The AMERICAN ACADEMY of HIV MEDICINE®

HIV SPECIALIST

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

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HIV Clinical Update

STRIBILD is indicated as a complete single-tablet regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve.

Powerful performance in HIV[1]

STRIBILD is the first integrase inhibitor–based single-tablet regimen[2]

- **STRIBILD achieves strong efficacy with an overall rapid reduction in viral load[3,4]**
  - Noninferior efficacy at week 48
    - 90% of subjects taking STRIBILD reached undetectable viral loads compared to 87% of subjects taking ATV + RTV + FTC/TDF
    - 88% of subjects taking STRIBILD reached undetectable viral loads compared to 84% of subjects taking EFV/FTC/TDF
- **Convenient single-tablet regimen dosing**
  - 1 tablet taken once daily with food
  - Do not initiate in patients with eGFR <70 mL/min; discontinue in patients with eGFR <50 mL/min; not recommended in patients with severe hepatic impairment
- **Safety and tolerability profile through 48 weeks**
  - The most common adverse drug reactions (all severity grades) reported in ≥5% of subjects were nausea (16%), diarrhea (12%), abnormal dreams (9%), headache (7%), and fatigue (5%)
  - 3.7% of subjects taking STRIBILD discontinued therapy due to adverse events compared to 5.1% of subjects taking either ATV + RTV + FTC/TDF or EFV/FTC/TDF

BOXED WARNING

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 STRIBILD, in combination with other antiretrovirals.**
- **STRIBILD is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of STRIBILD 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 human immunodeficiency virus-1 (HIV-1) and have discontinued EMTRIVA or VIREAD, which are components of STRIBILD. 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 STRIBILD. If appropriate, initiation of anti-hepatitis B therapy may be warranted.**

Please see additional Important Safety Information on the next page.

Study designs: STRIBILD was assessed in 2 randomized, double-blind, active-controlled, phase 3, noninferiority clinical trials in treatment-naïve, HIV-1–infected subjects with baseline estimated creatinine clearance >70 mL/min. Study 103 compared STRIBILD (n = 353) to ATV + RTV + FTC/TDF (n = 355); Study 102 compared STRIBILD (n = 348) to a single-tablet regimen consisting of EFV/FTC/TDF (n = 352). The primary endpoint of both studies was the proportion of subjects with viral suppression (<50 copies/mL) at week 48 according to FDA snapshot analysis.

Baseline characteristics: Viral load: In Studies 103 and 102, respectively, 41% and 33% of subjects had baseline viral loads >100,000 copies/mL. **CD4 count:** Mean baseline CD4+ cell count was 370 cells/mm^3 (range 5 to 1132) in Study 103, and 386 cells/mm^3 (range 3 to 1348) in Study 102; 13% of subjects in both studies had CD4+ cell counts <200 cells/mm^3.

Abbreviations: ATV, atazanavir; EFV, efavirenz; eGFR, estimated glomerular filtration rate; FTC, emtricitabine; RTV, ritonavir; TDF, tenofovir disoproxil fumarate.

Important Safety Information (*continued*)

Contraindications

- **Coadministration:** Do not use with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. Do not use with drugs that strongly induce CYP3A as this may lead to a loss of virologic response and possible resistance to STRIBILD. Use with the following drugs is contraindicated: alfuzosin, rifampin, dihydroergotamine, ergotamine, methylergonovine, cisapride, lovastatin, simvastatin, pimozide, sildenafil for pulmonary arterial hypertension, triazolam, oral midazolam, and St. John's wort.

Warnings and precautions

- **New onset or worsening renal impairment:** Cases of acute renal failure and Fanconi syndrome have been reported with the use of tenofovir DF and STRIBILD. Monitor estimated creatinine clearance (CrCl), urine glucose, and urine protein in all patients prior to initiating and during therapy; additionally monitor serum phosphorus in patients with or at risk for renal impairment. Cobicistat may cause modest increases in serum creatinine and modest declines in CrCl without affecting renal glomerular function; patients with an increase in serum creatinine >0.4 mg/dL from baseline should be closely monitored for renal safety. Do not initiate STRIBILD in patients with CrCl below 70 mL/min. Discontinue STRIBILD if CrCl declines below 50 mL/min. Avoid concurrent or recent use with a nephrotoxic agent.
- **Use with other antiretroviral products:** STRIBILD is a complete regimen for the treatment of HIV-1 infection. Do not coadminister with other antiretroviral products, including products containing any of the same active components; products containing lamivudine; products containing ritonavir; or with adefovir dipivoxil.
- **Decreases in bone mineral density (BMD)** and cases of osteomalacia have been seen in patients treated with tenofovir DF. Consider monitoring BMD in patients with a history of pathologic fracture or risk factors for bone loss.
- **Fat redistribution** and accumulation have been observed in patients receiving antiretroviral therapy.
- **Immune reconstitution syndrome,** including the occurrence of autoimmune disorders with variable time to onset, has been reported.

Adverse reactions

- **Common adverse drug reactions** in clinical studies (incidence ≥5%; all grades) were nausea (16%), diarrhea (12%), abnormal dreams (9%), headache (7%), and fatigue (5%).

Drug interactions

- **CYP3A substrates:** STRIBILD can alter the concentration of drugs metabolized by CYP3A or CYP2D6. Do not use with drugs highly dependent on these factors for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening adverse events.
- **CYP3A inducers:** Drugs that induce CYP3A can decrease the concentrations of components of STRIBILD. Do not use with drugs that strongly induce CYP3A as this may lead to loss of virologic response and possible resistance to STRIBILD.
- **Antacids:** Separate STRIBILD and antacid administration by at least 2 hours.
- **Prescribing information:** Consult the full prescribing information for STRIBILD for more information on potentially significant drug interactions, including clinical comments.

Dosage and administration

- **Adult dosage:** One tablet taken orally once daily with food.
- **Renal impairment:** Do not initiate in patients with CrCl below 70 mL/min. Discontinue in patients with CrCl below 50 mL/min.
- **Hepatic impairment:** Not recommended in patients with severe hepatic impairment.

Pregnancy and breastfeeding

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

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

References: 1. STRIBILD [package insert]. Foster City, CA: Gilead Sciences, Inc; 2012. **2.** US Food and Drug Administration. Antiretroviral drugs used in the treatment of HIV infection. http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/hivandaidsactivities/ucm118915.htm. Accessed May 7, 2013. **3.** DeJesus E, Rockstroh JK, Henry K, et al; for the GS-236-0103 Study Team. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet.* 2012;379(9835):2429-2438. **4.** Sax P, DeJesus E, Mills A, et al; for the GS-US-236-0102 Study Team. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. *Lancet.* 2012;379(9835):2439-2448.

STRIBILD™

elvitegravir 150mg/ cobicistat 150mg/ emtricitabine 200mg/ tenofovir disoproxil fumarate 300mg tablets

Performance by design

Learn more at www.**STRIBILD**.com/hcp

STRIBILD™ (elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets, for oral use

Brief summary of full Prescribing Information. See full Prescribing Information. Rx only.

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

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

STRIBILD is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of STRIBILD 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 human immunodeficiency virus-1 (HIV-1) and have discontinued EMTRIVA or VIREAD, which are components of STRIBILD. 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 STRIBILD. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[See Warnings and Precautions]*.

INDICATIONS AND USAGE:
STRIBILD is indicated as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naive.

DOSAGE AND ADMINISTRATION:
The recommended dose is one tablet taken orally once daily with food.

Renal Impairment: Do not initiate in patients with estimated creatinine clearance (CrCl) below 70 mL/min. Discontinue if CrCl declines below 50 mL/min during treatment *[See Warnings and Precautions, Adverse Reactions, Use in Specific Populations]*.

