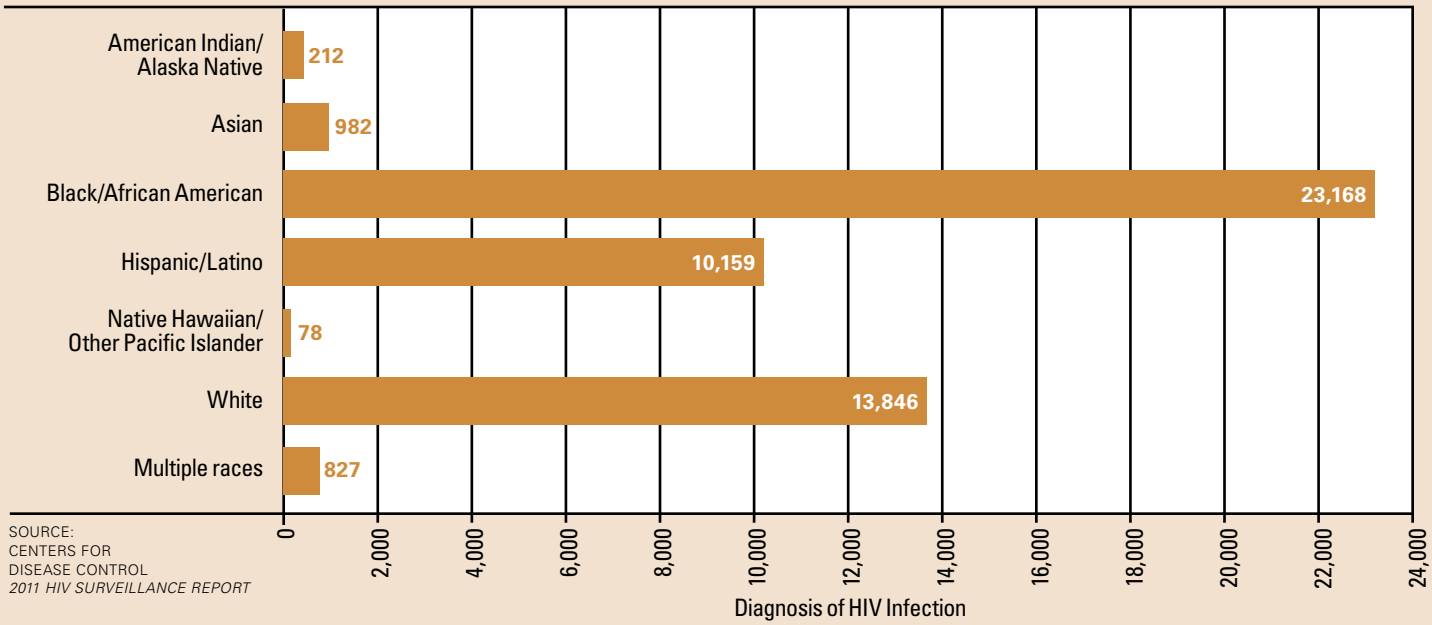
Injection drug use continues to be a risk factor for Latinos, particularly those living in Puerto Rico. In addition, both casual and chronic substance users may be more likely to engage in risky sexual behaviors, such as unprotected sex, when they are under the influence of drugs or alcohol.

The presence of certain sexually transmitted infections (STIs) can significantly increase one's chances of contracting HIV infection. A person who has both HIV infection and certain STIs has a greater chance of infecting others with HIV. The rates of STIs remain high among Latinos.

Cultural factors may affect the risk of HIV infection. Some Latinos may avoid seeking testing, counseling, or treatment if infected out of fear of discrimination, stigmatization or

Challenges of Care

Diagnoses of HIV infection by race/ethnicity and selected characteristics, 2011—United States



SOURCE:
CENTERS FOR
DISEASE CONTROL
2011 HIV SURVEILLANCE REPORT

immigration status. Traditional gender roles and the stigma around homosexuality may add to prevention challenges.

Greater acculturation into the US culture has both negative (engaging in behaviors that increase the risk for HIV infection) and positive (communicating with partners about practicing safer sex) effects on the health behaviors of Latinos.

Socioeconomic factors such as poverty, migration patterns, lower educational attainment, inadequate health insurance, limited access to health care or language barriers add to Latino HIV infection rates. These factors may limit Latinos'

Due to fear of disclosure, undocumented immigrants may be less likely to access HIV prevention services, get an HIV test, or receive adequate treatment and care if living with HIV.

In the following pages, you will find articles written by your peers from around the nation who are meeting these challenges. They include physicians, a nurse practitioner, a pharmacist—all of whom discuss the obstacles they confront and how they are responding. You will find an overwhelming sense of satisfaction expressed in their words, as well as words of concern, even outrage, as they discuss the challenge of treating patients, many of whom must live in the shadows for fear of deportation and separation from their loved ones.

Yes, there are language problems that can become a barrier to care if not addressed appropriately. But there are cultural issues, traditions, and economic factors, even some unique medical conditions that must be understood, recognized and dealt with. Indeed, racism, classism, sexism, homophobia, all must be confronted. Some of our authors are Latinos themselves, but not all, and those practitioners share their experiences as they treat patients desperately in need of help who are so different from themselves.

We hope you find the following pages enlightening and informative, as they bring the cold, hard facts found in this latest CDC report to life. We invite your comments – and express our deep appreciation to our authors who have shared their experiences with us.

Please note: Many of the articles that follow were written before the release of the CDC's 2011 Surveillance Report and cite statistics available prior to that time. While the numbers have changed in some instances, the circumstances and the facts surrounding them remain the same. HIV

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Beliefs,

BY TIM NOLAN, ANP, AAHIVS

Gustavo had initially left his native Michoacan (Mexico) in 2007, fleeing the increasingly violent drug war and its surrounding poverty. His hope, like all those who had migrated north (el Norte) before him, was to find steady work in the United States, enabling him to send money back to his impoverished family.

After an arduous, life-threatening crossing of the border, he found employment in housekeeping at a hotel in the rural South. Gustavo's hopes were crushed in 2009 when after several weeks of increasing fatigue and fever, he was hospitalized and told he had AIDS, and was subsequently treated for extra-pulmonary tuberculosis.

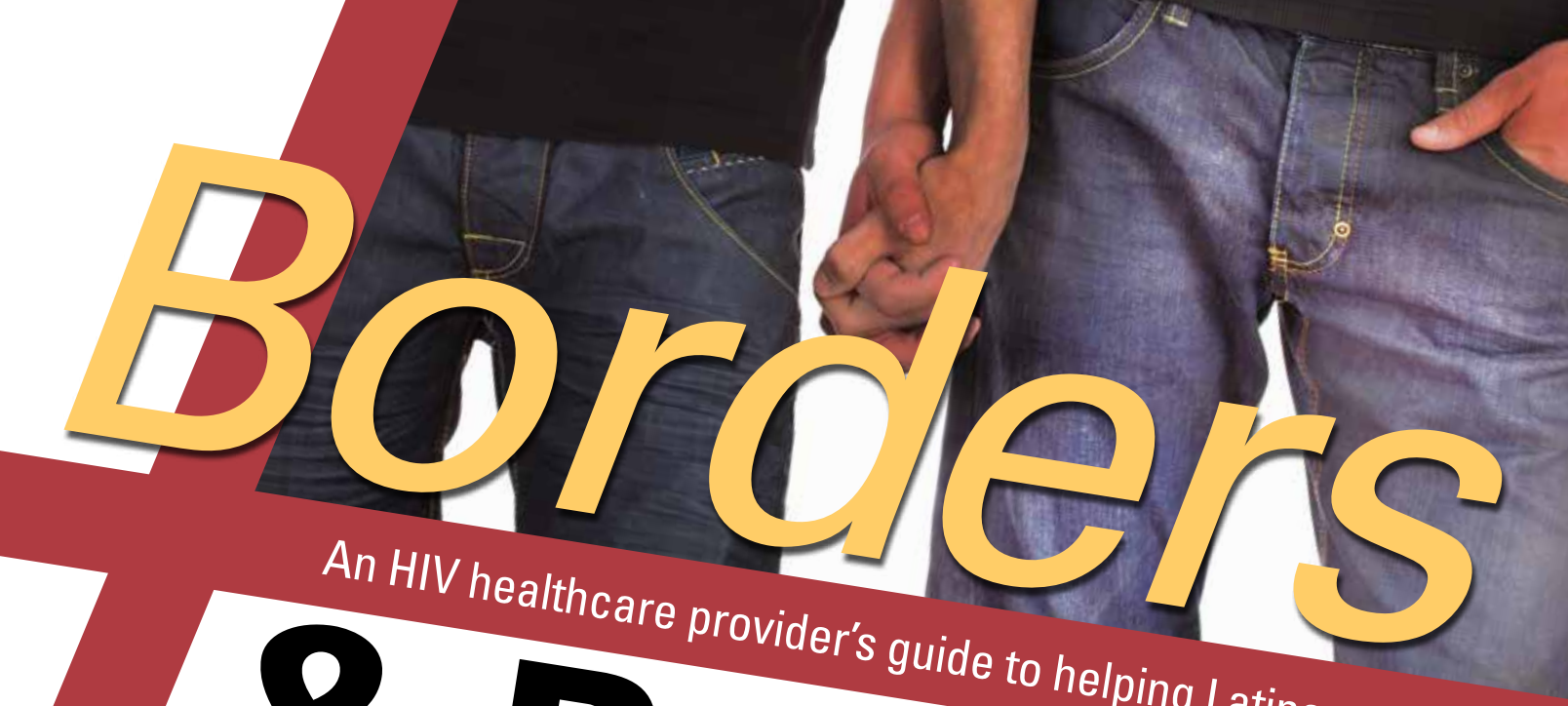
With this life-changing event, Gustavo joined the over 7,000 Latinos in the U.S. who were diagnosed with AIDS in 2009 (CDC). HIV/AIDS has now become the fourth leading cause of death among Latinos in the 35-44 age group, and the rate of new infections among Latino men today far exceeds that of white me.

As those of us who provide HIV care on a regular basis see more and more Latino men and women in our clinics, new challenges surface as we deal with a disease that we know so well, but now in a people and culture which for many of us are quite new and foreign.

Why is the rate of infection among Latinos increasing? Why do so many, like Gustavo, present to us at such late stages of the disease? What new challenges do their cultural differences, language and belief systems bring to our established ways of providing care and understanding this epidemic? How can these challenges be seen instead as the unique gifts to our practices, which they truly are?

HIV Among Latinos in the United States

It is clear that Latinos are disproportionately affected by HIV/AIDS in the U.S. Statistics show that 10,159 Hispanics were diagnosed with HIV in 2011. In 2011, Latinos accounted for 21 percent of new infections in this country while representing only 16 percent of the population. This infection rate is most dramatically affecting the Latino men who have sex with men (MSM) population. In the same year, Latino MSMs accounted for nearly 7 in 10 (68 percent) new HIV infections



Borders & Barriers

An HIV healthcare provider's guide to helping Latino patients

among Latinos overall and nearly 8 in 10 (79 percent) new infections among Latino men.

Among women, Latinas accounted for 1,400, or 15 percent of new HIV infections, and their HIV incidence rate was more than 4 times the rate for white women according to the CDC 2011 Surveillance Report.

More concerning than even these startling demographics are the number of late testers we encounter in the Latino community. A "late tester" is defined as a person whose HIV+ diagnosis is made through HIV testing less than one year before they receive an AIDS diagnosis- defined by the CDC as a CD4+ count of less than 2w00, or through the development of an AIDS-defining opportunistic infection.

In 2006, 42 percent of Latinos diagnosed with HIV infection developed AIDS within 12 months. This rate, approaching 50 percent, was higher than any other racial or ethnic group. Like Gustavo, most of these individuals sought testing or had an HIV test performed because of a presenting illness or hospitalization.

Barriers to Care

What are the cultural and societal barriers that prevent these high-risk Latinos from receiving more effective HIV prevention education? What are the cultural taboos and stigmas attached to HIV/AIDS, and the risk behaviors that cause it, which might be unique to the Latino population? What accounts for the remarkably high rate of late HIV testers in the Latino population?

A key resource in beginning to understand these issues lies in Rafael Diaz' and George Ayala's landmark study, "Social Discrimination and Health: The Case of Latino Gay Men and HIV Risk."

Diaz and Ayala, building on the well-known work of Dr. Paul Farmer, place both HIV/AIDS disease prevalence and care outcomes in the context of existing social inequalities, commenting that "preventable diseases and deaths are far more common among the poor and the disenfranchised" (p vi). They identify three primary forms of social discrimination found within varying Latino communities - homophobia, racism and poverty-and they describe these as further "borders" to care. These borders are different from "la frontera," the existing U.S. border, but they can be as dauntingly insurmountable.

"Borders are embedded in racism, sexism, homophobia and classism," Juan Carlos Velazquez points out in the study's preface (Diaz & Ayala, p. iv).

Border "patrols," found both within and without the cultural group in the form of critical parents, church, homophobia, Immigration and Customs Enforcement (ICE), a wave of anti-immigrant and English-only laws... all slowly chip away at the self-esteem of the Latino immigrant community and even more specifically at gay Latino men, the group with the highest HIV infection rate (Diaz & Ayala, p.v).

Their research substantiates their theory that all of these border issues can lead to higher rates of risky behavior among gay Latino men. In the end, these factors can ultimately result in a prevailing sense of doom and an overriding perception

of an inability to control these risks in relation to the individual's social setting. In five different studies of gay men in the U.S., Latinos consistently reported the highest rates of unprotected sex and intercourse.

Diaz' and Ayala's powerful conclusion is that as HIV providers who work with Latino communities and other disenfranchised populations, we must move beyond our long-standing focus on condom use as HIV prevention and antiretrovirals as the beginning and end of HIV/AIDS treatment. We must place both the disease and our work with it in the context of social inequalities and the need for structural change.

"If we are to be effective in our fight against AIDS and any other public health tragedies that feed on human powerlessness, HIV prevention workers and advocates must also be agents of social and cultural change." (Diaz and Ayala, p. viii).

Latino Communities

In working with the Latino population, over time one can become more keenly aware that there is not one distinct Latino culture or community, but many. The importance of understanding this is that in this wide variety of "peoples," there exist just as many beliefs *and* barriers which can affect the individual's ability to care for their HIV disease.

These belief systems can be influenced by a patient's family and their place within it, religion, immigration status, gender, and sexuality among others. These factors help determine in many ways how they perceive and deal with their HIV-positive status and how they receive the healthcare information we provide. Ultimately, by gaining a deeper understanding of the unique qualities present in the variety of Latino cultures, healthcare providers can move beyond seeing each patient simply as another "Latino" and anticipating the resulting need for an interpreter. Our growing understanding allows us to "interpret" the clinical visit, approaching each patient as an individual, with unique cultural beliefs, background and story.

A primary factor driving these differences is the Latino patient's country of origin and its unique culture. One of the first questions Latinos will often ask of each other is "Where are you from" ("De donde es?"). This locating of an individual within a regional setting can provide one with an immense amount of information, including a sense as to the historical politics and economics of the country they have left and a further understanding of what they may have left behind, including poverty, war, persecution and vital family members.

If the Latino patient is native to the U.S., his or her parents' country of origin and culture remains vitally important in understanding their approach to their illness and engagement in care. Born and raised in the U.S., the native Latino will most likely more resemble our other patients in their knowledge and use of the healthcare system and our surrounding culture.

But the "borders" that Diaz and Ayala have explored, both internal and external to their family and cultural systems, will continue to influence their relationship with the medical provider and their engagement in care. In the end, it is beneficial in this patient-provider relationship to understand that, although each are Latino, a Puerto Rican from East Harlem, a young Mexican-American from East L.A. and an undocumented immigrant from El Salvador remain very distinct from each other with unique cultural and family backgrounds that influence their approach to this disease. Our understanding of this improves our relationship with them and ultimately their care outcomes.

There are many other factors which may also influence the Latino individual's approach to their daily life and their need for consistent healthcare with an HIV-positive diagnosis. It is helpful to know which generation of immigrant they are.

If the person is first generation American, what was his or her reason for leaving the homeland? It can often be helpful to know how his or her crossing of the border went, as this can often be a complicated journey filled with emotion, trauma and violence. For some, it may be at this border crossing where his or her initial exposure to HIV occurred, described in stories of rape or sex with impoverished sex workers who are also victims of the border situation.

Similarly, it is important to know how long the individual has lived in the U.S., where he or she lived prior to coming to our region, and what other family members live in the U.S. These questions can often reveal lives filled with isolation, violence, poverty, trauma and persecution, either in their past or current situations. The patient's answers also can help in our eliciting and addressing continued high risk behaviors and may be an entryway into diagnosing mental health disorders such as PTSD or depression and determining the subsequent need to involve behavioral health in the provision of care.

Knowledge of these factors in your patients' lives, a knowledge that can be developed over several clinical visits, facilitates a deeper trust or "confianza" between the patient

"If we are to be effective in our fight against AIDS and any other public health tragedies that feed on human powerlessness, HIV prevention workers and advocates must also be agents of social and cultural change."

—Diaz and Ayala, p. viii

and provider. This trust, of course, has an indirect impact on the individual's adherence to care and therapy, which is vital in HIV management. Beyond this constant theme of adherence; however, we must recognize that our ultimate goal must include the empowerment and restoration.

Practical "Tips" for Providers

As Latino patients present to us with a unique set of challenges, we as HIV specialty providers can work to acquire a distinct set of tools to provide them with integrated care. These tools of course vary from region to region, but there are some basics:

- **Speak the language.** Although for many of us who are new to Spanish, this can be a daunting thought; it is extremely important. Even if we approach the patient with broken, poorly-accented wording, our effort to speak their language builds respect and removes one of the most significant borders preventing a trusting patient-provider relationship. It is only by holding our clinical visits in their language that we can hope to explore the intricacies and unique complexities of their lives amidst their HIV disease. There are many language immersion programs that can benefit medical providers, but the most useful and most affordable immersion opportunity is the one that walks into your clinic every day. Many may also choose to utilize the variety of translation apps now available.
- **Understand the immigration issue and become involved.** This is the biggest concern facing the majority of our Latino patients today, whether it involves them directly or a family member. For many of our patients, even simply traveling to and from their clinic visits places them at risk of encountering a law enforcement officer and the resulting possibility of deportation. Patients lose family members and loved ones overnight to current immigration policies and the deportation of individuals innocent of committing any crime. It is not essential to know our patients' immigration status, but it is essential to understand that for many of them, and for many of their family members and partners, this is a vital issue. Remaining up-to-date on both the federal government's and our own state's ever-changing immigration policies helps us to understand how these play out in our patients' lives and allows us, as Diaz and Ayala pointed out, to become agents for social change.
- **Read Rafael Diaz' and George Ayala's "Social Discrimination and Health: The Case of Latino Gay Men and HIV Risk,"** easily available in PDF-format on-line. It is an extremely fascinating and helpful study which examines HIV disease in context of its larger social settings and challenges us as HIV medical providers to move beyond providing care in our clinics and becoming advocates for greater social change.
- **Understand the unique qualities of the varying Latino cultures.** Start to seek out the things that make each Latino group distinct. Attend Latino cultural events outside of our work. Learning more about a given country or region, its history and its current socio-political situation can only give us further information about our patients. We are where we come from.

This is where we can begin. As we care for more Latinos in our HIV practice, we can gain a deeper understanding of the unique challenges they present to us in relation to both their HIV disease and their psychosocial needs. In the end, caring for the wide spectrum of Latino patients can only enrich us and further our commitment to providing care amidst this continuing epidemic. HIV

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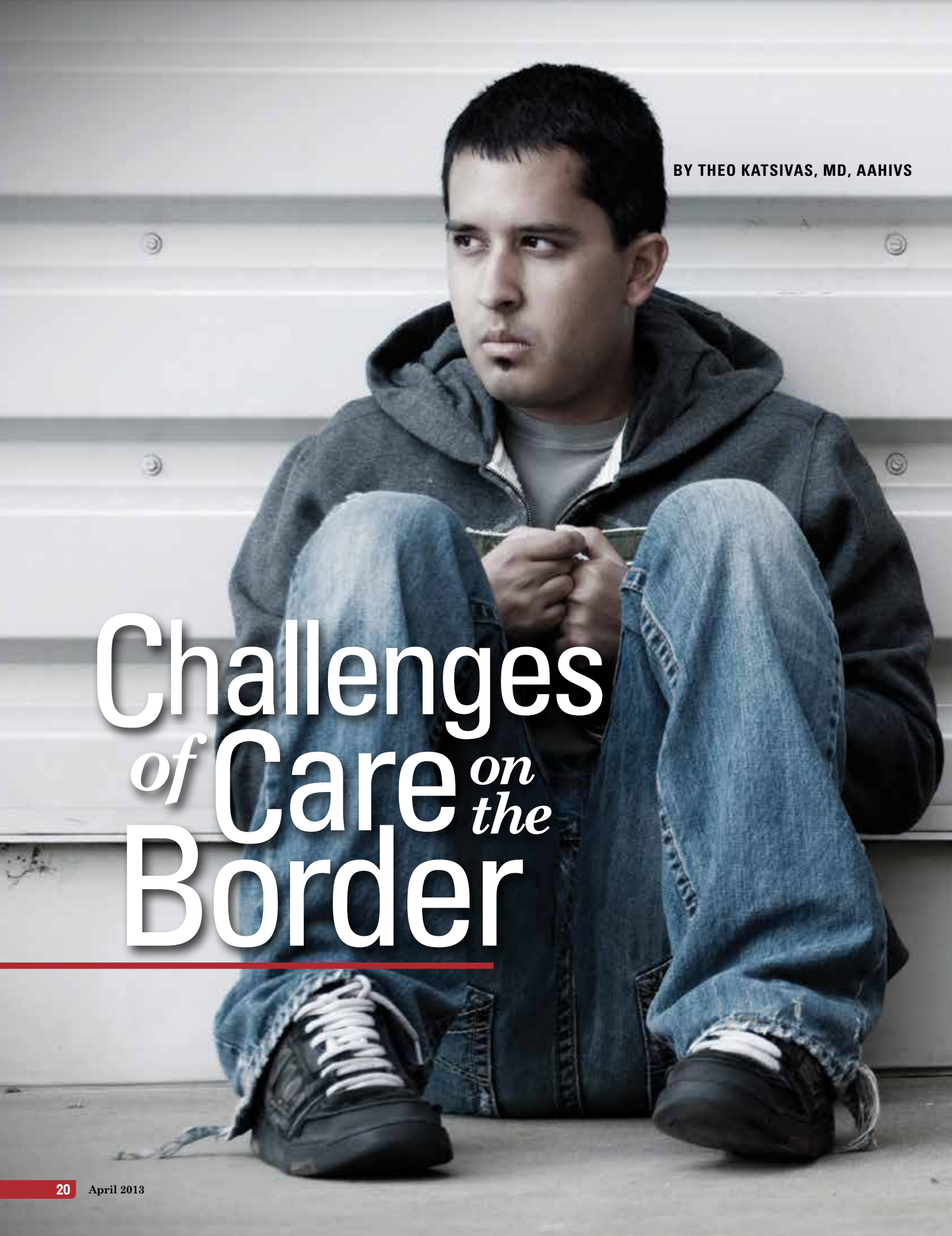

BY THEO KATSIVAS, MD, AAHIVS

Challenges *of* Care *on the* Border

I HAVE BEEN WORKING AT SAN YSIDRO HEALTH CENTER AT THE HIV PRIMARY CARE PROGRAM for about 60 percent of my clinical time under a contract with our University of California San Diego Owen Clinic. As academic faculty doing research and working in a US/Mexico Border area clinic in Southern California, I have first-hand experience related to Latino/Hispanic HIV care.

My work involving HIV began in 1999 as an Internal Medicine trainee physician and since 2004 I've been on staff as Internist/Infectious Disease specialist at USCD's Owen Clinic, which offers HIV care services to over 3,000 patients, about 25 percent of whom are Latino/Hispanic. At the San Ysidro Health Center, we have some 700 patients, about 95 percent of whom are Latino/Hispanic. I also offer volunteer work on HIV care, across the border in Tijuana, where conditions are quite different from those in the U.S.

Unfortunately, the virus disproportionately affects Mexican Americans and other Latinos who live in the U.S., and that includes women. Women who come in for prenatal screening are sometimes found to be HIV positive and, at the same time, discovering that their primary partner is bisexual/MSM and has been positive for some time. So, clearly, testing is an issue with our population here.

Stigma is a difficult problem as well. There is sometimes an attitude that a man's primary sexual relations are at home, but he can do whatever he wants outside the home. Obviously, prevention messages simply do not reach this population.

Once a patient is diagnosed, getting into care is easy, and in Southern California, language is usually not a barrier. At our San Ysidro clinic, most of our providers are bilingual or Spanish speaking, and our clinic seems to have great outcomes. Having providers who speak the language and are culturally sensitive to caring for Latino/Hispanic patients is a key to our success.

Family, Community Support

Caring for Latinos is one of the most rewarding things that has happened in my professional life. I find that my patients are extremely grateful for care and have amazing support within community and family. Once the shock of diagnosis is over, families usually rally around the family member who is affected.

I have witnessed amazing stories of people who support their gay son who just came out and is infected. I have had very interesting discussions with several partners as well as families that came together to support their loved one who is now a patient. That is a very positive thing.

At our program at San Ysidro, we are actively involved in setting up support groups, therapy sessions, group therapy, social support, cooking classes, and social outings. So the community is addressing the problem of HIV infection. But, on the other side of the border, there is much more stigma and there are more issues with access to care, as well as testing services.

Most of our patients in the San Ysidro Clinic are virologically controlled (ie they are undetectable). However, our two main barriers are substance abuse and mental health issues. Access to services for the treatment for those issues are problematic. It is difficult for me to link patients to a psychiatrist, with waits often as long as three or four months. Sometimes I have to treat mental health problems in the primary HIV care clinic with the consulting help of my Psychiatrist colleagues, until they can get an appointment slot to see the patient.

Another treatment barrier involves Mexican immigrants who return to Mexico from the U.S. Although returning immigrants will have access to care, the truth is that this care often is lacking. It is not easy to have a steady supply of ARV treatment available all the time. Sometimes it is discontinued. I have witnessed stories of lack of ARV regimens and the availability of medication for returning migrants and deportees who are sent back or decide to go back to Mexico.

The use of alternative and herbal medications for HIV care occurs often in Latinos, and I have heard horror stories of extreme abuse of those medications, especially across the border. There are clinics that treat HIV with "oxygen treatment" or "silver salt" intravenous infusions. Sometimes these patients end up in our hospital. I am not opposed to using alternatives treatments as complementary to ARVs, but would like to see solid study results on the efficacy of those treatments. I support my patients having acupuncture, massage and perhaps regular herbal teas of some sort. But some herbs are presented as a miracle cure, and that ends up being a barrier to care. I am very cautious of my patients using such alternatives to care and am not happy when I hear about them using these herbal medications.

I am happy to be working with this population and being the main provider who serves our San Diego-Tijuana border area. It is challenging work, but satisfying to see the community rallying around patients and helping to form a close knit, successful program. HIV

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THINKSTOCK

INDICATION

ATRIPLA® (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate [DF] 300 mg) is indicated for use alone as a complete regimen or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients at least 12 years of age and weighing ≥40 kg (88 lbs).

SELECTED IMPORTANT SAFETY INFORMATION

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

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

ATRIPLA is not approved for the treatment of chronic hepatitis B virus (HBV) infection, and the safety and efficacy of ATRIPLA have not been established in patients coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued EMTRIVA® (emtricitabine) or VIREAD® (tenofovir DF), which are components of ATRIPLA. 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 ATRIPLA. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

*Baseline viral load >100,000 copies/mL.

† Baseline viral load ≤100,000 copies/mL.