Hepatic Impairment: No dose adjustment is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding use in patients with severe hepatic impairment (Child-Pugh Class C). STRIBILD is not recommended for use in patients with severe hepatic impairment *[See Use in Specific Populations]*.

CONTRAINDICATIONS:
Coadministration: Do not use with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening adverse events, or with drugs that strongly induce CYP3A as this may decrease STRIBILD plasma concentrations leading to a loss of virologic response and possible resistance *[See Drug Interactions]*:

- Alpha 1-adrenoreceptor antagonists: alfuzosin. Potential for hypotension.
- Antimycobacterial: rifampin. May lead to a loss of virologic response and possible resistance to STRIBILD.
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine. Potential for acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
- GI motility agents: cisapride. Potential for cardiac arrhythmias.
- Herbal products: St. John's wort (*Hypericum perforatum*). May lead to a loss of virologic response and possible resistance to STRIBILD.
- HMG CoA reductase inhibitors: lovastatin, simvastatin. Potential for myopathy, including rhabdomyolysis.
- Neuroleptics: pimozide. Potential for cardiac arrhythmias.
- PDE-5 inhibitors: sildenafil when dosed as REVATIO for the treatment of pulmonary arterial hypertension. A safe and effective dose has not been established; the potential for sildenafil-associated adverse events (visual disturbances, hypotension, priapism, and syncope) is increased.
- Sedative/hypnotics: orally administered midazolam, triazolam. Potential for prolonged or increased sedation or respiratory depression.

WARNINGS AND PRECAUTIONS:
Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with nucleoside analogs, including tenofovir DF, a component of STRIBILD, 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 STRIBILD 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. STRIBILD is not approved for the treatment of chronic HBV infection and the safety and efficacy of STRIBILD 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 STRIBILD. 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 STRIBILD. 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 tenofovir DF and with STRIBILD *[See Adverse Reactions]*. In clinical trials of STRIBILD over 48 weeks (N=701), 8 (1.1%) subjects in the STRIBILD group and 1 (0.1%) subject in the combined comparator groups discontinued study drug due to a renal adverse event. Four (0.6%) of the subjects who received STRIBILD developed laboratory findings consistent with proximal renal tubular dysfunction leading to discontinuation of STRIBILD compared to none in the comparator groups. Two of these 4 subjects had renal impairment (CrCl less than 70 mL/min) at baseline. The laboratory findings in these 4 subjects improved but did not completely resolve in all subjects upon discontinuation. Renal replacement therapy was not required. STRIBILD should be avoided with concurrent or recent use of a nephrotoxic agent. ***Monitoring:*** CrCl, urine glucose and urine protein should be documented in all patients prior to initiating therapy. STRIBILD should not be initiated in patients with CrCl below 70 mL/min. Routine monitoring of CrCl, urine glucose, and urine protein should be performed during STRIBILD therapy in all patients. Additionally, serum phosphorus should be measured in patients at risk for renal impairment. Although cobicistat may cause modest increases in serum creatinine and modest declines in CrCl without affecting renal glomerular function *[See Adverse Reactions]*, patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg/dL from baseline should be closely monitored for renal safety. STRIBILD should be discontinued if CrCl declines below 50 mL/min.

Use with Other Antiretroviral Products: STRIBILD is a complete regimen for the treatment of HIV-1 infection and should not be coadministered with other antiretroviral products. STRIBILD should not be coadministered with products containing any of the same active components (ATRIPLA, COMPLERA, EMTRIVA, TRUVADA, VIREAD); or with products containing lamivudine (COMBIVIR, EPIVIR, EPIVIR-HBV, EPZICOM, TRIZIVIR). STRIBILD should not be administered with adefovir dipivoxil (HEPSERA).

Decreases in Bone Mineral Density (BMD): In previous clinical trials, tenofovir DF has been associated with decreases in BMD and increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N telopeptide), suggesting increased bone turnover. Serum parathyroid hormone levels and 1.25 Vitamin D levels were also higher in subjects receiving VIREAD. The effects of tenofovir DF-associated changes in BMD on 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 tenofovir DF *[See Adverse Reactions]*. In Study 103, BMD was assessed by DEXA in a non-random subset of 120 subjects. Mean percentage decreases in BMD from baseline to Week 48 in the STRIBILD group (N=54) were comparable to the atazanavir + ritonavir + emtricitabine/tenofovir DF group (N=66) at the lumbar spine (-2.6% versus -3.3%, respectively) and at the hip (-3.1% versus -3.9%, respectively). In Studies 102 and 103, bone fractures occurred in 9 subjects (1.3%) in the STRIBILD group, 6 subjects (1.7%) in the efavirenz/emtricitabine/tenofovir DF group, and 6 subjects (1.7%) in the atazanavir + ritonavir + emtricitabine/tenofovir DF group. These findings were consistent with data from an earlier 144-week trial of treatment-naive subjects receiving tenofovir DF + lamivudine + efavirenz. Assessment of 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 in all patients. If bone abnormalities are suspected appropriate consultation should be obtained.

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

Immune Reconstitution Syndrome (IRS): IRS has been reported in patients treated with combination antiretroviral therapy, including STRIBILD. 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-Barre syndrome) have 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: The safety assessment of STRIBILD is based on pooled data from 1408 subjects in two Phase 3 trials, Study 102 and Study 103, in antiretroviral treatment-naive HIV-1 infected adult subjects. A total of 701 subjects received STRIBILD once daily for at least 48 weeks. The proportion of subjects who discontinued treatment with STRIBILD due to adverse events, regardless of severity, was 3.7%.

Treatment Emergent Adverse Drug Reactions: Treatment emergent adverse drug reactions (all grades) reported in ≥5% of subjects receiving STRIBILD (N=701) in Studies 102 and 103 (Week 48 analysis) were: nausea (16%); diarrhea (12%); abnormal dreams (9%); headache (7%); and fatigue (5%). Frequencies of adverse reactions are based on all treatment emergent adverse events, attributed to study drugs. See ***WARNINGS AND PRECAUTIONS*** for a discussion of renal adverse events from clinical trials experience with STRIBILD.

Laboratory Abnormalities: Treatment emergent laboratory abnormalities (Grades 3-4) occurring in ≥2% of subjects receiving STRIBILD (N=701) in Studies 102 and 103 (Week 48 analysis) were: creatine kinase (≥10.0 x ULN), 5%; urine RBC (hematuria) (>75 RBC/HPF), 3%; AST (>5.0 x ULN), 2%; and amylase (>2.0 x ULN), 2%. For subjects with serum amylase >1.5 x ULN, lipase test was also performed. The frequency of increased lipase (Grades 3-4) occurring in STRIBILD (N=58) was 12%. Proteinuria (all grades) occurred in 39% of subjects receiving STRIBILD. Cobicistat has been shown to decrease CrCl due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. In Studies 102 and 103, decreases in CrCl occurred early in treatment with STRIBILD, after which they stabilized. Mean ± SD changes after 48 weeks of treatment were 0.14 ± 0.13 mg/dL for serum creatinine and -13.9 ± 14.9 mL/min for estimated glomerular filtration rate (eGFR) by Cockcroft-Gault method. Elevation in serum creatinine (all grades) occurred in 7% of subjects.

Serum Lipids: In the clinical trials of STRIBILD, 11% of subjects were on lipid lowering agents at baseline. While receiving study drug through Week 48, an additional 4% of subjects were started on lipid lowering agents. Through 48 weeks, 1% or fewer subjects in any treatment arm experienced Grades 3-4 elevations in fasting cholesterol (greater than 300 mg/dL) or fasting triglycerides (greater than 750 mg/dL). Mean changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides reported in subjects receiving STRIBILD (N=701) in Studies 102 and 103 (Week 48 analysis) were: total cholesterol (fasted): baseline 166 mg/dL (N=675), week 48 change +11 (N=606); HDL-cholesterol (fasted): baseline 43 mg/dL (N=675), week 48 change +6 (N=605); LDL-cholesterol (fasted): baseline 100 mg/dL (N=675), week 48 change +10 (N=606); triglycerides (fasted): baseline 122 mg/dL (N=675), week 48 change +13 (N=606). The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 values.

Emtricitabine and Tenofovir DF: ***Adverse drug reactions:*** In addition to the adverse drug reactions observed with STRIBILD, the following adverse drug reactions occurred in at least 5% of treatment-experienced or treatment-naive subjects receiving emtricitabine or tenofovir DF with other antiretroviral agents in other clinical trials: depression, 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:*** In addition to the laboratory abnormalities observed with STRIBILD, the following laboratory abnormalities have been previously reported in subjects treated with emtricitabine or tenofovir DF with other antiretroviral agents in other clinical trials: Grades 3-4 laboratory abnormalities of ALT (M: greater than 215 U/L; F: greater than 170 U/L), alkaline phosphatase (greater than 550 U/L), bilirubin (greater than 2.5 x ULN), serum glucose (less than 40 or greater than 250 mg/dL), glycosuria (greater than or equal to 3+), neutrophils (less than 750/mm^3), fasting cholesterol (greater than 240 mg/dL), and fasting triglycerides (greater than 750 mg/dL). ***Postmarketing Events:*** The following adverse reactions have been identified during post approval use of tenofovir DF: allergic reaction (including angioedema), lactic acidosis, hypokalemia, hypophosphatemia, dyspnea, pancreatitis, increased amylase, abdominal pain, hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT), rash, rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy, acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria, and asthenia. The following adverse reactions listed above may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, and hypophosphatemia.

DRUG INTERACTIONS:
See ***CONTRAINDICATIONS*** *for additional serious adverse reactions.*

STRIBILD is a complete regimen for the treatment of HIV-1 infection. STRIBILD should not be administered with other antiretroviral medications for treatment of HIV-1 infection. Complete information regarding potential drug-drug interactions with other antiretroviral medications is not provided.

STRIBILD should not be used in conjunction with protease inhibitors or non-nucleoside reverse transcriptase inhibitors due to potential drug interactions including altered and/or suboptimal pharmacokinetics of cobicistat, elvitegravir, and/or the coadministered antiretroviral products. STRIBILD should not be administered concurrently with products containing ritonavir or regimens containing ritonavir due to similar effects of cobicistat and ritonavir on CYP3A.

Potential for STRIBILD to Affect Other Drugs: Cobicistat is an inhibitor of CYP3A and CYP2D6. The transporters that cobicistat inhibits include p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. Coadministration of STRIBILD with drugs that are primarily metabolized by CYP3A or CYP2D6, or are substrates of P-gp, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of such drugs. Elvitegravir is a modest inducer of CYP2C9 and may decrease the plasma concentrations of CYP2C9 substrates.

Potential for Other Drugs to Affect One or More Components of STRIBILD: Elvitegravir and cobicistat are metabolized by CYP3A. Cobicistat is also metabolized, to a minor extent, by CYP2D6. Drugs that induce CYP3A activity are expected to increase the clearance of elvitegravir and cobicistat, resulting in decreased plasma concentration of cobicistat and elvitegravir, which may lead to loss of therapeutic effect of STRIBILD and development of resistance. Coadministration of STRIBILD with other drugs that inhibit CYP3A may decrease the clearance and increase the plasma concentration of cobicistat.

Drugs Affecting Renal Function: Because emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of STRIBILD with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of emtricitabine, tenofovir, and other renally eliminated drugs.

Established and Other Potentially Significant Interactions: The drug interactions described are based on studies conducted with either STRIBILD, the components of STRIBILD as individual agents and/or in combination, or are predicted drug interactions that may occur with STRIBILD. The list includes potentially significant interactions but is not all inclusive. **An alteration in dose or regimen may be recommended for the following drugs when coadministered with STRIBILD:**

- Acid Reducing Agents: antacids. Separate STRIBILD and antacid administration by at least 2 hours.
- Antiarrhythmics: amiodarone, bepridil, digoxin, disopyramide, flecainide, systemic lidocaine mexiletine, propafenone, quinidine. Caution warranted and therapeutic concentration monitoring recommended.
- Antibacterials: clarithromycin, telithromycin. Clarithromycin: no dose adjustment required for patients with CrCl ≥60 ml/min; the dose should be reduced by 50% for patients with CrCl between 50 and 60 mL/min. Telithromycin: concentrations of telithromycin and/or cobicistat may be increased.
- Anticoagulants: warfarin. International normalized ratio (INR) monitoring recommended.
- Anticonvulsants: carbamazepine, oxcarbazepine phenobarbital, phenytoin, clonazepam, ethosuximide. Phenobarbital, phenytoin, carbamazepine, and oxcarbazepine: may lead to loss of virologic response and possible resistance to STRIBILD. Alternative anticonvulsants should be considered. Clonazepam and ethosuximide: clinical monitoring recommended.
- Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs), Tricyclic Antidepressants (TCAs), trazodone. Dose titration of the antidepressant and monitoring for antidepressant response recommended.
- Antifungals: itraconazole, ketoconazole, voriconazole. Ketoconazole and itraconazole: the maximum daily dose should not exceed 200 mg/day. Voriconazole: an assessment of benefit/risk ratio is recommended to justify use.
- Anti-gout: colchicine. Do not coadminister in patients with renal or hepatic impairment. For other patients, modify the dose and/or regimen as described in the full PI for STRIBILD.
- Antimycobacterials: rifabutin, rifapentine. May lead to loss of virologic response and possible resistance to STRIBILD. Coadministration not recommended.
- Beta-Blockers: metoprolol, timolol. Clinical monitoring recommended and a dose decrease of the beta blocker may be necessary.
- Calcium Channel Blockers: amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil. Caution warranted and clinical monitoring recommended.
- Corticosteroids (Systemic): dexamethasone. May lead to loss of virologic response and possible resistance to STRIBILD.
- Corticosteroids (Inhaled/Nasal): fluticasone. Alternative corticosteroids should be considered, particularly for long term use.
- Endothelin Receptor Antagonists: bosentan. Discontinue bosentan at least 36 hours prior to initiating STRIBILD. For patients taking STRIBILD for at least 10 days, start or resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.
- HMG CoA Reductase Inhibitors: atorvastatin. Initiate with the lowest starting dose and titrate carefully while monitoring for safety.
- Hormonal Contraceptives: norgestimate/ethinyl estradiol. Coadministration with STRIBILD resulted in decreased plasma concentrations of ethinyl estradiol and an increase in norgestimate. The effects of increased progesterone exposure are not fully known. The potential risks and benefits of coadministration should be considered, particularly in women who have risk factors for progesterone exposure. Alternative (non hormonal) methods of contraception can be considered.
- Immunosuppressants: cyclosporine, rapamycin, sirolimus, tacrolimus. Therapeutic monitoring recommended.
- Inhaled Beta Agonist: salmeterol. Coadministration not recommended due to the increased risk of salmeterol cardiovascular adverse events, including QT prolongation, palpitations, and sinus tachycardia.
- Neuroleptics: perphenazine, risperidone, thioridazine. Decrease in dose of the neuroleptic may be needed.
- Phosphodiesterase-5 (PDE5) Inhibitors: sildenafil, tadalafil, vardenafil. *Dosage for erectile dysfunction:* sildenafil, a single dose not exceeding 25 mg in 48 hours; vardenafil, a single dose not exceeding 2.5 mg in 72 hours; tadalafil, a single dose not exceeding 10 mg in 72 hours; increase monitoring for PDE-5 associated adverse events. *Dosage for pulmonary arterial hypertension (PAH):* tadalafil: stop tadalafil at least 24 hours prior to initiating STRIBILD; start or resume at 20 mg once daily in patients receiving STRIBILD for at least 1 week and increase to 40 mg once daily based on individual tolerability.
- Sedative/hypnotics: Benzodiazepines. Parenteral midazolam: coadministration should be done in a setting ensuring close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation; dose reduction should be considered, especially if more than a single dose is administered. Other sedative/hypnotics: dose reduction may be necessary and clinical monitoring recommended.