‡ Study 934: A randomized, open-label, active-controlled, multicenter study comparing tenofovir disoproxil fumarate (TDF) 300 mg + emtricitabine (FTC) 200 mg vs zidovudine (AZT) 300 mg/lamivudine (3TC) 150 mg, in combination with EFV 600 mg, in 511 antiretroviral-naive patients. From weeks 96 to 144, patients received TDF/FTC fixed-dose combination in place of TDF + FTC. Mean baseline CD4+ cell count was 245 cells/mm^3 and median baseline HIV-1 RNA was 5.01 log_{10} copies/mL. TLOVR analysis (N=487) excluded 22 patients with baseline NNRTI resistance and 2 patients who were treatment experienced.[1,4]

§ Other reasons for discontinuation include lost to follow-up, patient withdrawal, noncompliance, protocol violation, and other reasons.

Controlling the virus is up to ATRIPLA.

My world is up to me.

ATRIPLA (efavirenz/emtricitabine/tenofovir disoproxil fumarate): a single-tablet HIV regimen that provides powerful efficacy and demonstrated long-term data through 3 years[1]

#1 prescribed HIV regimen for 5 years, with over 5 million prescriptions written[2,3]

In a 3-Year Clinical Trial in Treatment-Naive Adult Patients[1,4]...

- **Powerful and reliable virologic control through 3 years in patients with high* and low† baseline viral loads[1,4]**
  - In Study 934, 84% of treatment-naive adult patients taking ATRIPLA as its components (n=244) achieved viral load <400 copies/mL vs 73% with Combivir® (zidovudine/lamivudine) + EFV (n=243) through 48 weeks (primary endpoint).‡ The difference in the proportion of patients who achieved and maintained HIV-1 RNA <400 copies/mL through 48 weeks largely resulted from the higher number of discontinuations due to adverse events and other reasons§ in the Combivir group in this open-label study. Through 144 weeks, 71% of patients taking ATRIPLA (n=227) maintained viral load <400 copies/mL vs 58% with Combivir + EFV (n=229), 73% (88/120) of patients taking ATRIPLA with high baseline viral load* achieved and maintained viral load <400 copies/mL vs 59% (66/112) with Combivir + EFV, and 68% (73/107) of patients taking ATRIPLA with low baseline viral load† achieved and maintained viral load <400 copies/mL vs 57% (67/117) with Combivir + EFV[1,4]
- **Low rate (3%) of virologic failure[1,4]**
  - In Study 934, 3% of treatment-naive adult patients taking ATRIPLA (n=227) experienced virologic failure vs 6% with Combivir + EFV (n=229) through 144 weeks[1,4]
- **Low percentage of patients developed NNRTI (5%) and NRTI (1%) resistance-associated mutations[4]**
  - In Study 934, through 144 weeks, resistance to EFV occurred in 5% (n=13) of patients in the ATRIPLA arm and 9% (n=21) of patients in the Combivir + EFV arm, primarily caused by the K103N mutation. The M184V/I mutation, associated with resistance to FTC, was observed in 1% (n=2) of patients in the ATRIPLA arm and 4% (n=10) of patients in the Combivir + EFV arm. No patients developed the K65R mutation, which is associated with reduced susceptibility to tenofovir[4]
- **Demonstrated long-term safety and tolerability profile, with a low rate (5%) of discontinuation due to AEs[1,4]**
  - In Study 934, through 144 weeks, the most frequently reported Grade 2-4 adverse reactions reported in ≥5% of subjects receiving ATRIPLA were diarrhea (9%), nausea (9%), fatigue (9%), depression (9%), dizziness (8%), sinusitis (8%), upper respiratory tract infection (8%), rash event (7%), headache (6%), insomnia (5%), anxiety (5%), and nasopharyngitis (5%)[1]
  - Through 144 weeks, 5% of patients in the ATRIPLA group discontinued due to adverse events vs 12% in the Combivir + EFV group; discontinuation for other reasons was 20% in the ATRIPLA group and 22% in the Combivir + EFV group[4]
  - The most common adverse reactions that led to discontinuations were: investigator-defined insomnia (n=2; <1%) and rash (n=2; <1%) in the ATRIPLA arm; investigator-defined anemia (n=14; 6%) in the Combivir + EFV arm[4]

Please see Important Safety Information, including Boxed WARNINGS, and Brief Summary of Full Prescribing Information on the following pages.

AE = adverse event; EFV = efavirenz; FTC = emtricitabine; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; TLOVR = time to loss of virologic response.

ATRIPLA®
(efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) Tablets

IMPORTANT SAFETY INFORMATION

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

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir DF, a component of ATRIPLA (efavirenz/emtricitabine/tenofovir disoproxil fumarate), in combination with other antiretrovirals.

ATRIPLA is not approved for the treatment of chronic hepatitis B virus (HBV) infection, and the safety and efficacy of ATRIPLA have not been established in patients coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued EMTRIVA® (emtricitabine) or VIREAD® (tenofovir DF), which are components of ATRIPLA. 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 ATRIPLA. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Contraindications

- ATRIPLA is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to efavirenz, a component of ATRIPLA.
- Coadministration of ATRIPLA with bepridil, cisapride, midazolam, pimozide, triazolam, or ergot derivatives is contraindicated, since competition for CYP3A by efavirenz could result in inhibition of metabolism of these drugs and create the potential for serious and/or life-threatening adverse reactions.
- ATRIPLA should not be administered concurrently with voriconazole because of significantly decreased voriconazole plasma concentrations and significantly increased efavirenz plasma concentrations.
- Concomitant use of ATRIPLA with St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products is not recommended since this may lead to loss of virologic response and possible resistance to efavirenz or to non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Warnings and Precautions

- Efavirenz plasma concentrations may be altered by substrates, inhibitors, or inducers of CYP3A. Efavirenz may alter plasma concentrations of drugs metabolized by CYP3A or CYP2B6.
- Since ATRIPLA contains emtricitabine and tenofovir DF, ATRIPLA should not be coadministered with COMPLERA® (emtricitabine/rilpivirine/tenofovir DF), EMTRIVA® (emtricitabine), TRUVADA® (emtricitabine/tenofovir DF), or VIREAD® (tenofovir DF). Since ATRIPLA contains efavirenz, ATRIPLA should not be coadministered with SUSTIVA® (efavirenz) unless needed for dose-adjustment when coadministered with rifampin. Due to similarities between emtricitabine and lamivudine, ATRIPLA should not be coadministered with drugs containing lamivudine, including Combivir® (lamivudine/zidovudine), Epivir® or Epivir-HBV® (lamivudine), Epzicom® (abacavir sulfate/lamivudine), or Trizivir® (abacavir sulfate/lamivudine/zidovudine).
- ATRIPLA should not be administered with HEPSERA® (adefovir dipivoxil).
- Serious psychiatric adverse experiences, including severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonfatal suicide attempts (0.5%, 0%), aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.2%, 0.3%), have been reported in patients receiving efavirenz and control regimens, respectively. In addition to efavirenz, factors identified in a clinical trial that were associated with an increase in psychiatric symptoms included a history of injection drug use, psychiatric history, and use of psychiatric medication. There have been occasional reports of suicide, delusions, and psychosis-like behavior, but it could not be determined if efavirenz was the cause. Patients with serious psychiatric adverse experiences should be evaluated immediately to determine whether the risks of continued therapy outweigh the benefits.
- Fifty-three percent of patients reported central nervous system (CNS) symptoms (including dizziness [28.1%], insomnia [16.3%], impaired concentration [8.3%], somnolence [7.0%], abnormal dreams [6.2%], and hallucinations [1.2%]) when taking efavirenz compared to 25% of patients receiving control regimens. These symptoms usually begin during Days 1-2 of therapy and generally resolve after the first 2-4 weeks of therapy; they were severe in 2.0% of patients, and 2.1% of patients discontinued therapy. After 4 weeks of therapy, the prevalence of CNS symptoms of at least moderate severity ranged from 5% to 9% in patients treated with regimens containing efavirenz. Nervous system symptoms are not predictive of the less frequent psychiatric symptoms. Patients receiving ATRIPLA should be alerted to the potential for additive CNS effects when ATRIPLA is used concomitantly with alcohol or psychoactive drugs. Patients who experience CNS symptoms such as dizziness, impaired concentration, and/or drowsiness should avoid potentially hazardous tasks such as driving or operating machinery.
- It is recommended that creatinine clearance (CrCl) be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with ATRIPLA, and routine monitoring of CrCl and serum phosphorus be performed for patients at risk of renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil. ATRIPLA should not be given to patients with CrCl <50 mL/min. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir DF. ATRIPLA should be avoided with concurrent or recent use of a nephrotoxic agent.
- ATRIPLA (efavirenz/emtricitabine/tenofovir disoproxil fumarate) may cause fetal harm when administered during the first trimester to a pregnant woman. Women should not become pregnant or breastfeed while taking ATRIPLA. Barrier contraception must always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives). Because of the long half-life of efavirenz, adequate contraceptive measures are recommended for 12 weeks after discontinuation of ATRIPLA. If the patient becomes pregnant while taking ATRIPLA, she should be apprised of the potential harm to the fetus.
- Mild-to-moderate rash is a common side effect of efavirenz. In controlled clinical trials in adults, 26% of patients treated with efavirenz experienced new-onset skin rash compared with 17% of patients treated in control groups. ATRIPLA should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever.
  - Rash was reported in 46% (26/57) of pediatric patients receiving efavirenz. Grade 3 or 4 rash was reported in 5% of pediatric patients compared to 0.9% of adults receiving efavirenz.
- Liver enzymes should be monitored before and during treatment in patients with underlying hepatic disease, including hepatitis B or C infection; in patients with marked transaminase elevations; and when ATRIPLA is administered with ritonavir or other medications associated with liver toxicity. A few of the postmarketing reports of hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, were characterized by a fulminant course, progressing in some cases to transplantation or death. Liver enzyme monitoring should be considered for patients without pre-existing hepatic dysfunction or other risk factors.
- Bone mineral density (BMD) assessment should be considered for patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Decreases in BMD have been seen with tenofovir DF. Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of tenofovir DF.
- Use ATRIPLA with caution in patients with a history of seizures. Convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures.
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including the components of ATRIPLA. Autoimmune disorders (e.g., Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.
- Redistribution/accumulation of body fat has been observed in patients receiving antiretroviral therapy.

Adverse Reactions

- In Study 934, through 144 weeks, the most frequently reported Grades 2-4 adverse reactions in ≥5% of subjects receiving efavirenz + emtricitabine + tenofovir DF were diarrhea (9%), nausea (9%), fatigue (9%), depression (9%), dizziness (8%), sinusitis (8%), upper respiratory tract infection (8%), rash event (7%), headache (6%), insomnia (5%), anxiety (5%), and nasopharyngitis (5%).
- The most common adverse reactions (incidence ≥10%, any severity) occurring in Study 934 include diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash.
- Skin discoloration, associated with emtricitabine, may also occur.
- **Pediatric patients:** In addition to common adverse events reported in adults, anemia (7%) and hyperpigmentation (32%) were observed in pediatric patients treated with emtricitabine.

Drug Interactions

- Coadministration of ATRIPLA with didanosine should be undertaken with caution. Patients receiving this combination should be monitored closely for didanosine-associated adverse reactions.
- Lopinavir/ritonavir has been shown to increase tenofovir concentrations. Patients on lopinavir/ritonavir plus ATRIPLA should be monitored for tenofovir-associated adverse reactions. ATRIPLA should be discontinued in patients who develop tenofovir-associated adverse reactions.
- Coadministration of ATRIPLA and atazanavir is not recommended. Efavirenz and tenofovir DF have been shown to decrease concentrations of atazanavir. Atazanavir has also been shown to increase tenofovir concentrations.
- Saquinavir should not be used as the only protease inhibitor in combination with ATRIPLA.
- **See Full Prescribing Information for complete list of drug-drug interactions.**

Hepatic Impairment

ATRIPLA is not recommended for patients with moderate or severe hepatic impairment because of insufficient data; use caution in patients with mild hepatic impairment.

Dosage and Administration

The dose of ATRIPLA for patients at least 12 years of age and weighing ≥40 kg (88 lbs) is 1 tablet (containing 600 mg of efavirenz, 200 mg of emtricitabine, and 300 mg of tenofovir DF) once daily taken orally on an empty stomach. Dosing at bedtime may improve the tolerability of nervous system symptoms. ATRIPLA is not recommended for use in patients <12 years of age or in patients with CrCl <50 mL/min. When ATRIPLA is administered with rifampin to patients weighing ≥50 kg, an additional 200 mg/day of efavirenz is recommended.

Please see Brief Summary of Full Prescribing Information, including Boxed WARNINGS, on the following pages.

References: 1. ATRIPLA [package insert]. Foster City, CA: Bristol-Myers Squibb & Gilead Sciences, LLC. **2.** Source Healthcare Analytics, Source® PHAST Prescription Monthly, January 2006-May 2012. **3.** Source Healthcare Analytics, Source® PHAST Prescription Monthly, September 2007-May 2012. **4.** Data on File, Gilead Sciences, Inc.

Bristol-Myers Squibb

ATRIPLA® (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets

℞ ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

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

ATRIPLA is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of ATRIPLA have not been established in patients coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued EMTRIVA or VIREAD, which are components of ATRIPLA. 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 ATRIPLA. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[See Warnings and Precautions]*.

INDICATIONS AND USAGE

ATRIPLA® (efavirenz/emtricitabine/tenofovir disoproxil fumarate) is indicated for use alone as a complete regimen or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.

CONTRAINDICATIONS

Hypersensitivity: ATRIPLA is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to efavirenz, a component of ATRIPLA.

Contraindicated Drugs: For some drugs, competition for CYP3A by efavirenz could result in inhibition of their metabolism and create the potential for serious and/or life-threatening adverse reactions (e.g., cardiac arrhythmias, prolonged sedation, or respiratory depression). Drugs that are contraindicated or not recommended for use with ATRIPLA include: bepridil, cisapride, midazolam, pimozide, triazolam, voriconazole, ergot derivatives, and St. John's wort (*Hypericum perforatum*).

WARNINGS AND PRECAUTIONS

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs including tenofovir DF, a component of ATRIPLA, 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 ATRIPLA 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. ATRIPLA is not approved for the treatment of chronic HBV infection, and the safety and efficacy of ATRIPLA have not been established in patients coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued emtricitabine or tenofovir DF, two of the components of ATRIPLA. In some patients infected with HBV and treated with emtricitabine, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. Patients who are 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 ATRIPLA. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

ATRIPLA should not be administered with HEPSERA® (adefovir dipivoxil) *[See Drug Interactions]*.

Drug Interactions: Efavirenz plasma concentrations may be altered by substrates, inhibitors, or inducers of CYP3A. Likewise, efavirenz may alter plasma concentrations of drugs metabolized by CYP3A or CYP2B6 *[See Contraindications and Drug Interactions]*.

Coadministration with Related Products: Related drugs not for coadministration with ATRIPLA include COMPLERA™ (emtricitabine/rilpivirine/tenofovir DF), EMTRIVA® (emtricitabine), TRUVADA® (emtricitabine/tenofovir DF), and VIREAD® (tenofovir DF), which contain the same active components as ATRIPLA. SUSTIVA® (efavirenz) should not be coadministered with ATRIPLA unless needed for dose-adjustment (e.g. with rifampin) *[See Dosage and Administration (2) in Full Prescribing Information, Drug Interactions]*. Due to similarities between emtricitabine and lamivudine, ATRIPLA should not be coadministered with drugs containing lamivudine, including Combivir (lamivudine/zidovudine), Epivir, or Epivir-HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), or Trizivir (abacavir sulfate/lamivudine/zidovudine).

Psychiatric Symptoms: Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. In controlled trials of 1008 subjects treated with regimens containing efavirenz for a mean of 2.1 years and 635 subjects treated with control regimens for a mean of 1.5 years, the frequency (regardless of causality) of specific serious psychiatric events among subjects who received efavirenz or control regimens, respectively, were: severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonfatal suicide attempts (0.5%, 0%), aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.2%, 0.3%). When psychiatric symptoms similar to those noted above were combined and evaluated as a group in a multifactorial analysis of data from Study AI266006 (006), treatment with efavirenz was associated with an increase in the occurrence of these selected psychiatric symptoms. Other factors associated with an increase in the occurrence of these psychiatric symptoms were history of injection drug use, psychiatric history, and receipt of psychiatric medication at trial entry; similar associations were observed in both the efavirenz and control treatment groups. In Study 006, onset of new serious psychiatric symptoms occurred throughout the trial for both efavirenz-treated and control-treated subjects. One percent of efavirenz-treated subjects discontinued or interrupted treatment because of one or more of these selected psychiatric symptoms. There have also been occasional postmarketing reports of death by suicide, delusions, and psychosis-like behavior, although a causal relationship to the use of efavirenz cannot be determined from these reports. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risks of continued therapy outweigh the benefits *[See Adverse Reactions]*.

Nervous System Symptoms: Fifty-three percent (531/1008) of subjects receiving efavirenz in controlled trials reported central nervous system symptoms (any grade, regardless of causality) compared to 25% (156/635) of subjects receiving control regimens. These symptoms included dizziness (28.1% of the 1008 subjects), insomnia (16.3%), impaired concentration (8.3%), somnolence (7.0%), abnormal dreams (6.2%), and hallucinations (1.2%). Other reported symptoms were euphoria, confusion, agitation, amnesia, stupor, abnormal thinking, and depersonalization. The majority of these symptoms were mild-moderate (50.7%); symptoms were severe in 2.0% of subjects. Overall, 2.1% of subjects discontinued therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2–4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5% to 9% in subjects treated with regimens containing efavirenz and from 3% to 5% in subjects treated with a control regimen. Patients should be informed that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms *[See Warnings and Precautions]*. Dosing at bedtime may improve the tolerability of these nervous system symptoms *[See Dosage and Administration (2) in Full Prescribing Information]*.

Patients receiving ATRIPLA (efavirenz/emtricitabine/tenofovir disoproxil fumarate) should be alerted to the potential for additive central nervous system effects when ATRIPLA is used concomitantly with alcohol or psychoactive drugs.

Patients who experience central nervous system symptoms such as dizziness, impaired concentration, and/or drowsiness should avoid potentially hazardous tasks such as driving or operating machinery.

New Onset or Worsening Renal Impairment: Emtricitabine and tenofovir are principally eliminated by the kidney; however, efavirenz is not. Since ATRIPLA is a combination product and the dose of the individual components cannot be altered, patients with creatinine clearance below 50 mL/min should not receive ATRIPLA. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir DF *[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 ATRIPLA. 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. ATRIPLA should be avoided with concurrent or recent use of a nephrotoxic agent.

Reproductive Risk Potential: *Pregnancy Category D* - Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving ATRIPLA. Barrier contraception must always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of ATRIPLA is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of ATRIPLA. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. There are no adequate and well-controlled trials of ATRIPLA in pregnant women. ATRIPLA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options *[See Use in Specific Populations]*.

Rash: In controlled clinical trials, 26% (266/1008) of subjects treated with 600 mg efavirenz experienced new-onset skin rash compared with 17% (111/635) of subjects treated in control groups. Rash associated with blistering, moist desquamation, or ulceration occurred in 0.9% (9/1008) of subjects treated with efavirenz. The incidence of Grade 4 rash (e.g., erythema multiforme, Stevens-Johnson syndrome) in subjects treated with efavirenz in all trials and expanded access was 0.1%. Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with efavirenz (median time to onset of rash in adults was 11 days) and, in most subjects continuing therapy with efavirenz, rash resolves within 1 month (median duration, 16 days). The discontinuation rate for rash in clinical trials was 1.7% (17/1008). ATRIPLA can be reinitiated in patients interrupting therapy because of rash. ATRIPLA should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash.

Experience with efavirenz in subjects who discontinued other antiretroviral agents of the NNRTI class is limited. Nineteen subjects who discontinued nevirapine because of rash have been treated with efavirenz. Nine of these subjects developed mild-to-moderate rash while receiving therapy with efavirenz, and two of these subjects discontinued because of rash.

Rash was reported in 26 of 57 pediatric subjects (46%) treated with efavirenz *[See Adverse Reactions]*. One pediatric subject experienced Grade 3 rash (confluent rash with fever), and two subjects had Grade 4 rash (erythema multiforme). The median time to onset of rash in pediatric subjects was 8 days. Prophylaxis with appropriate antihistamines before initiating therapy with ATRIPLA in pediatric patients should be considered.

Hepatotoxicity: Monitoring of liver enzymes before and during treatment is recommended for patients with underlying hepatic disease, including hepatitis B or C infection; patients with marked transaminase elevations; and patients treated with other medications associated with liver toxicity *[See also Warnings and Precautions]*. A few of the postmarketing reports of hepatic failure occurred in patients with no pre-existing hepatic disease or other identifiable risk factors *[See Adverse Reactions]*. Liver enzyme monitoring should also be considered for patients without pre-existing hepatic dysfunction or other risk factors. In patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range, the benefit of continued therapy with ATRIPLA needs to be weighed against the unknown risks of significant liver toxicity *[See Adverse Reactions]*.

Decreases in Bone Mineral Density: Assessment of bone mineral density (BMD) should be considered for patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained. In a 144-week trial of treatment-naive adult subjects receiving tenofovir DF, decreases in BMD were seen at the lumbar spine and hip in both arms of the trial. There was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving tenofovir DF + lamivudine + efavirenz 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 trial and this reduction was sustained through 144 weeks. Twenty-eight percent of tenofovir DF-treated subjects vs. 21% of the comparator subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the tenofovir DF group and 6 subjects in the comparator group. Tenofovir DF was associated with significant increases in biochemical markers of bone metabolism, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving tenofovir DF.

In a clinical trial of HIV-1 infected pediatric subjects 12 years of age and older (Study 321), bone effects were similar to adult subjects. Under normal circumstances BMD increases rapidly in this age group. In this trial, the mean rate of bone gain was less in the tenofovir DF-treated group compared to the placebo group. Six tenofovir DF-treated subjects and one placebo-treated subject had significant (greater than 4%) lumbar spine BMD loss at 48 weeks. Among 28 subjects receiving 96 weeks of tenofovir DF, Z-scores declined by -0.341 for lumbar spine and -0.458 for total body. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in tenofovir DF-treated pediatric subjects 12 years of age and older suggest increased bone turnover, consistent with the effects observed in adults.

The effects of tenofovir DF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. For additional information, 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 tenofovir DF *[See Adverse Reactions]*.

Convulsions: Convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures. Caution must be taken in any patient with a history of seizures. Patients who are receiving concomitant anticonvulsant medications primarily metabolized by the liver, such as phenytoin and phenobarbital, may require periodic monitoring of plasma levels *[See Drug Interactions]*.

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including the components of ATRIPLA (efavirenz/emtricitabine/tenofovir disoproxil fumarate). 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. Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

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.

ADVERSE REACTIONS

Efavirenz, Emtricitabine and Tenofovir DF - The following adverse reactions are discussed in other sections of the labeling *[See Boxed Warning and Warnings and Precautions]:* Lactic acidosis and severe hepatomegaly with steatosis, severe acute exacerbations of hepatitis B, psychiatric symptoms, nervous system symptoms, new onset or worsening renal impairment, rash, hepatotoxicity, decreases in BMD, immune reconstitution syndrome, and drug interactions.

For additional safety information about SUSTIVA (efavirenz), EMTRIVA (emtricitabine), or VIREAD (tenofovir DF) in combination with other antiretroviral agents, consult the prescribing information for these products.

Adverse Reactions from Clinical Trials Experience: *Clinical Trials in Adult Subjects* - Study 934 was an open-label active-controlled trial in which 511 antiretroviral-naive subjects received either emtricitabine + tenofovir DF administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254). The most common adverse reactions (incidence greater than or equal to 10%, any severity) include diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. Adverse reactions observed in Study 934 were generally consistent with those seen in previous trials of the individual components. Grades 2–4 adverse reactions, based on treatment-emergent adverse events, at a frequency ≥5% in subjects receiving efavirenz, emtricitabine and tenofovir DF and zidovudine/lamivudine + efavirenz (active control) through 144 weeks, respectively, were: diarrhea (9%, 5%), nausea (9%, 7%), fatigue (9%, 8%), depression (9%, 7%), dizziness (8%, 7%), sinusitis (8%, 4%), upper respiratory tract infections (8%, 5%), rash event (7%, 9%), headache (6%, 5%), nasopharyngitis (5%, 3%), insomnia (5%, 7%), anxiety (5%, 4%), and vomiting (2%, 5%).

In Study 073, subjects with stable, virologic suppression on antiretroviral therapy and no history of virologic failure were randomized to receive ATRIPLA or to stay on their baseline regimen. The adverse reactions observed in Study 073 were generally consistent with those seen in Study 934 and those seen with the individual components of ATRIPLA when each was administered in combination with other antiretroviral agents.

In addition to the adverse reactions in Study 934 and Study 073 the following adverse reactions were observed in clinical trials of efavirenz, emtricitabine, or tenofovir DF in combination with other antiretroviral agents.

Efavirenz - The most significant adverse reactions observed in subjects treated with efavirenz are nervous system symptoms, psychiatric symptoms, and rash *[See Warnings and Precautions]*. Selected adverse reactions of moderate-severe intensity observed in greater than or equal to 2% of efavirenz-treated subjects in two controlled clinical trials included pain, impaired concentration, abnormal dreams, somnolence, anorexia, dyspepsia, abdominal pain, nervousness, and pruritus. Pancreatitis has also been reported, although a causal relationship with efavirenz has not been established. Asymptomatic increases in serum amylase levels were observed in a significantly higher number of subjects treated with efavirenz 600 mg than in control subjects.

Emtricitabine and Tenofovir DF - Adverse reactions that occurred in at least 5% of treatment-experienced or treatment-naive subjects receiving emtricitabine or tenofovir DF with other antiretroviral agents in clinical trials include arthralgia, increased cough, dyspepsia, fever, myalgia, pain, abdominal pain, back pain, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), pneumonia, rhinitis and rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction). Skin discoloration has been reported with higher frequency among emtricitabine-treated subjects.

Clinical Trials in Pediatric Subjects - ***Efavirenz*** - In a pediatric clinical trial in 57 NRTI-experienced subjects aged 3 to 16 years, the type and frequency of adverse experiences was generally similar to that of adult subjects with the exception of a higher incidence of rash, which was reported in 46% (26/57) of pediatric subjects compared to 26% of adults, and a higher frequency of Grade 3 or 4 rash reported in 5% (3/57) of pediatric subjects compared to 0.9% of adults *[See Warnings and Precautions]*. For additional information, please consult the SUSTIVA prescribing information.

Emtricitabine - In addition to the adverse reactions reported in adults, anemia and hyperpigmentation were observed in 7% and 32%, respectively, of pediatric subjects (3 months to less than 18 years of age) who received treatment with emtricitabine in the larger of two open-label, uncontrolled pediatric trials (N=116). For additional information, please consult the EMTRIVA prescribing information.

Tenofovir Disoproxil Fumarate - In a pediatric clinical trial conducted in subjects 12 to less than 18 years of age, the adverse reactions observed in pediatric subjects who received treatment with tenofovir DF were consistent with those observed in clinical trials of tenofovir DF in adults *[See Warnings and Precautions]*.

Laboratory Abnormalities: *Efavirenz, Emtricitabine and Tenofovir DF* - Laboratory abnormalities observed in Study 934 through 144 weeks were generally consistent with those seen in previous trials; significant observations in ≥1% of subjects include: any ≥Grade 3 laboratory abnormality (30%, 26%), fasting cholesterol (>240 mg/dL) (22%, 24%), creatine kinase (males >990 U/L, females >845 U/L) (9%, 7%), serum amylase (>175 U/L) (8%, 4%), alkaline phosphatase (>550 U/L) (1%, 0%), AST (males >180 U/L, females >170 U/L) (3%, 3%), ALT (males >215 U/L, females >170 U/L) (2%, 3%), hemoglobin (<8.0 mg/dL) (0%, 4%), hyperglycemia (>250 mg/dL) (2%, 1%), hematuria (>75 RBC/HPF) (3%, 2%), glycosuria (≥3+) (<1%, 1%), neutrophils (<750 mm^3) (3%, 5%), and fasting triglycerides (>750 mg/dL) (4%, 2%) in the emtricitabine + tenofovir DF + efavirenz group and the zidovudine/lamivudine + efavirenz group, respectively. Laboratory abnormalities observed in Study 073 were generally consistent with those in Study 934. Additionally, Grade 3/4 laboratory abnormalities of increased bilirubin (greater than 2.5 x ULN), increased pancreatic amylase (greater than 2.0 X ULN) increased or decreased serum glucose (less than 40 or greater than 250 mg/dL), and increased serum lipase (greater than 2.0 x ULN) occurred in up to 3% of subjects treated with emtricitabine or tenofovir DF with other antiretroviral agents in clinical trials.