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

USE IN SPECIFIC POPULATIONS:
Pregnancy: STRIBILD is Pregnancy Category B; however, there are no adequate and well-controlled studies in pregnant women. STRIBILD 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 STRIBILD, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

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

Pediatric Use: Safety and effectiveness in children less than 18 years of age have not been established.

Geriatric Use: Clinical studies of STRIBILD did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Renal Impairment: STRIBILD should not be initiated in patients with CrCl below 70 mL/min. STRIBILD should be discontinued if CrCl declines below 50 mL/min during treatment with STRIBILD. *[See Warnings and Precautions, Adverse Reactions].*

Hepatic Impairment: No dose adjustment is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. STRIBILD is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C) as no pharmacokinetic or safety data are available in these patients *[See Dosage and Administration].*

OVERDOSAGE:
If overdose occurs the patient must be monitored for evidence of toxicity. Treatment consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

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DEPARTMENTS

The AMERICAN ACADEMY of HIV MEDICINE

HIV SPECIALIST

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

VOLUME 5 / NUMBER 3 • FALL 2013

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

October 1, 2013

OCTOBER has finally arrived and with it the beginning of enrollment for state insurance exchanges created through the Affordable Care Act (ACA). Yes, there are other important dates in this new healthcare policy shift—January 1, 2014—and others down the road. Yet this time is certainly as historic as the implementation of Social Security in the 1930's and Medicare in the 1960's.

The ACA does not solve all of our healthcare needs, as some would hope; and it does not usher in the end of the world, as others predict. However it does bring the United States closer to our Constitutional goal of Life, Liberty and the Pursuit of Happiness for all Americans.

James M. Friedman

The coming few years of ACA implementation may not be easy for many of us. There certainly will probably be bumps in the road. Some provisions already have been delayed. Others may need to be adjusted. Almost certainly some patients will fall through the cracks, and others may end up paying more for their health insurance.

For healthcare practitioners in the short term, ACA will add complexity to an already complex practice landscape. For HIV patients in particular, a smooth transition is imperative to keep HIV patients in care and on their medications. It is in the "cascade" of HIV care in America that we **already** see the greatest drop off in continuity.

As many of you know, in early September, the Academy announced the development of a new online tool to help HIV practitioners through the transition process, the Health Reform Resource Center. Housed on the AAHIVM website (www.aahivm.org), the Resource Center for HIV Providers, assists practitioners in learning about the specific developments in the health care systems in their state, including the State Insurance Exchanges (Marketplaces), any Medicaid Managed Care plans offered in the state, and their state's decisions on the Medicaid Expansion Option.

The resource also offers specific directions on steps providers can take to connect their practice to those systems in order to retain access to patients. The content will be continuously updated to reflect new information, especially in regards to the Marketplaces.

In addition, we are working with the Center for Health Law and Policy Innovation at Harvard School of Law to disseminate a tool that they are developing that will help HIV providers and their patients make better and informed decisions on which Exchange plans are best for them.

As you know earlier this year the U.S. Preventive Services Task Force gave HIV routine testing an "A" grade for individuals 15 to 65. That means testing will be covered by the Health Insurance Exchanges..

What you may not know is that many healthcare service programs funded by the U.S. Public Health Service do not require routine testing for HIV. This includes the Community Health Centers program that serves approximately 20 million poor and underserved Americans—many of whom are at high risk for HIV. For the 20 percent of Americans who are infected but don't know it, CHCs and every other healthcare service program funded by the PHS (SAMHSA, IHS) should be required to conduct routine testing. NOW.

Yes, as Annie sang to us, "The Sun Will Come Out Tomorrow." And the "Tomorrows" of transition will not be easy. But in the end we will be a better healthcare system and a better nation. HIV

IN THE NEWS

AAHIVM Marks National HIV & Aging Awareness Day by Announcing Major Grant from Archstone Foundation

The American Academy of HIV Medicine was recently awarded a substantial grant from the Archstone Foundation to further its work in the area of HIV and aging. The grant will allow AAHIVM to begin the second phase of the organization's *HIV & Aging Consensus Project*, which will consist of the implementation of an interactive web-based project to seek out and document the experiences of HIV care providers treating elderly Americans with HIV disease.

"We are very appreciative of this grant from the Archstone Foundation," said James M. Friedman, AAHIVM executive director. "It is essential that we build a virtual community for our HIV care providers in order for them to share best practices for managing the care of older HIV patients."

The key objectives of the HIV & Aging Consensus Project are to assess how the presence of both HIV and common age-associated diseases alter the optimal treatment of HIV, as well as treatment for co-morbidities. As part of the project, AAHIVM published a document, "***Recommended Treatment Strategies for Clinicians Managing Older Patients with HIV***," in November 2011. An excerpt of this report was included in the Congressional record and recently quoted in a briefing to the US Senate Special Committee on Aging on Capitol Hill.

The report guides HIV practitioners and other medical professionals who treat older patients with HIV disease on best practices for diagnosing, treating, and referring older adults with HIV. The full document can be found on the AAHIVM website at www.aahivm.org/hivandagingforum

HIV

NYU Researchers Discover HIV-1 Replication Pathway

A team of researchers led by Dr. David N. Levy, associate professor of Basic Science and Craniofacial Biology at the New York University College of Dentistry (NYUCD), has discovered a new way that HIV-1 reproduces itself, which could advance the search for new ways to combat infection.

For decades, scientists have been confident that HIV-1 must insert its genetic material into a cell's DNA in order to reproduce. Dr. Levy's National Institutes of Health (NIH) funded research, "HIV-1 replication without integration," published online in the *Journal of Virology*, with lead author Dr. Benjamin Trinité, a post-doctoral fellow in Dr. Levy's laboratory, has shown HIV-1 can sometimes skip this integration step entirely.

"Although this is not the virus' main method for replicating, having this option available can help HIV survive," said Dr. Levy. "These new findings suggest one mechanism by which HIV may be surviving in the face of antiviral drugs, and suggests new avenues for research into eliminating infection."

The integration step is highly inefficient and actually fails up to 99 percent of the time, leaving most viruses stranded outside of the safe harbor of cell's DNA. It has been assumed that these stranded, or "unintegrated" viruses were unable to reproduce, but Dr. Levy's team found that if conditions are right they can generate new viruses that infect new cells.

The team also found that the unintegrated viruses can survive for many weeks in cells, allowing HIV to "hide out" in a dormant state.

"There is intense interest by researchers in the idea that new drugs might be developed to help to completely eliminate the virus from infected individuals," said Dr. Levy. "We think that the new replication mechanism we have found could provide a target for drugs designed to eliminate infection."

Dr Levy notes an interesting phenomenon, which other researchers have observed, is that some bacteria which live in the mouth can stimulate HIV-1 to emerge from its dormant state.

"NYUCD has some terrific groups of researchers who are expert in oral flora and HIV, so we'll be quite interested in working with them to find out how oral health might influence the new replication pathway my group has discovered," added Dr. Levy.

The study was supported by grants from NIH/NIAID: R01AI078783 (DNL) and R01AI093998 (DNL and DW). The study can be found on the Journal of Virology website at http://jvi.asm.org

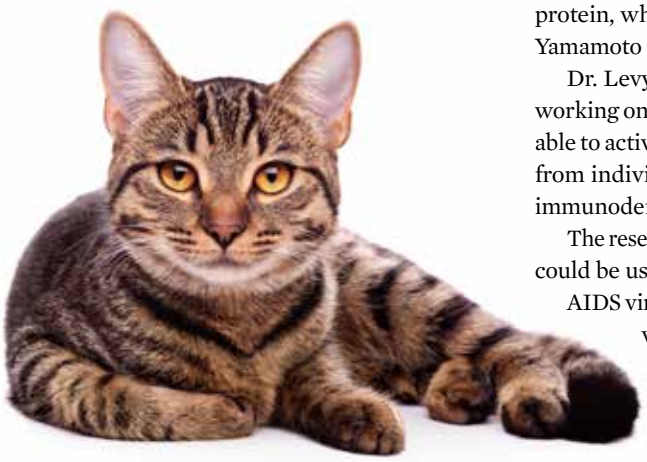
HIV

ISTOCKPHOTO

New Study: Cats May Hold Secret to HIV Vaccine

Researchers have discovered that blood from patients infected with HIV shows an immune response against a feline AIDS virus protein, a discovery they say may hold the key to an HIV vaccine.

The discovery was made in a study by Jay A. Levy, MD, professor of medicine at the University of California, San Francisco, study author, and Janet Yamamoto, Ph.D, professor of retroviral immunology at the College of Veterinary Medicine at the University of Florida.



"Since FIV (feline immunodeficiency virus) and HIV-1 are distant cousins and their sequences are similar, we used the T cells from HIV positive human subjects to see if they can react and induce anti-HIV activity to small regions of FIV protein, which lead to the current story," Dr. Yamamoto told *Medical News Today*.

Dr. Levy and Dr. Yamamoto said they are working on a T cell-based HIV vaccine that is able to activate an immune response in T cells from individuals against the feline acquired immunodeficiency syndrome (AIDS) virus.

The researchers believe the feline AIDS virus could be used to discover areas of the human AIDS virus, which could lead to a new HIV vaccine-development strategy.

"We had difficulty in identifying ways to select regions on HIV-1 for HIV-1 vaccine," reported Prof. Yamamoto. "Our work shows how to select the viral regions for HIV-1 vaccine. The regions on FIV or their counterpart on HIV-1 that have anti-HIV T cell activities can be used as a component for human HIV-1 vaccine."

Comparing the reactions of the FIV peptides with the reactions of HIV peptides, the researchers discovered one peptide region on FIV that triggered patients' T-cells to kill HIV. They found that the feline viral region by human cells seeks to be "evolutionarily conserved," meaning that it is present in many viruses across animal species. They said this feline viral region must be crucial as it is unable to mutate in order for the virus to survive.

Dr. Levy stressed that their findings do not mean that the feline AIDS virus infects humans. "Rather, the cat virus resembles the human virus sufficiently so that this cross-reaction can be observed."

The team's findings are published in the *Journal of Virology*. HIV

Key to HIV Long-Term Immunity Identified in Study

Scientists from Northwestern Medicine in Chicago have discovered a new clue about why some patients can control the HIV virus long term without taking antiviral drugs. They say the finding may be useful in shortening drug treatment for other HIV patients.

About 1 percent of people with HIV do not require medication because they have a more abundant supply of the immune protein APOBEC3G (A3) in resting memory T cells, which scientists say represents a second line of defense in the immune system.

"Preserving and even increasing this defense in cells may make more HIV-infected persons into controllers and prevent HIV from rebounding to high and damaging levels when anti-HIV medications are stopped," said Richard D'Aquila, M.D., the director of the Northwestern HIV Translational Research Center. He is the senior author of the study, published Oct. 16 in the journal PLOS ONE.

Dr. D'Aquila also is the Howard Taylor Ricketts Professor of Medicine at Northwestern University Feinberg School of Medicine and a physician at Northwestern Memorial Hospital. He and colleagues now are working to develop a medicine that would boost the A3 protein.

A3 is a critical part of the newly characterized intrinsic immune system, and it resides in many cells of the immune system including resting T cells. Unlike the adaptive immune system, which fails to recognize the virus once it mutates its pieces, the intrinsic immune "recognizes the basic guts of the virus—the nucleic acids—that HIV can't change and then damages those nucleic acids," Dr. D'Aquila said. He theorizes that the controllers' first line of defense slows down the ability of HIV to destroy all the A3.

"Perhaps starting anti-HIV drugs very soon after HIV is caught, rather than the current practice of waiting until later to start, would work like the controllers' first line of defense," D'Aquila suggested. "If we preserve A3, it could minimize HIV's spread through the body as this protein seems to do in controllers."

Otherwise, D'Aquila theorizes, all reserves of the protein are wiped out if HIV replicates unchecked for several months.

"Early-as-possible detection—much easier with our new technology—and early drug treatment will be the future of HIV therapy," D'Aquila said. He added that the Affordable Care Act mandates that insurance companies pay for routine HIV testing, which they did not always cover in the past.

The study was done in collaboration with MariaPia De Pasquale and Yordanka Kourteva, formerly at Vanderbilt University School of Medicine, where D'Aquila did the experiments. HIV

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Intestinal Bacteria May Worsen HIV Disease

A new study of HIV infection by UC San Francisco researchers points to changes in intestinal bacteria as a possible explanation for why successfully treated HIV patients nonetheless prematurely experience life-shortening chronic diseases.

These changes in gut bacteria may perpetuate inflammation initially triggered by the body's immune response to HIV, according to the study, reported online in the journal *Science Translational Medicine*.

In recent years, such persistent inflammation has been proposed as a cause of the early onset of common chronic diseases found in HIV patients who now can live for decades without immune system destruction and death due to infection thanks to lifelong treatment with antiretroviral drugs. Likewise, in the general population, ongoing inflammation has been linked in some studies to chronic conditions such as heart disease, dementia and obesity.

Studies have shown that inflammation is induced by HIV in both treated and untreated patients, and is associated with — and possibly causes — disease in both, according to Joseph M. McCune, MD, PhD, chief of the Division of Experimental Medicine at UCSF and a senior author of the study. McCune has been investigating the causes of chronic inflammation in HIV-infected patients and has treated patients with HIV for more than three decades.

"We want to understand what allows the virus to persist in patients who have HIV disease, even after treatment," he said. "In this study, we see that bacteria in the gut may play a role."

The study was initiated by Ivan Vujkovic-Cvijin, a graduate student working in McCune's lab in collaboration with Susan Lynch, PhD, an associate professor in the Division of Gastroenterology at UCSF and an expert on the human microbiome, the collection of microbes that live in and on the human body. Researchers estimate that humans have about ten times as many bacterial cells as human cells, and earlier studies have demonstrated that some of the microbes found within the intestines are able to drive immune responses, Lynch said.

"We thought the gut microbiome might be different in HIV-infected individuals, and that the high degree of immune activation in the patients might be associated with and possibly due to the presence of specific members of the bacterial community," Lynch said. Vujkovic-Cvijin identified bacterial species in biopsied patient samples by tracking a gene that is distinct among different bacterial species. Working with co-first author, Richard Dunham, PhD, a UCSF postdoctoral fellow, he also tracked markers of inflammation in the blood.

The researchers compared seven untreated HIV patients, including six with active infection and one long-term patient who never developed AIDS; 18 HIV patients in whom ongoing drug treatment had reduced HIV in the blood to undetectable levels; and nine uninfected individuals matched for other health risks. The patients are part of a group being monitored through ongoing UCSF research led by UCSF StevenDeeks, MD, and Jeffrey Martin, MD, MPH, at San Francisco General Hospital and Trauma Center.