Hepatic Events: In Study 934, 19 subjects treated with efavirenz, emtricitabine, and tenofovir DF and 20 subjects treated with efavirenz and fixed-dose zidovudine/lamivudine were hepatitis B surface antigen or hepatitis C antibody positive. Among these coinfected subjects, one subject (1/19) in the efavirenz, emtricitabine and tenofovir DF arm had elevations in transaminases to greater than five times ULN through 144 weeks. In the fixed-dose zidovudine/lamivudine arm, two subjects (2/20) had elevations in transaminases to greater than five times ULN through 144 weeks. No HBV and/or HCV coinfected subject discontinued from the trial due to hepatobiliary disorders *[See Warnings and Precautions]*.

Postmarketing Experience: The following adverse reactions have been identified during postapproval use of efavirenz, emtricitabine, or tenofovir DF. 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.

Efavirenz - Abnormal coordination, abnormal vision, aggressive reactions, agitation, allergic reactions, arthralgia, asthenia, ataxia, cerebellar coordination and balance disturbances, constipation, convulsions, delusions, dyspnea, emotional lability, erythema multiforme, flushing, gynecomastia, hepatic enzyme increase, hepatic failure, hepatitis, hypercholesterolemia, hypertriglyceridemia, hypoesthesia, malabsorption, mania, myalgia, myopathy, neuropathy, neurosis, palpitations, paranoia, paresthesia, photoallergic dermatitis, psychosis, redistribution/accumulation of body fat *[See Warnings and Precautions]*, Stevens-Johnson syndrome, suicide, tinnitus, tremor, and vertigo. A few of the postmarketing reports of hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, were characterized by a fulminant course, progressing in some cases to transplantation or death.

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

Tenofovir DF - Abdominal pain, acute renal failure, acute tubular necrosis, allergic reaction including angioedema, asthenia, dyspnea, Fanconi syndrome, hepatic steatosis, hepatitis, hypokalemia, hypophosphatemia, increased amylase, increased creatinine, increased liver enzymes (most commonly AST, ALT, gamma GT), interstitial nephritis (including acute cases), lactic acidosis, muscular weakness, myopathy, nephrogenic diabetes insipidus, osteomalacia (manifested as bone pain and which may contribute to fractures), pancreatitis, polyuria, proteinuria, proximal renal tubulopathy, rash, renal failure, renal insufficiency and rhabdomyolysis.

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

DRUG INTERACTIONS

Efavirenz: Efavirenz has been shown *in vivo* to induce CYP3A and CYP2B6. Other compounds that are substrates of CYP3A or CYP2B6 may have decreased plasma concentrations when coadministered with efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits CYP2C9, 2C19, and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Coadministration of efavirenz with drugs primarily metabolized by these isozymes may result in altered plasma concentrations of the coadministered drug. Therefore, appropriate dose adjustments may be necessary for these drugs. Drugs that induce CYP3A activity (e.g., phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations *[See Dosage and Administration (2) in Full Prescribing Information]*.

Emtricitabine and Tenofovir DF: Since emtricitabine and tenofovir are primarily eliminated by the kidneys, coadministration of ATRIPLA (efavirenz/emtricitabine/tenofovir disoproxil fumarate) with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated drugs. Some examples include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, and valganciclovir.

Coadministration of tenofovir DF 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. Suppression of CD4+ cell counts has been observed in patients receiving tenofovir DF with didanosine 400 mg daily. Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations. Patients receiving lopinavir/ritonavir with ATRIPLA should be monitored for tenofovir-associated adverse reactions. ATRIPLA should be discontinued in patients who develop tenofovir-associated adverse reactions. Coadministration of atazanavir with ATRIPLA is not recommended since coadministration of atazanavir with either efavirenz or tenofovir DF has been shown to decrease plasma concentrations of atazanavir. There are insufficient data to support dosing recommendations for atazanavir, with or without ritonavir in combination with ATRIPLA.

Efavirenz, Emtricitabine and Tenofovir DF: Other important drug interaction information for ATRIPLA is summarized below. The drug interactions described are based on trials conducted with efavirenz, emtricitabine or tenofovir DF as individual agents or are potential drug interactions; no drug interaction trials have been conducted using ATRIPLA (efavirenz/emtricitabine/tenofovir disoproxil fumarate). The list includes potentially significant interactions, but is not all inclusive.

Established and Other Potentially Significant Drug Interactions*: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interaction

Antiretroviral agents: Protease Inhibitors — *Atazanavir:* ↓atazanavir concentration, ↑tenofovir concentration. Coadministration of atazanavir with ATRIPLA is not recommended. Coadministration of atazanavir with either efavirenz or tenofovir DF decreases plasma concentrations of atazanavir. The combined effect of efavirenz plus tenofovir DF on atazanavir plasma concentrations is not known. Also, atazanavir has been shown to increase tenofovir concentrations. There are insufficient data to support dosing recommendations for atazanavir or atazanavir/ritonavir in combination with ATRIPLA. *Fosamprenavir calcium:* ↓amprenavir concentration. Fosamprenavir (unboosted): Appropriate doses of fosamprenavir and ATRIPLA with respect to safety and efficacy have not been established. Fosamprenavir/ritonavir: An additional 100 mg/day (300 mg total) of ritonavir is recommended when ATRIPLA is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when ATRIPLA is administered with fosamprenavir plus ritonavir twice daily. *Indinavir:* ↓indinavir concentration. The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz. *Lopinavir/ritonavir:* ↓lopinavir concentration, ↑tenofovir concentration. A dose increase of lopinavir/ritonavir to 600/150 mg (3 tablets) twice daily may be considered when used in combination with efavirenz in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). **Patients should be monitored for tenofovir-associated adverse reactions. ATRIPLA should be discontinued in patients who develop tenofovir-associated adverse reactions.** *Ritonavir:* ↑ritonavir concentration,↑efavirenz concentration. When ritonavir 500 mg every 12 hours was coadministered with efavirenz 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (e.g., dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when ATRIPLA is used in combination with ritonavir. *Saquinavir:* ↓saquinavir concentration. Should not be used as sole protease inhibitor in combination with ATRIPLA.

CCR5 co-receptor antagonist — *Maraviroc:* ↓maraviroc concentration. Efavirenz decreases plasma concentrations of maraviroc. Refer to the full prescribing information for maraviroc for guidance on coadministration with ATRIPLA.

NRTI — *Didanosine:* ↑didanosine concentration. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. **In patients weighing >60 kg, the didanosine dose should be reduced to 250 mg if coadministered with ATRIPLA. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg. Coadministration of ATRIPLA and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. For additional information, please consult the Videx/Videx EC (didanosine) prescribing information.**

Other Agents: Anticoagulant — *Warfarin:* ↑or ↓warfarin concentration. Plasma concentrations and effects potentially increased or decreased by efavirenz.

Anticonvulsants — *Carbamazepine:* ↓carbamazepine concentration, ↓efavirenz concentration. There are insufficient data to make a dose recommendation for ATRIPLA. Alternative anticonvulsant treatment should be used. *Phenytoin, Phenobarbital:* ↓anticonvulsant concentration, ↓efavirenz concentration. Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.

Antidepressants — *Bupropion:* ↓ bupropion concentration. The effect of efavirenz on bupropion exposure is thought to be due to the induction of bupropion metabolism. Increases in bupropion dosage should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded. *Sertraline:* ↓sertraline concentration. Increases in sertraline dose should be guided by clinical response.

Antifungals — *Itraconazole:* ↓itraconazole and hydroxy-itraconazole concentration. Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered. *Ketoconazole:* ↓ketoconazole concentration. Drug interaction trials with ATRIPLA and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole. *Posaconazole:* ↓posaconazole concentration. Avoid concomitant use unless the benefit outweighs the risks.

Anti-infective — *Clarithromycin:* ↓clarithromycin concentration, ↑14-OH metabolite concentration. Clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of ATRIPLA is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered. Other macrolide antibiotics, such as erythromycin, have not been studied in combination with ATRIPLA.

Antimycobacterials — *Rifabutin:* ↓rifabutin concentration. Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week. *Rifampin:* ↓efavirenz concentration. If ATRIPLA is coadministered with rifampin to patients weighing 50 kg or more, an additional 200 mg/day of efavirenz is recommended.

Calcium channel blockers — *Diltiazem:* ↓diltiazem, desacetyl diltiazem, and N-monodesmethyl diltiazem concentrations. Diltiazem dose adjustments should be guided by clinical response (refer to the full prescribing information for diltiazem). No dose adjustment of ATRIPLA is necessary when administered with diltiazem. *Others (e.g., felodipine, nicardipine, nifedipine, verapamil*): ↓calcium channel blocker. No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of CYP3A. The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the full prescribing information for the calcium channel blocker).

HMG-CoA reductase inhibitors — *Atorvastatin:* ↓atorvastatin concentration, *Pravastatin:* ↓pravastatin concentration, *Simvastatin:* ↓simvastatin concentration. Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased with efavirenz. Consult the full prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.

Hormonal contraceptives — *Oral: Ethinyl estradiol/Norgestimate:* ↓active metabolites of norgestimate. A reliable method of barrier contraception must be used in addition to hormonal contraceptives. Efavirenz had no effect on ethinyl estradiol concentrations, but progestin levels (norelgestromin and levonorgestrel) were markedly decreased. No effect of ethinyl estradiol/norgestimate on efavirenz plasma concentrations was observed. *Implant: Etonogestrel:* ↓etonogestrel. A reliable method of barrier contraception must be used in addition to hormonal contraceptives. The interaction between etonogestrel and efavirenz has not been studied. Decreased exposure of etonogestrel may be expected. There have been postmarketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.

Immunosuppressants — *Cyclosporine, tacrolimus, sirolimus, and others metabolized by CYP3A:* ↓immunosuppressant. Decreased exposure of the immunosuppressant may be expected due to CYP3A induction by efavirenz. These immunosuppressants are not anticipated to affect exposure of efavirenz. Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least 2 weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with ATRIPLA (efavirenz/emtricitabine/tenofovir disoproxil fumarate).

Narcotic analgesic — *Methadone:* ↓methadone concentration. Coadministration of efavirenz in HIV-1 infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

***This list is not all inclusive.**

Efavirenz Assay Interference: Cannabinoid Test Interaction: Efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results have been observed in non-HIV-infected volunteers receiving efavirenz when the Microgenics Cedia DAU Multi-Level THC assay was used for screening. Negative results were obtained when more specific confirmatory testing was performed with gas chromatography/mass spectrometry. For more information, please consult the SUSTIVA prescribing information.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category D *[See Warnings and Precautions]*

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients who become pregnant by calling (800) 258-4263.

Efavirenz: As of July 2010, the Antiretroviral Pregnancy Registry has received prospective reports of 792 pregnancies exposed to efavirenz-containing regimens, nearly all of which were first-trimester exposures (718 pregnancies). Birth defects occurred in 17 of 604 live births (first-trimester exposure) and 2 of 69 live births (second/third-trimester exposure). One of these prospectively reported defects with first-trimester exposure was a neural tube defect. A single case of anophthalmia with first-trimester exposure to efavirenz has also been prospectively reported; however, this case included severe oblique facial clefts and amniotic banding, a known association with anophthalmia. There have been six retrospective reports of findings consistent with neural tube defects, including meningomyelocele. All mothers were exposed to efavirenz-containing regimens in the first trimester. Although a causal relationship of these events to the use of efavirenz has not been established, similar defects have been observed in preclinical studies of efavirenz.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1. Studies in rats have demonstrated that both efavirenz and tenofovir are secreted in milk. It is not known whether efavirenz, emtricitabine, or tenofovir 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 breastfeed if they are receiving ATRIPLA.**

Pediatric Use: ATRIPLA should only be administered to pediatric patients 12 years of age and older with a body weight greater than or equal to 40 kg (greater than or equal to 88 lbs). Because ATRIPLA is a fixed-dose combination tablet, the dose adjustments recommended for pediatric patients younger than 12 years of age for each individual component cannot be made with ATRIPLA *[See Warnings and Precautions, Adverse Reactions and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

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

Hepatic Impairment: ATRIPLA is not recommended for patients with moderate or severe hepatic impairment because there are insufficient data to determine an appropriate dose. Patients with mild hepatic impairment may be treated with ATRIPLA at the approved dose. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering ATRIPLA to these patients *[See Warnings and Precautions and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Renal Impairment: Because ATRIPLA is a fixed-dose combination, it should not be prescribed for patients requiring dosage adjustment such as those with moderate or severe renal impairment (creatinine clearance below 50 mL/min) *[See Warnings and Precautions]*.

OVERDOSAGE

If overdose occurs, the patient should be monitored for evidence of toxicity, including monitoring of vital signs and observation of the patient's clinical status; standard supportive treatment should then be applied as necessary. Administration of activated charcoal may be used to aid removal of unabsorbed efavirenz. Hemodialysis can remove both emtricitabine and tenofovir DF, but is unlikely to significantly remove efavirenz from the blood.

Efavirenz - Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.

Emtricitabine - Limited clinical experience is available at doses higher than the therapeutic dose. In one trial single doses of emtricitabine 1200 mg were administered to 11 subjects. No severe adverse reactions were reported.

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

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

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir DF, a 4-hour hemodialysis session removed approximately 10% of the dose.

PATIENT COUNSELING INFORMATION See FDA-approved patient labeling (Patient Information) in Full Prescribing Information.