"We found that HIV-infected people have a very different gut microbiome than people who are uninfected," Vujkovic-Cvijin said. "In particular, infected people harbor more bacteria that can cause harmful inflammation, like *Pseudomonas, Salmonella, E. coli, and Staphylococcus."*

The degree to which normal bacterial communities in the colon were disrupted corresponded to the levels of an inflammatory molecule, IL-6, in the blood, and also to the production of an enzyme calledindoleamine 2,3-dioxygenase. The enzyme can impair the gut's ability to function as a barrier, thereby allowing bacteria and molecules produced by bacteria to enter the body to fuel even more inflammation. Species of bacteria that can mimic the action of this enzyme also were more abundant in HIV-infected participants, Vujkovic-Cvijin found.

The researchers do not believe there is a single bacterial species responsible for disrupting the integrity of the gut nor do they propose a specific probiotic bacterial treatment to restore a healthy gut. Nonetheless, Lynch said, manipulating microbial populations is a promising idea.

"It appears that changes in the microbiome perpetuate a vicious cycle that drives inflammation in HIV-infected patients," she said. "We are considering a restoration ecology approach to restore appropriate microbial colonization patterns and healthy functioning of the gut microbiome."

McCune believes that inflammation may also play a role in maintaining the persistence of HIV, even in those with no circulating virus in the bloodstream. "Our dream is to be able to make the virus go away, allowing HIV-infected people to lead longer lives without the need for life-long therapy," he said. "Perhaps restoring the microbiome to normal will be one strategy to make that happen."

The research was funded by the National Institutes of Health, the National Science Foundation, UCSF, and the Harvey V. Berneking Living Trust. To learn more, visit http://www.ucsf.edu/news. **HIV**

THINKSTOCK

BY BOB GATTY

Focus on Clinical, Research Developments

THIS ISSUE OF *HIV SPECIALIST* is largely devoted to bringing you the latest information available regarding important research and clinical developments in HIV. We hope you find it informative and helpful.

Our cover story by AAHIVM deputy executive director Bruce Packett details a new paper on **viral load diagnostics**, now available on the AAHIVM website, www.aahivm.org, which explores clinical dilemmas commonly encountered when using available assays.

The current understanding of viral dynamics, technical aspects of pVL assays, as well as the risk factors, clinical significance, and management of patients experiencing low-level viremia (LLV) and very low-level viremia (VLLV) provide insights that are useful in routine patient care, the report says.

Complimenting that article is an analysis, "**Behind the Limit of Detection**," by Olivier Peraud, Ph.D., and Johnnie Lee, MD, MPH, FACP, of Roche Diagnostics, which discusses key components of molecular viral load testing and recommended strategies to be employed.

"As HIV evolves and mutates, it is essential to stay one step ahead in both therapeutic regimens and viral load monitoring," the authors write, adding that "In viral load monitoring, the ability to detect low levels of HIV-1 remains paramount, as there is growing evidence of its clinical utility and connection to outcomes."

The authors add, "It is an exciting time for the HIV field as cures have been reported, new drugs are being developed and novel technology delivers more robust and sensitive viral load assays. Clinicians are now better equipped to make the therapeutic decisions that will most benefit their patients."

Turning to "Managing Occupational Exposure to HIV," Jeffrey T. Kirchner, DO, FAAFP, AAHIVS, details recently updated recommendations for the management of healthcare personnel who experience exposure to blood or other body fluids that may contain human immunodeficiency virus (HIV).

"It is an exciting time for the HIV field as cures have been reported, new drugs are being developed and novel technology delivers more robust and sensitive viral load assays."

The new guidelines have simplified the approach to post-exposure prophylaxis (PEP) and recommend medication regimens that contain three antiretroviral drugs, Dr. Kirchner writes, adding that a "hierarchy" of specific drugs was selected based on safety, tolerability, toxicity, frequency of dosing and pill burden.

Dr. Kirchner chairs the *HIV Specialist* Editorial Advisory Group.

In our "At the Forefront" column, James M. Sosman, MD, FACP, AAHIVS details "**Emerging Sexually Transmitted Infection Superbugs Impacting HIV Care.**"

Dr. Sosman notes a spike in all sexually transmitted infections (STIs) within the HIV-infected population, particularly among men who have sex with men (MSM). "Most worrisome," he says, "has been the parallel increase in resistance of *Neisseria gonorrhoeae* and *Treponema pallidum* to antibiotics.

HIV clinicians can help prevent the transmission of resistant gonorrhea and syphilis by regularly screening sexually active HIV patients for STIs, he adds, providing prevention messages, implementing routine risk-reduction counseling, providing prompt and effective antibiotic treatment and initiating earlier antiretroviral therapy (ART).

Novel approaches to immunotherapy are needed, write Irina Y. Tcherepanova, Ph.D and Charles A. Nicolette, Ph.D, noting that residual virus persists in latently infected cells, and that after cessation of ART, virus replication invariably reinitiates from those reservoirs.

"Therapeutic vaccines designed to augment antiviral immunity in patients already infected are a promising adjunct to currently available treatments," they suggest.

However, the authors add that the development of successful immunotherapies for HIV faces many challenges. "Particularly confounding is the abnormal immune functionality of HIV-infected individuals where naturally occurring productive cell mediated anti-HIV responses decrease during progression of HIV infection."

The authors discuss the outlook for progress as research continues.

The "Best Practices" column is authored by D. Trew Deckard, PA-C, MHS, AAHIVS, who discusses "**Prevention with Positives**"—the increased incorporation by HIV providers of prevention into the clinical care of their patients with the goal of reducing the risk of transmission of the virus.

Deckard outlines the most recent U.S. Department of Health and Human Services guidelines for the use of ART in HIV-infected adults and adolescents, which recommend prevention as a key component of patient management. He also discusses the importance of clear communication with patients and working with other care providers "to offer patients a more holistic approach and ensure the best outcome."

Finally, our clinical "package" includes a discussion by Julie Stoltey, MD, MPH and Rachel McLean, MPH, of the US. Preventive Services Task Force recommendation that one-time, universal HCV screening be implemented for all individuals born during 1945-1965.

In "**Screen All Baby Boomers for Hepatitis C**," the authors say the recommendations have important clinical and public health implications, including the potential to increase the proportion of persons with HCV who are aware of their infection and may be linked to care.HIV

Viral Load DIAGNOSTICS

IN THE FEBRUARY 2011 ISSUE OF *HIV SPECIALIST*, I reported on an AAHIVM member survey that was conducted on the topic of viral load diagnostics, generally, and the patient management implications of the newer real-time PCR assays (with much lower level detection), specifically.

What we found was that the phenomenon of "viral blips" with the more sensitive assays was worrying to both patients and providers, and causing some confusion about when to order expensive follow-up labs and when to consider the possibility of virologic failure and ARV resistance.

While many more providers are now likely familiar with the most recent U.S. Department of Health and Human Services guidelines on the threshold for virologic failure, there is still a need for specific clinical information on how to interpret viral diagnostic labs and how best to manage patients with low-level viremia (50 copies to 400 copies) and very low-level viremia (20 copies to 50 copies).

A Guide for HIV Care Providers

Paraphrasing the final quote in that 2011 article from Dr. Jeffrey Kircher, *HIV Specialist* Editorial Advisory Board chair, we suggested that HIV provider groups like the Academy should be responding to the need demonstrated by this survey study by offering provider education on the management of viral blips and low-level viremia. With support from some of the biggest manufacturers of the newer real-time assays, AAHIVM followed up by sponsoring a research "white paper" on the topic of viral load diagnostics and viral blip management, which we are pleased to present in this issue of *HIV Specialist*.

The lead author on this paper is the noted HIV expert, Dr. Babafemi Taiwo, associate professor of medicine in the Division of Infectious Diseases of the Feinberg School of Medicine at Northwestern University. Dr. Taiwo and Dr. Patrick Ryscavage, assistant professor of medicine at the University of Maryland, closely tackle the clinical issues around persistent low-level viremia, viral blips, viral dynamics following therapy initiation, resistance, virologic failure, immunological trends, the latest data on viral load testing technologies and more. We hope that this short, easy-reference resource helps fill a clinical need in the delivery of quality HIV care.

The executive summary of the study follows. The complete report can be accessed at www.aahivm.org/viralload.

–Bruce Packett, Deputy Executive Director, AAHIVM

Executive Summary

I. Introduction

The goal of combination antiretroviral therapy (cART) is to suppress HIV replication so that viral evolution and resistance are prevented, immunologic function and clinical health are restored, and HIV transmission is curtailed. Plasma HIV concentration, commonly termed plasma viral load (pVL), has been shown to be a reliable marker of clinical disease progression and treatment response. "Suppression" of pVL has emerged as the primary determinant of treatment success.[1,2] The target pVL during suppression has changed through the years, largely in parallel with the development of pVL assays with progressively lower limits of HIV RNA detection. For many years, the commonly used pVL assays had a lower limit of detection of 50 copies per milliliter (cpm). Suppression below 50 cpm was then validated in many studies as associated with cessation of new HIV resistance, immunologic restoration, durable virologic response, and a marked reduction in HIV transmission.[2–4] Based on these findings, pVL suppression, below 50 cpm, was recommended as the goal of cART.[5,6] More recently, real time HIV PCR assays with limits of HIV RNA detection below 50 cpm (i.e, 48, 40 and 20 cpm) have become widely adopted.

Two clinical dilemmas are commonly encountered when using available assays. First is how to interpret and manage very low-level viremia (VLLV) of 20 to 50 cpm detected with the new real time HIV PCR assays. Second is how to interpret and manage low-level viremia (LLV) of approximately 50 cpm to 400 or 500 cpm. The current understanding of viral dynamics, technical aspects of pVL assays, as well as the risk factors, clinical significance, and management of patients experiencing LLV and VLLV provide some insights that are useful in routine patient care.

Real-time PCR pVL assays have begun to replace the existing end point PCR platforms, providing a fully automated, high throughput alternative to traditional assays, with enhanced assay performance.

II. What happens to HIV plasma viral load when a patient is started on cART?

Following cART initiation, HIV-1 decays in a predictable fashion through at least three phases, reflecting the different half-lives of HIV-1 infected cell types.[7,8] Among adherent patients on long term cART, the majority will achieve viral suppression to less than 50 cpm by 12-24 weeks of therapy.[9] Viral decay continues beyond this until, after months to years, most reach a plateau of 1–10 cpm.[9–13] The source of this stable residual viremia is a topic of debate. The prevailing opinions are that residual viremia reflects either stable, periodic release of HIV virus from latently infected cells, and/or ongoing viral replication.[14] There is consensus that HIV cannot be cured by cART because all efforts to eradicate residual viremia by intensifying cART have failed.

III. How is HIV viral load measured?

The three nucleic acid-based molecular diagnostic methods for quantifying HIV RNA include reverse transcriptase polymerase chain reaction (RT-PCR), nucleic acid sequence-based amplification (NASBA), and branch copy DNA (b-DNA) (Table 1). Most contemporary assays utilize RT-PCR technology. Enhancements to standard RT PCR technology led to ultrasensitive end point PCR assays with a lower limit of detection of approximately 50 cpm. These assays were widely adopted in research and clinical practice. More recently, real-time PCR pVL assays have begun to replace the existing end point PCR platforms, providing a fully automated, high throughput alternative to traditional assays, with enhanced assay performance.[15] These assays detect RNA target with detection limits of 20–48 cpm and can qualitatively detect HIV RNA below these limits of quantification.

IV. What clinical issues have arisen in the era of real time HIV PCR testing?

The increased sensitivity of real time pVL assays has led to higher inter-and intra-assay variability around lower quantification limits.[16] In particular, real time HIV PCR assays appear to report detectable LLV at a higher frequency than traditional end point HIV PCR assays.[17–22] LLV used to be defined as a pVL of 50–1000 cpm but many recent studies are restricting the definition to 50–400 cpm or 50–500 cpm. LLV can be further stratified by its temporal pattern, such that transient LLV preceded and followed by a pVL <50 cpm, is termed a viral blip, and ≥2 consecutive LLV episodes is termed persistent LLV. The clinical significance and management of LLV has gained increasing attention over the last decade, but this focus has intensified in the era of real time HIV PCR testing. Finally, the ability to routinely detect HIV RNA below 50 cpm now challenges clinicians and researchers to interpret the significance of these findings.

V. Management Considerations

A. Viral Blips

i. Incidence and Risk Factors

Viral blips can be expected in up to approximately one-third of cART recipients, depending on factors such as the cART regimen and length of observation.[23–35] The magnitude of viremia during viral blips is often <200 cpm but may be much higher.[25,31,33,36,37] Risk factors (Table 2) may include advanced HIV disease stage prior to cART, poor adherence, and use of less potent ARV combinations (see "VLLV risk factors" below).

ii. Clinical significance

The significance of viral blips can be approached according to viremia magnitude (Table 3). Low level (<400 cpm) viral blips do not appear to increase risk for HIV resistance, virologic failure, or immunologic deterioration. High level (>400 cpm) viral blips, however, have been associated with increased likelihood of new drug resistance, virologic failure, and, possibly, decline in CD4 T cell trajectory in some patients, though it is not proven that these events are actually caused by the blip. The 400 cpm cut-off should be regarded as a guide as there are exceptions to

Table 1: Commercially available nucleic acid-based testing assays

Assay	Roche COBAS Amplicor HIV-1 Monitor v1.5[1]	bioMérieux NucliSENSE EasyQ HIV-1 v2.0	Siemens Versant HIV-1 v3.0	Abbott RealTime HIV-1 Assay	COBAS Ampliprep/ COBAS TaqMan HIV-1 Test, v2.0.	Siemens VERSANT HIV-1 RNA 1.0 (kPCR)
Year FDA Approved	1999	2001	2002	2007	2010	Not approved in U.S.[2]
Linear Range	Standard: 400->750[5] cpm Ultrasensitive: 50->100[5] cpm	10-10[6]	50-500,000 cpm	40-10[6] cpm	20-10[6] cpm	37-11[6] cpm
Target Region	*gag* gene	*gag* gene	*pol* gene	*pol* gene (integrase region)	g*ag* gene and LTR regions of the HIV-1 genome	*pol* gene lintegrase region)
HIV-1 Subgroup Detection	Group M subtypes A–H	NABSA	Group M	Group M, subtypes A–H, Group O and Group N	Group M, subtypes A–H, Group O	Group M, O
Time to Result	8 hours	3 hours	25 hours	4 hours	5.5 hours	6.5-7 hours
Nucleic acid testing approach	End point RT PCR	NASBA	bDNA	Realtime RT PCR	Realtime RT PCR	Realtime RT PCR

Abbreviations: cpm: copies/mL; NASBA: nucleic acid sequence-based amplification; bDNA: branched chain DNA; RT PCR: reverse transcriptase polymerase chain reaction

[1] This product will no longer be on the market in the U.S. after March 2014.

[2] Approved for use in Europe

this general rule. Limited studies suggest absence of a strong association between viral blips and chronic inflammation/immune activation.[23,38,39] The effect of viral blips on morbidity/mortality and HIV transmission has not been studied.

iii. Management

Viremia >50 cpm should prompt an adherence assessment and repeat testing should be performed at an interval based on the magnitude as well as patient risk factors, including time on current cART >12 months, a history of ARV resistance, and lower potency cART regimens (Figure 1). Low magnitude (<200 cpm) viremia is unlikely to be of clinical significance unless other risk factors are present (as above), whereas high magnitude viral blips should trigger a more urgent adherence assessment and prompt repeat pVL testing (such as within 3–6 weeks). Repeat pVL testing should always be performed using the same assay if possible. There is no clear benefit to empiric cART change and/or intensification following a viral blip. It is prudent to avoid routine pV testing within a few days of vaccination or during an acute illness since these have been associated with occurrence of blips in some, though not all, studies.