The Effective Latino Clinic: A Checklist for Success

BY ALISSON SOMBREDERO, MD

AS A LATINO HIV SPECIALIST, I often wonder why Latinos living with HIV face so many barriers to care. In the clinic where I routinely diagnose patients with CD4 counts less than 200 cells/mm3 and opportunistic diseases, I am reminded of the early 1980's. Several studies have shown that Latinos living with HIV are less able to access and remain engaged in HIV care. Our goal as a treatment community should be to address these barriers and turn them into opportunities to help the HIV infected Latino population achieve better health outcomes.

A culturally competent and Spanish speaking Latino HIV clinic can be extremely effective in achieving this, and although we, at the Positive Health Program (PHP), part of the HIV Division at UCSF, are in the early stages of creating this space for our Latino patients, the components of an effective Latino HIV clinic have become clear.

Here is a checklist to consider:

- Hire Spanish speaking staff, familiar with Latino cultural practices and values, including front desk clerks, medical assistants, nurses, laboratory technicians, social workers, case managers, substance abuse counselors, clinical pharmacists, primary care providers and mental health specialists.
- Provide clinicians who treat the patients with warmth and respect of the patient's traditions, home remedies and practices.
- Have a multidisciplinary team with twice a month meetings to discuss patient briefings and case conferences.
- Create a "one stop shop," where the patient can access ambulatory outpatient care, as well as supportive services like getting help completing applications and forms for benefits and health insurance, domestic violence and immigration services, housing and transportation benefits, food stamps and vouchers, Spanish language materials (brochures, pictures and videos) with a range of literacy levels need to be provided.
- Establish treatment adherence program using pill boxes, pictures, direct observed therapy, alarms or text messaging, educational Spanish speaking videos.
- Offer home or clinic delivery of HIV medications and referral to a Spanish speaking pharmacy.
- Provide flexible schedules for the working population, as well as child care for patients who are parents.
- Develop networks of referrals to agencies that serve Latinos.
- Create focus groups to identify and understand the Latino clinic population needs.
- Train and hire patient navigators and peer advocates to support new patients in case the patient preference is a one-on-one approach
- Conduct support and educational groups targeted to Latino subgroups, like MSM, heterosexual men, women, transgender, hepatitis C, treatment adherence, substance abuse among others.
- Validate the importance of social groups, arts, crafts, food, in order to decrease social isolation.

The ideal Latino clinic will translate to higher rates of patients engaged and retained in HIV care, adherent to antiretrovirals, with higher rates of HIV viral load suppression, lower number of patients with low CD4 counts and opportunistic infections. Overall, we hope for a healthier HIV Latino population. HIV

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Linking Immigration Reform to a LATINO AIDS FREE Generation

BY JOHN HELLMAN

FOLLOWING THE RESULTS OF THE 2012 ELECTION, there has been an emphasis to address the problems of our immigration system, primarily because of the growing Latino electorate. Remarks by both President Obama during his State of the Union address and the bipartisan effort in the Senate have created an encouraging environment to address the many problems with the United States immigration system.

According to the Pew Research Center, of the almost 52 million Latinos in the United States, close to 19 million, or about 36 percent, are foreign born. This statistic includes naturalized citizens, green card holders, and undocumented men and women. According to estimates, of these 19 million, 8.4 million are undocumented Latinos, which represents approximately 76 percent of the total undocumented population.

During his speech, President Obama recognized a need for new dialogue concerning HIV and AIDS.. While speaking to nation's role as a global force, the President said the "United States will join our allies to eradicate such extreme poverty in the next

two decades…by realizing the promise of an AIDS-free generation." President Obama's commitment to HIV/AIDS has been highlighted particularly by the first-ever National HIV/AIDS Strategy, which he announced in 2009. A significant part of the strategy focuses on the need to target our resources and attention towards the most heavily impacted populations and regions, which include Latinos and Latinas. According to the Kaiser Family Foundation, Latinos accounted for 20 percent of new HIV infections and 19 percent of people living with HIV as of 2009, and 22 percent of new AIDS diagnoses as of 2010.

So what is the relationship between immigration reform and HIV/AIDS? Why is immigration reform critical to improving health outcomes and reducing health disparities?

According to the CDC, for Latinos, 29 percent of HIV diagnoses and 31 percent of AIDS diagnoses were born outside of the United States and U.S. territories. Two of the critical components of the National HIV/AIDS Strategy - "Increasing Access to Care and Improving Health Outcomes for People Living with HIV" and "Reducing HIV-Related Disparities and Health Inequities"—require an in-depth understanding of the populations being affected by HIV and AIDS.

Immigration and HIV Care

A little over 13 million Latino immigrants are non-citizens, which includes green card holders, undocumented immigrants, and those with different types of visas. These different statuses can often affect many aspects of an immigrant's life, such as whether or not they are aware of their rights, their knowledge of available services, their level of English proficiency, and their ability to regularly travel to their countries of origin. In other words, different kinds of immigrants are here for different reasons. There is a different sense of how "being healthy" can be organized into their lives. For example, many immigrants do not access health care services until they are very ill, and then the hospital emergency room is the go-to place for care.

Additionally, "undocumented," "immigrant," and "Latino" are often conflated at a time when being undocumented is heavily stigmatized. States like Arizona and Alabama have been hailed as models with legislation that equates immigrants to criminals. Although there has been a shift to work on fixing our immigration system, President Obama's policy has resulted in 1.5 million deportations over the last four years, more than any president on record. Many immigrants are fearful that accessing any type of service, including public services that they are entitled to by law, may result in deportation.

A discussion of access to HIV care would be incomplete without talking about the Patient Protection and Affordable Care Act (ACA). The ACA has been hailed as the lynch-pin for the so-called AIDS free generation, and is even cited multiple times in the National HIV/AIDS Strategy as a key component to ending the epidemic. The cost of treating HIV is high, and having access to quality health insurance is essential to getting high quality care for anyone living with HIV.

In general, health insurance access is a major problem for Latinos in the United States. According to the Pew Research Center, 30 percent of Latinos lack health insurance, and almost half of uninsured Latinos are foreign-born. Approximately 27 percent of foreign-born Latinos are considered to be in poverty. Medicaid expansion, one of the primary mechanisms of the ACA, would dramatically increase the amount of Latinos with health insurance, making it much easier to access care.

Immigration reform that offers a pathway to citizenship and addresses this problem of access to care would improve the health offerings for millions of Latinos, and move us closer to effectively engaging the AIDS epidemic.

However, this transition is not seamless. Immigrants have multiple barriers to accessing health insurance under the ACA, ranging from long waiting periods to become eligible to not being able to access health insurance completely. Undocumented immigrants have very few options to pay for expensive HIV care if they are uninsured, and other priorities, such as rent or food, often come first. Immigration reform that offers a pathway to citizenship and addresses this problem of access to care would improve the health offerings for millions of Latinos, and move us closer to effectively engaging the AIDS epidemic.

The Role of the HIV Care Provider

While effective immigration reform could go a long way to helping all foreign-born Latinos have greater access to health care and HIV care services, it cannot solve the problem entirely.

HIV care providers must educate and engage the Latino immigrant community in a culturally appropriate way. Although it is generally the rule that patients are the primary drivers in accessing care (people go to the doctor's office, not the other way around), community engagement towards people who especially do not access any medical care is essential.

Conversations about "acculturation" and "assimilation" often miss a very basic point about immigration--that not all immigrants are here for the same reasons. Even among native born Latinos and non-Latinos, different people must be engaged in different ways given how they organize their lives. Latino immigrants are no different. Education and engagement must be tailored to their needs in order to better connect them to health care services.

This, coupled with immigration reform that will better shape the environment in which we all live, will put us in a better position to fully engage the AIDS epidemic and better serve all people living with HIV. HIV

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A Provider Calls for Immigration Reform

Can Politics Make a Difference?

BY LUIS A. MARCOS, MD, MPHC

A middle age Hispanic man from Mexico lived in the U.S. for about ten years. After four weeks in the intensive care unit, he died.

As a native Spanish speaker, I listened to his story. His job was the same as thousands of immigrant day laborers working in the fields, in harsh heat for low pay, and in some cases below the minimum wage (if they lack proper documentation). Alone in the U.S. with all his family in Mexico, he was one of those 11 million undocumented immigrants "sin papeles" (without documents).

My patient's sole purpose in life was to earn money to send to his family in Mexico. Ironically, he was a medical student in Mexico, but he could no longer afford the expenses and tuition of this education. The oldest of 8 brothers and sisters, his parents could not support him, so he decided to come to the U.S. to work and earn money to help his siblings get the education he could not afford for himself.

A few days before he died he told to me: "*Todo esta bien, lo se, ellos tendran un mejor futuro no como el mio*" ("Everything is fine, I know it, they will have a better future different from mine.").

Living undocumented in the U.S. was a nightmare for this young man, always living in fear and in the "shadows," something he only did for the sake of his family. He had hoped to return to his native Mexico, but of course, that dream did not materialize. He had bought a one-way bus ticket to Mexico, but he got too sick to travel just a few days before leaving.

My patient, who did not have health insurance, told me he had been feeling sick for several months before coming to the intensive care unit because he no longer could walk. He had developed shortness of breath for weeks and finally was diagnosed with HIV during his admission to the hospital. He told me that he was not sure how he acquired the HIV infection, but he suspected it was from a prostitute whom he frequently visited.

Unfortunately, this story repeats itself almost every day in the U.S. Sadly, in my short career, I have been a witness to many. I know that I am not alone.

Two years ago I lost another Hispanic patient with HIV who needed surgery to have his spleen removed. But, he did not have health insurance because he was undocumented. So, he came to the emergency room every time he was sick and received platelet transfusions. In the end, money was wasted and the patient died.

In such cases, for Hispanic patients with HIV, particularly those who are *sin papeles,* the tragedy of their disease affects entire families who also become victims—true silent victims who are often ignored.

Latinos and Latinas who are documented care deeply about their undocumented bretheren, and they are increasingly wielding the political and economic power that is theirs.

But today, the power of politics offers hope.

With the rapid growth of the Hispanic population and its great voting potential, politicians can no longer ignore their issues. That was apparent in the last Presidential election, and it grows ever more evident by the day. Latinos and Latinas who are documented care deeply about their undocumented bretheren, and they are increasingly wielding the political and economic power that is theirs.

But let's stop and think beyond politics and illnesses. The undocumented Hispanic population with HIV infection is incalculable. How can we accurately calculate this number if these people remain in the shadows, afraid to even go to the hospital for a simple illness or to get tested? Certainly, local community health clinics can see them. But they do not show up because of the fear of deportation. So instead, when it is too late, they are brought in against their will, perhaps even unconscious.

Then, because they do not speak English, they are unable to communicate their symptoms to their doctors.

This illustrates the need for more Spanish-speaking physicians in the U.S. As the Hispanic population continues to increase, do not we need more Hispanic physicians? Should we not accommodate the need of the actual population living in the U.S.? It needs to evolve according to the population trend so that the supply of Spanish-speaking bilingual physicians meets the demand—a move that could actually help reduce healthcare costs.

Do I care more or less if a person has a stamp in their passport? As health care providers, we do not ask the migratory status of any human being who comes into our care. This is not part of our "history and physical." We have taken an oath and committed our careers to save lives without prejudice. We fight against diseases, infections, heart attacks, strokes, etc., not politics.

I told my patient, "It is not worth it. You should be able to live in your country and enjoy your life along with your brothers and sisters."

He said, "The problem is that they won't have a good life if I don't help them, so I need to live." At the end of his hospitalization, he could not walk; he was disoriented and bothered by the noise of the antibiotic pump alarms every single day. He was intubated for weeks and thus, could not talk during the last week of his life. We did everything possible to save his life. But after one month in the intensive care unit, he died.

Every day, after I would see him, I would ask myself the same question: How often does this happen in the U.S.? The government has been trying to make changes in immigration laws for a long time. If it is not addressed soon, more people will continue to die and the healthcare system will continue assuming the costs of this neglected situation. Here in the U.S., this is not an illegal immigration problem, or a Hispanic problem; it is an American problem and affects us ALL. **HIV**

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HARD TIMES for Latino

BY JON PERSICHINO, DO, AAHIVS

IN THE UNITED STATES, we depend on migrant workers for the majority of planting, nurturing, and harvesting of crops. Mostly Latin American, they are an essential source of economic development in our agricultural industry and an important part of the system that brings fruits and vegetables from the fields to the supermarket.

Some three million migrant workers travel away from their home countries, especially Mexico, to find these jobs in the United States. Usually, they spend months or even years away from family members.

Most are young, married men who are uneducated, undocumented, uninsured, poor and do not speak English. They earn annual incomes below the poverty level, despite working long hours in hot and humid weather in the fields. Tragically, this vulnerable and marginalized group in American society also is at increased risk of acquiring HIV infection while working in this country...

Risk Factors

There are many behavioral, social, cultural, and health care risk factors and barriers that place migrants at increased risk for HIV infection in and out of the United States. Below is a brief summary of the major points from published studies and also from personal and professional observations that support the growing concern for HIV disease in the migrant community.

Both migrant men and women are likely to engage in high-risk sexual behavior, especially when being so far from home. Migrant men often enter into sexual relationships with commercial sex workers and infrequently use condoms. Moreover, male migrant workers, who are often isolated from their families, are more likely to accept sexual solicitations from other men in the United States when work is hard to find.

Migrant women are not immune to high risk sexual behavior. When field work is scarce, female workers may turn to unprotected sex for money or drugs.

In addition, it is common practice for migrants to use and share nonsterile syringes to inject illicit drugs, vitamins, and antibiotics in the United States. Alcohol abuse is also prevalent.

As in many other segments of society, stigma and homophobia in the Latino culture leads to stronger misperceptions about HIV and can prevent or discourage migrants from pursuing education, testing, and treatment of the disease. Because of their lack of education, most workers believe they are at low risk for HIV infection.

Access and barriers to health care

Exact prevalence rate of HIV in the migrant community is unknown, but estimates range from 2.6-13 percent. Testing and diagnosis are difficult to obtain because of the constant mobility of migrants for work and the barriers to testing that are commonplace.

Although largely unknown, most migrant workers contract HIV while working and living in the United States. In effect, this has contributed to rising HIV infection rates, particularly among women in high-migrating cities and states of Mexico. The most common risk factor for these women in contracting HIV is through a male sexual partner who has traveled to the United States for work.

Medical care is restricted to many migrant workers due to their limited language abilities, income, lack of medical insurance, and United States citizenship. Rural specialty clinics who serve HIV patients are limited in the United States. It is even more difficult to find such clinics that are also equipped with the cultural and linguistic resources to better serve our migrant worker population.

Migrant Workers

Recommendations, Solutions

The promotion and development of migrant worker unions are necessary so stronger labor contracts can be negotiated. These contracts will ensure that workers are paid higher wages and equipped with employer-based medical insurance coverage.

Continued lobbying to convince Congress to help sustain and financially support the Ryan White Care Act is needed to provide financial support to the organizations involved in the education, prevention, testing, and treatment of HIV. This increased funding can also help to support the AIDS Drug Assistance Program (ADAP), which is crucial for the treatment of HIV for undocumented migrant workers. This action would allow migrant workers to access costly medications that would otherwise be unattainable, given their exclusion from attaining full-scale Medicaid and Medicare prescription drug benefits in the United States. With appropriate funding from the Ryan White Care Act and federal/state governmental incentives, more rural migrant community health centers can be at the forefront of HIV education, testing, counseling, and treatment services for migrant and seasonal workers.

HIV-positive migrant workers also should have access to specialists properly trained in HIV disease and care in the United States. Access to such specialty care can be problematic in rural areas. With governmental incentive programs such as the National Health Service Corp, in the form of loan repayment and scholarships, and the HIV credentialing program from the American Academy of HIV Medicine, primary care clinicians may be more amenable and qualified to practicing HIV medicine in rural communities.

Given the constant mobility of their work, which moves according to the seasons, and resulting discontinuity of care, infected migrant workers must receive ongoing HIV medical care by the establishments and communications of local, regional and international networks of treatment facilities both within and outside of the United States.

To control the emerging HIV epidemic on both sides of the U.S. and Mexico border, the President's Emergency Plan for AIDS Relief (PEPFAR) should provide funds to Mexico and other Latin American countries to support the collaborative efforts in the education, prevention, and treatment of HIV disease of those affected. Priority should be placed on distributing funds to the border and rural areas with high infection rates.

Further research is needed to examine the social and cultural factors that influence sex and drug-related decision-making amongst Latino male and female migrant workers.

The Bottom Line

Migrant workers are traveling to the U.S. in search of work and to pursue the American dream. Unfortunately, for many this dream is too often negatively impacted secondary to infection with HIV.

These workers deserve a safer passage into, within, and out of the United States. Since Latino migrant workers are vital for the economic development of our agricultural industry, additional resources are needed to address the behavioral, social, cultural, and health care risk factors and barriers that place migrant workers at increased risk for HIV infection. HIV

Source for details: Persichino & Ibarra, *HIV in Latino Migrant Workers in the United States*, In Health Care and Immigration- Understanding the Connections. Ethnic & Racial Studies, 35(1): 208, January 2012, Special Issue, ISSN 0141-9870

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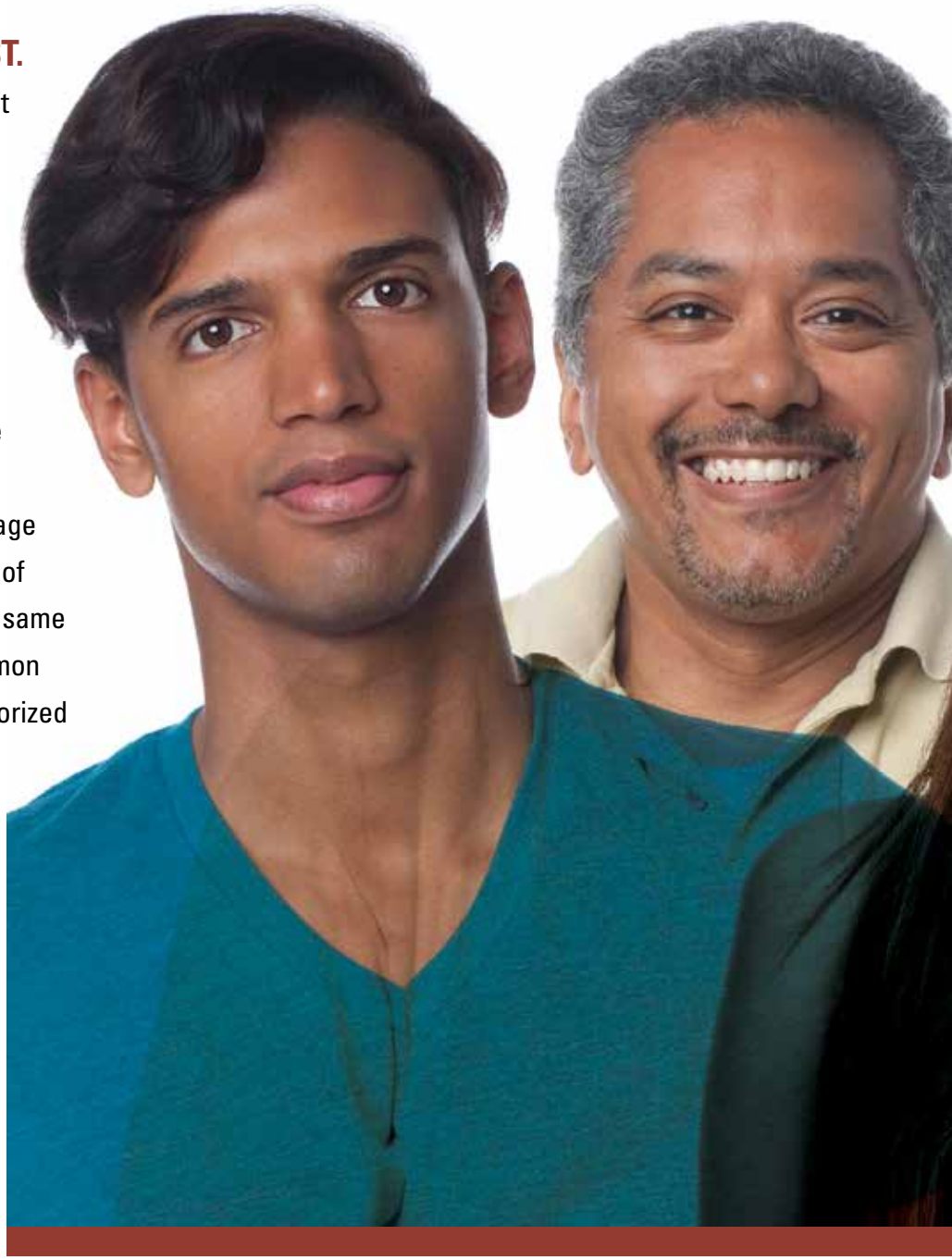
LATINOS AND HIV
Facing the

FOR US LATINOS, FAMILY ALWAYS COMES FIRST.



When growing up, my mother taught me that, though every person is unique, Hispanic people are more special than anyone else. I embraced this simple yet strong concept while aspiring to become a healthcare provider among the Hispanic population. The term "Hispanic" acknowledges a cultural group with a common heritage stemming from Spain's colonization of the Americas. Although sharing the same historical background—and a common language—Hispanics can be categorized both as a single ethnic group and subcategorized for their diverse idiosyncrasies (like Mexicans, Puerto Ricans , Cubans, and so forth).

According to 2010 Census figures, the Hispanic population in the United States reached 50.5 million, outnumbering the population of Canada.

TREATMENT:

Uniqueness

BY IVÁN MELÉNDEZ-RIVERA, MD, FAAFP, AAHIVS

Unfortunately, this Hispanic growth also reflects the alarming increase of HIV infections. Although representing the 16 percent of the total population of the United States, Latinos are still considered an ethnic minority, and as a result, they face very specific needs, including late access to medical care, and misperceptions and lack of knowledge about the U.S. healthcare system.

To face this inevitable statement, several challenges should be addressed when providing healthcare to the Latino population. Patient-Provider communication, if not the biggest of them all, is the most important when managing HIV infection, specifically due to language and health-literacy barriers.

Generally speaking, an average 40 to 80 percent of medical information exchanged with patients is immediately forgotten after a regular checkup; this amount proportionally increases during consultation time. Only half of the retained information is remembered (though not in a correct manner); spoken information approximately remains on a 17 percent-basis, in comparison to an 84 percent that is reinforced by the use of words and illustrations (pictograms).

In Puerto Rico, where I practice, a language barrier does not represent a problem for local providers, but engaging patients into a culture of healthcare consistency still is considered a dilemma. Puerto Ricans are diagnosed with HIV at a late stage in their lives and they only access healthcare when they feel very sick. Most people do not see the need to engage in medical care if they do not present any symptoms.

Latinos and the U.S. Health Care System

Developing a healthy relationship with a medical provider, as well as becoming a proactive part of the healthcare care team, is still a foreign concept for most Latino patients diagnosed with HIV. Considering the special uniqueness of this population, this fact may change with some important adjustments.

It is necessary to encourage patients to educate themselves about all his/her options, how to express his or her opinions, concerns, doubts and disagreements. Perhaps due to sociocultural reasons, most of Hispanic patients typically adopt a submissive attitude when consulting a healthcare provider. Latinos tend to reserve their complaints and assume an autodiscriminatory pattern. Whatever a doctor may say is taken as irrefutable, like a biblical truth of sorts, and as a result, patients do not even attempt to express any opinions or concerns.

Latinos do appreciate mutual respect in social relationships, especially with figures of authority. They strive to preserve personal integrity when interacting with others. Thus, as patients, when receiving any medical attention or drug treatment from an authority, they need to feel they are being "treated with respect" and valued as a person or else any medical advice will be discarded.

Also, Latinos have a different perception of time, with a more flexible understanding of punctuality. When establishing contact with a patient, saving time must be considered a less important factor than a warm, satisfactory social relationship. A Latino patient may perceive a hurried pace or fo-

BIGSTOCK PHOTO

Although representing the 16 percent of the total population of the United States, Latinos are still considered an ethnic minority, and as a result, they face very specific needs, including late access to medical care, and misperceptions and lack of knowledge about the U.S. healthcare system.

cus on saving time on the part of a caregiver as plain rudeness.

Sometimes, treatment is limited by the patient itself. They tend to avoid any contact with a medical provider concerned about their privacy, particularly afraid that someone might reveal their diagnosis. In Puerto Rico, this situation has been surpassed: patients can visit any Medicaid office for qualifications instead of referring them to a specific location—usually in their own community. That improves their concern for privacy.

Considering all aforementioned factors that affect the Hispanic/Latino population, treatment services must take into account:

- **Familiarity—**Be familiar with the patients life, especially his or her family situation. Understand that the family is the primary social unit and source of support. Ask about his or her family and remember to keep them as part of the conversation.
- **Pleasantness—**A polite, cordial social relation is truly valued; it is a central cultural value and a social expectation for this community. A friendly attitude shuns assertiveness, direct negative responses and criticism.
- **Personal approach—**It is a strong Latino preference to establish and maintain relationships with others that reflect a certain familiarity and warmth. Latinos may be more likely to trust and collaborate with someone with whom they had pleasant conversations.
- **Fatalism/determinism**—This constitutes the classic belief that fate determines life outcomes, including HIV/AIDS. For Latinos, this fate is basically unbeatable. This is a common ethos within Hispanic communities, which is often exacerbated by the marginalization that comes when dealing with social problems such as migration, poverty and racism. The perceptions of powerlessness coupled with fatalism can negatively impact any effort towards preventive HIV care.
- **Hierarchism—**An attitude of absolute respect for hierarchy and authority figures is strongly preserved in Latino cultures; the incorporation of this value into clinical consultation is critical.
- **Presentism—**An emphasis on the present, not the past or the future, poses enormous positive implications for HIV/AIDS outreach, screening and treatment. It is often difficult for providers to appreciate this cultural value since it conflicts with the biomedical concept of time, which is future-oriented.

The "Sex Talk": Unique on its own

Having the "Sex Talk" with our Hispanic community can be extremely challenging to any healthcare provider. This important conversation, which may be revealing of certain sex habits that may put the Latino patient at risk for HIV/AIDS, may be impaired by very unique qualities associated with Hispanic culture.

As a socio-cultural tradition, sex and sexuality are not openly discussed, producing a very peculiar "sexual silence." Especially for some Hispanic women, this sexual silence dictates a claim of decency—they should not know or talk to men about sex because it may suggest promiscuity. Sex behavior is commonly equated with discomfort and even considered as immoral or dangerous.

Both Hispanic men and women report high levels of discomfort about engaging in sex, which in turn, makes it difficult to successfully discuss the use of condoms as a safe practice during intercourse. One survey among Hispanic, unmarried adults found that 44 percent felt uncomfortable having sex with the lights on. This for sure raises a predicament: How can you enforce the use of condoms when people are literally "in the dark?"

When assessing tactics to establish a healthy conversation regarding preventing habits towards a safe sexual contact that prevents HIV infection, a caregiver must validate his/her patient's feelings (shame, guilt, for example), and avoid any prejudice or judgment. Identifying a staff member that has the skills to make this particular approach with patients will be very helpful to assure a comfortable environment.

Gender Roles and Machismo

The strong, powerful force of machismo among Hispanics radiates in every direction. Both Latino men and women feel their impact in various instances. For example, due to their machismo attitudes, male patients may experience serious discomfort when discussing his sexual habits to a female healthcare provider. Gender-discordance will also af-

One survey among Hispanic, unmarried adults found that 44 percent felt uncomfortable having sex with the lights on. This for sure raises a predicament: How can you enforce the use of condoms when people are literally "in the dark?"

fect women patients: They would not be particularly open to speak about their intimacy with male doctors, especially when issues like domestic violence or sexual abuse—both strongly linked with raising the risk of HIV infection due to male-dominant roles assumed during sexual intercourse.

Homosexuality brings this situation to another level: Most homosexual patients will not label themselves as gay ("maricón" or "pato", among other demeaning names used to reference homosexuals). Heterosexual men who have sex with other men usually say these acts are performed only to "relieve sexual tension, without acknowledging either physical attraction or emotional linkage to another man. Healthcare providers should be careful when addressing these issues, particularly avoiding any stereotyped wording that may sound offensive or derogatory.

Other Cultural Issues

To establish a respectful, long-lasting relationship that may enhance both trust and recurrence during prevention and/or follow-up to Hispanic patients infected with HIV, it is important to keep in mind other cultural influences that may alter the course of health care:

- **Alcohol consumption:** Consuming alcohol is culturally ingrained in Latino culture; it is part of every important festivity.
- **"Alternative" medicine:** It may not be perceived as the integration of recognized practices such as naturopathic medicine. A patient may seek help from a local pharmacy, a "botica" or whatever home remedies his "vecino" (neighbor) recommends.
- **Gossip:** This is one of the most destructive patterns in Latino cultures. Afraid of being recognized and gossiped around their neighbors (and even their relatives), most patients miss their medical appointments or the chance to receive any other professional help.
- **Religious Beliefs:** This may work either as a positive or a negative influence, depending on how much religiousness might alter any decision-making process.
- **Family:** There are strong familial bonds that may affect the possibility of receiving preventive advice or treatment. Family may interfere with such possibilities when ignoring or covering the situation just as a protective measure. It can also become a source of conflict, isolation and abandonment when dealing with HIV/AIDS, especially when sexual or religious values are strongly enforced within the family.

A Final Word of Advice

Hispanic/Latino communities are culturally rich and provide a wonderful opportunity to understand the measurement of diversity in our own world. As unique as Hispanics may be—and as challenging as they may appear—we should remember one basic principle that will always rule our practice: We are dealing with human beings. They may not share your cultural background or speak your language, but when they feel the connection, a strong bond can be established. This is particularly important in order to enhance prevention skills and raise awareness for protection in order to significantly reduce the risk of HIV infection within the Latino population.

When the moment arrives, just keep in mind these "pearls of wisdom," as unique as we Latinos are:

- Make the patient feel welcomed. A good handshake, reinforced with eye-to-eye connection establishes a bond of trust.
- Always ask about their family, pets, or how are things at home.
- Keep your posture as a form of parental guidance, but not as a person of punishment.

Making a positive effort will benefit our patients and will result in a decreased possibility of a new infection. Keep in mind uniqueness, and embrace it as a possibility to assess your own capacity to become a better caregiver. HIV

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Addressing Latino

WHEN TREATING HIV LATINO PATIENTS, it is essential to be cognizant of the many cultures that are included in this "label" and the diversity that lies within each of these cultures if the provider is to gain the patient's trust, which is so critical for success.

I am of Puerto Rican descent, and was born in South Bronx, so my perspective is based on my 26 years of experience treating patients in the northeastern U.S. But regardless of where you practice, you must recognize that Mexican American patients are different in many ways from those from other South American countries. Moreover, those born in the U.S. have different issues and concerns than first-generation immigrants.

If you are working with a Puerto Rican community and want to advance a health prevention effort, it is important to realize that their greatest risk of contracting the HIV virus is through injection drug use, and that risk is greatest among the male population.

But in treating Mexican-Americans and Cuban-American men, the most likely form of transmission is through unprotected MSM sexual activity. Dominican men also have a high likelihood of having acquired HIV through unprotected sex. So, it does not make much sense to go before a group of Cubans in Miami and talk about the dangers of injection drug use, because that is not the main problem in that community.

Poverty plays a huge role among Latinos in my community in Bridgeport, CT. Unlike many areas of the country, we are not regularly confronted with immigration issues. However, socio-economic status is directly related to greater health disparities and chronic health conditions in addition to HIV, such as diabetes, hypertension, depression, and drug and alcohol abuse.

Some 41 percent of my 630 HIV-positive patients have both HIV and Hepatitis C, as well as a number of other behavioral health conditions. Type 2 diabetes is also common with one in four Puerto Ricans having diabetes by the time they reach 50. Many also suffer from obesity and other conditions that are consequences of low socio-economic status.

I work at a federally qualified center in Connecticut, where 95 percent of my patients are either uninsured or underinsured. We access Ryan White funding here, which helps to provide coverage. We are always managing our patients under conditions where we do not have all of the resources that we need. Fortunately our Connecticut ADAP is a big help to us.

Diversity

BY RICHARD TORRES, MD, MPH, FACP, FACGS, AAHIVS

About Stigma

In my population, I do not see stigma as a notable issue, perhaps because our patients are mostly second or third generation and have become acculturated. One-third of our patients are heterosexual, one-third are injection drug users, and one-third are MSM. Most of our female patients acquired the virus through heterosexual activity, which means their male partners are not coming clean with them about their sexual activities—a common issue with Latinas. Our patients come from Peru, Cuba, Dominican Republic, Equador, Mexico, Costa Rica, and Puerto Rico.

However, with HIV-positive patients who are immigrants to this country, many will never discuss the topic because of privacy and cultural beliefs. Patients who are not native born are more likely to hold back information, so it is important for the provider to ask the necessary questions, not avoid them.

Often, Latino patients do not have good relations with their health care provider. Language and cultural differences play a big role, especially if the provider is not Latino. When I speak to them, I understand what they are saying and how they are saying it. When I speak to patient groups, many are completely unaware of their own status and why they are on medication. Many do not understand the history of HIV and do not realize they can live a normal life if they stay on treatment. Many of my patients don't have Internet because they are poor.

The language barrier between provider and patient often is huge, and there is a need for cross-cultural education so providers understand the differences between the Latino subgroups.

You can transcend the language barrier if you show empathy and even learn just a few phrases so people will understand that you care. HIV

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It is also essential to recognize and understand the importance of religion in the Latino culture. Some people believe it is God's will if they get sick and die.

BY JANIS ZADEL, NP, AAHIVS

Outside YOUR NATIVE CULTURE

I HAVE WORKED AS A NURSE PRACTITIONER for 32 years and have specialized in HIV for the past 22 years, including 20 years at Presbyterian Hospital in New York and now for the past two-and-one-half years at the Jersey City Medical Center. We treat many undocumented Latino patients, and that is a challenge.

But another challenge is to be working and caring for patients whose culture is much different than my own. You need to listen to their health beliefs, to what is important to them and find a way to explain things in a way that they will understand. But before I can do that, I must understand.

The first Latino population that I worked with was primarily Puerto Rican in East Harlem. Now at the Jersey City Medical Center, our patients come from everywhere south of the border.

We are a Ryan White funded clinic and many of our patients are working and have health insurance. But those who are undocumented must turn to ADAP and charity care, which, of course, is limited.

Family situations pose a challenge as well. Some people are married and might have U.S.-born children, but they, themselves, are never going to be eligible for citizenship. This limits their ability to cope with many of the problems they face.

Recently, I saw a man whose mother was dying in South America, but he could not go to be with her because he could not access HIV treatment there, and he would not have been able to get back into the U.S. The lack of ability to travel for undocumented workers with HIV is a huge problem.

There are some unique medical conditions that appear to be common with many patients with Latin American heritage, such as kidney disease.

It is also essential to recognize and understand the importance of religion in the Latino culture. Some people believe it is God's will if they get sick and die.

I have also found that often people born in the tropics are more likely to be antibody positive for toxoplasmosis, a parasitic disease caused by the protozoan Toxoplasma Gondi.[1] A 2004 study published in *Lancet* said seroprevalence was 75 percent in El Salvador. Those with a weakened immune system can become seriously ill and the parasite can cause encephalitis and neurologic diseases. It is an opportunistic infection and can be deadly.

It is also essential to recognize and understand the importance of religion in the Latino culture. Some people believe it is God's will if they get sick and die. This is part of the stigma around HIV because many think that whatever they did was a sin, and this is punishment. I have to explain, "No, this is a virus, not a punishment."

I have also had many people tell me that it is God's will whether they get better. I often hear, "Well, I went to church and they prayed over me, and I know He will heal me." This is painful for me to hear, especially when they reject medication due to this belief. This is where peer educators are so helpful. They will often tell the patients, "Why do you think God made all the scientists and doctors and nurses? He made them so they can help you." That approach helps people concerned about taking medications for religious reasons accept treatment.

Working with Latinos is the same as anyone working outside of their native population. You must make the effort to get to know the culture. Make the effort to bring out what their health beliefs are and what motivates them so you can relate to them and provide the help and care that they need. HIV

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BY ANNA PEDERSEN, PHARMD, AAHIVP

On the Frontlines

The Pharmacist: Addressing Barriers to Adherence

AS A PHARMACIST working with the HIV community, my number one job is to address barriers that can prevent HIV patients from adhering to their treatment and medication protocol. These barriers often include untreated mental health, substance use, cost, stigma surrounding HIV, side effects, and the simple burden of taking the required pills.

Working primarily with the Latino community infected with HIV, it is clear to me that those barriers can increase significantly. Then, add in such factors as language barriers, transportation difficulties and scheduling conflicts for shift workers or migrant workers—not to mention, the overall medication experience for a culture unaccustomed to needing prescriptions in the first place.

Clearly, HIV care providers increasingly are turning into chronic disease specialists, and in the Latino community there a higher rates of diabetes and coronary artery disease, without the added risks of HAART. Pharmacists can provide recommendations for the best agents to use while treating these patients and help them achieve their therapeutic goals.

Take advantages of this resource and ask that your pharmacist meet with your patients to discuss their diabetes, insulin titrations, need for preventive cares, and other issues involving medications. Here are some steps to overcoming some of these barriers:

- Utilize your social workers and case managers to ensure that patients stay insured and understand the importance of insurance. In some immigrant populations, the idea of insurance is not understood. In most cases, having no insurance means interruptions in therapy.
- Utilize ADAP and patient assistance offered by most HIV drug companies for those uninsured patients who meet income guidelines. If a patient is privately insured, utilize co-pay cards to help decrease high co-pay requirements. Patient assistance can also be used to fill insurance coverage gaps.
- When meeting with your patients, discuss their other health problems, such as diabetes or hypertension. Pharmacists can provide recommendations for the best agents to use during treatment, and help get patients to meet therapeutic goals.
- Try to overcome language barriers by employing fluent staff or onsite interpreters. There are numerous phone translation services also available. When using an interpreter, direct all discussions to the patient and not the interpreter. Patients appreciate conversing in their own language, but if you are using an interpreter but speak to them directly, they will more easily connect with you and understand what you are saying.
- Offer mail or delivery services for patients who cannot come in to the pharmacy during hours to accommodate shift or migrant workers.
- Utilize your state's AIDS services organizations to provide transportation for patients.
- Include your pharmacist as part of your health care team. They can provide up-to-date refill histories and an idea of adherence. Pharmacists can let you know what is affordable for the patient, and provide invaluable education regarding medication uses, side effects and drug interactions. Pharmacists can provide clinical insight for your patients, as well. HIV

THINKSTOCK

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BY RODGER D. MacARTHUR, M.D.

Advances in Symptom Management in Persons with HIV Infection

As a result of advances in combination antiretroviral therapy (cART), HIV-infected persons are living for decades after the diagnosis, and now have close to a normal life expectancy. Indeed, someone infected in the United States today at the age of 26 has a life expectancy of at least another 40 years.[1] Not only has longevity increased, but so also has the quality of life, as HIV-infected persons are initiating cART earlier, and as medications with fewer side effects have replaced older, more side effect-prone medications as "preferred" therapies.[2] However, side effects from these medications do occur, and it is important for health care providers to be aware of them and to manage them appropriately. Chief among common side effects is noninfectious diarrhea that often is associated with antiretroviral therapy (ART).

The protease inhibitor (PI) class of antiretrovirals is used in combination with, typically, two nucleoside reverse transcriptase inhibitors (NRTIs) for approximately 35% of HIV-infected persons on antiretroviral therapy in the United States. PIs are very effective at rapidly suppressing HIV RNA, and, when combined with the very potent cytochrome p450 inhibitor ritonavir, are seldom limited by the development of drug-limiting mutations.

However, this class is associated with gastrointestinal side effects, including diarrhea, in 10 – 25% of persons taking them. The PIs cause diarrhea by increasing chloride ion secretion into the intestinal lumen, accompanied by an influx of water (secretory diarrhea). The PI-associated diarrhea is rarely life-threatening, but can be substantially life-altering, especially when daily watery bowel movements occur in association with cramping and urgency.

Until recently, there was no specific therapy available for the treatment of antiretroviral-associated diarrhea.[3] Anti-motility agents, like immodium and Lomotil®, nonspecifically inhibit gut motility and often are associated with objectionable and potentially dangerous post-diarrhea constipation. Typically, patients were unable to find relief, which resulted in a negative impact on both quality of life and treatment compliance.

On December 31, 2012, the U.S. Food and Drug Administration (FDA) approved crofelemer (Fulyzaq®), the first specific treatment for HIV-infected persons on antiretroviral therapy with noninfectious diarrhea. Unlike Imodium and Lomotil, crofelemer provides an antisecretory effect that doesn't affect gut motility.

Crofelemer is an intraluminally-active, minimally-absorbed oral antidiarrheal medication that blocks chloride ion secretion by inhibiting the cystic fibrosis transmembrane conductance regulator (CFTR) protein and the calcium-activated chloride channel (CaCC). In blocking chloride secretion, crofelemer reduces the high volume water loss that may cause other symptoms including dehydration and electrolyte imbalance.

This first-in-class drug has impressive efficacy and a safety profile comparable to placebo.[4] In a randomized, double-blind, placebo-controlled and placebo-free multi-center study, 374 patients on cART with a history of diarrhea for a month or longer were evaluated. The data revealed an impressive clinical response for those receiving crofelemer compared to patients in the placebo group. Additionally, the drug did not influence the efficacy or safety of the patients HIV medications. Crofelemer will be available by prescription in the U.S. by the end of March 2013.

As providers, we are charged with not only providing the best care to treat diseases at hand but also are accountable for looking at the side effects that may be associated with treatment and offering a plan of action for minimizing the impact of symptoms. Newly FDA approved medications, including crofelemer, can help us realize our goal. It is also important to ask early and often about complications our patients may be experiencing. Coupled with recognizing expanding treatment options, open communication can help lead the way for us to continually improve treatment compliance of and quality of life for our patients. HIV

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