B. Persistent low level viremia

i. Incidence and risk factors

Approximately 4-8% of the HIV population receiving cART experience persistent LLV.[24–27] The magnitude of viremia among those with persistent LLV is typically low (median 113–267 cpm in some studies).[23,25,37,40] Potential risk factors largely overlap with those associated with viral blips (Table 2).

ii. Clinical significance

There are several well-documented adverse clinical outcomes associated with persistent LLV (Table 3). These include the development of antiretroviral resistance,[23,37,40–46] increased risk of virologic failure,[23–25,47,48] and increased markers of immune activation.[23,49] The effect of persistent LLV on CD4 T cell trajectory, morbidity and mortality, and HIV transmission remain largely understudied. There is biologically plausibility for increased HIV transmission among those with persistent LLV compared to those with consistent pVL suppression.[50]

iii. Management

Intensive adherence counseling is essential for all patients with persistent LLV. The management of persistent LLV of 400-1000 cpm should be genotype-guided, as at least two commercial laboratories in the U.S. will accept samples for genotypic analysis in this pVL range.[51,52] If genotyping is successful and resistance is detected, a new regimen should be constructed with at least two, and ideally three, active ARVs. Patients with no evidence of resistance should continue their regimen and intensify adherence. Among those with persistent LLV of 50–400 cpm, an attempt should be made to obtain genotypic analysis, as many centers can perform in-house assays (not FDA approved). Reported success rates are as high as 75% for pVL 50–249 cpm, and ~90% for pVL 250–499 cpm.[43] Although this has not been evaluated in prospective trials, some experts recommend empirically modifying the regimen if resistance information is not available and the pVL remains ≥200 cpm despite intensified adherence. Other factors that may further support empiric treatment modification include a relatively high

Table 2: Identified risk factors for low level viremia and viremia < 50 cpm

Study	N	Frequency	Duration of follow up (months)	LLV and viremia < 50 definition (cpm)	Risk Factors
VIRAL BLIPS					
Havlir 2001	101	29%	54	>50	• Higher pre-cART HIV RNA
Sungkanuparph 2006	382	34%	24	50-1000	• Higher pre-cART CD4+ T cell count < 200 cells/mm3
Mira 2002	330	11%	11	51-1000	None
Sklar 2002	448	27%	16	>50	• Health payer status (non-private insurance)
Martinez 2005	43	19%	18	>50	• Higher baseline level of residual viremia (7.5 vs 3 cpm)
Grennan 2012	3550	21%	32	50-999	• Boosted PI (vs. NNRTI) -based cART • Higher pre-cART HIV RNA (>105 cpm)
Posadecki 2007	223	27%	22	50-1000	• cART adherence
Raboud 2002	165	21%	NA	>50	• cART adherence
Geretti 2008	1386	19%	26	50-400	• Boosted PI (vs. NNRTI) -based cART
Easterbrook 2002	767	16%	28	>400	• Younger age • Male
Greub 2002	2055	24%	22	51-500	• Mono- or dual- ARV therapy before cART
Masquelier 2005	219	9%	18	>500	NA
Garcia-Gasco	2720	29%	96	51-500	None
PERSISTENT LLV					
Raboud 2002	165	30%	NA	>50	NA
Greub 2002	2055	8%	18	51-500	NA
Karlsson 2004	46	39%	27	50-1000	• Lower pre-cART CD4+ T cell count
Geretti 2008	1386	6%	26	50-400	• Boosted PI (vs. NNRTI) -based cART
Sungkanuparph 2006	362	28%	30	51-1000	None
Taiwo 2011	1158	6%	NA	51-1000	• Boosted PI (vs. NNRTI) -based cART • Higher pre-cART HIV RNA (>106) • Lower pre-cART CD4+ T cell count
VIREMIA BELOW 50cpm					
Doyle 2012	1247	60%	12	<40 RNA detected or 40-49	• Duration of viral suppression • Higher pre-cART HIV RNA • Lower pre-cART CD4+ T cell count • Younger age • Boosted PI (vs. NNRTI) -based cART • cART adherence
Maggiolo 2012	1214	29%	12	3-50	• Boosted PI (vs. NNRTI) -based cART • Duration of viral suppression <50 cpm • Higher pre-cART HIV RNA
Widdrington 2011	139	50%	36	<40, RNA detected	• Non-NNRTI-based cART
Henrich 2012	778	23%	22	<48, RNA detected	None
Alvarez 2013	290	54%	12	20-29 or 30-39	• Duration of viral suppression <50 cpm
Havlir 2005	100	61%	17	2.5-50	• Higher proviral HIV DNA in PBMC • Higher pre-cART HIV RNA • Stavudine (vs. tenofovir) therapy
Gianotti 2012	739	40%	11	1-49	• Higher blip ratio prior to T_0 • Male gender • Non-NNRTI-based cART
Charpentier 2012	656	6%	NA	20-50 (≥ 2 measurements)	• Pre-cART CDC stage • Higher blip ratio prior to T_0

Abbreviations: cpm: copies/mL; cART; combination antiretroviral therapy; PI: protease-inhibitor; ARV: antiretroviral; NNRTI: non-nucleoside reverse transcriptase inhibitor; PBMC: peripheral blood mononuclear cells

Table 3: Summary of literature regarding clinical consequences of low level viremia and viremia < 50 cpm

LLV Category		HIV Resistance2 (Baseline Available)	Virologic Failure/Rebound	Immunologic Change
Viral Blips	Low Magnitude (<400 cpm1)	**NO** **SUPPORTING STUDIES:** Havlir 2001; Nettles 2005; Posadecki 2007; Nettles 2005 **CONTRADICTING STUDIES:** Macias	**NO** **SUPPORTING STUDIES:** Sungkanuparph 2005; Mira 2002; Sklar 2002; Nettles 2005; Posadecki 2007; Raboud 2002; Geretti 2008	**NO** **SUPPORTING STUDIES:** Mira; Sklar; Garcia Gasco
	High Magnitude (≥400 cpm1)	**UNKNOWN**	**YES** **SUPPORTING STUDIES:** Sklar 2002; Grennan 2012; Moore 2002; Masquelier; Easterbrook;Greub 2002*; Raboud 2002 **CONTRADICTING STUDIES:** Martinez No	**YES** **SUPPORTING STUDIES:** Easterbrook; Martinez **CONTRADICTING STUDIES:** Masquelier
Persistent LLV	Low Magnitude (<400 cpm1)	**YES** **SUPPORTING STUDIES:** Taiwo 2011; Mackie 2010; Li 2012; Karlsson 2004; Gonzalez 2013	**YES** **SUPPORTING STUDIES:** Geretti; Raboud 2002; Greub 2002; Karlsson 2004	**NO** **SUPPORTING STUDIES:** Taiwo 2011 Lo Re
	High Magnitude (>400 cpm)	**YES** **SUPPORTING STUDIES:** Pellegrino 2012; Mackie; Tobin; Delaugerre; Aleman; Taiwo 2011[3]	**YES** **SUPPORTING STUDIES:** Sungkanuparph 2006	**UNKNOWN** **SUPPORTING STUDIES:** Sklar 2002[4]
Viremia below 50 cpm		**NO**[5]	**UNKNOWN** **SUPPORTING STUDIES:** Doyle, Maggiolo, Henrich, Alvarez **CONTRADICTING STUDIES:** Gianotti, Widdrington, Charpentier	**NO** **SUPPORTING STUDIES:** Widdrington; Charpentier, Havlir 2005 **CONTRADICTING STUDIES:** Gianotti

[1] 400 cpm cut-off is a guide only as there are exceptions to the general trend
[2] Odds ratios (OR) 0.85, 0.75–0.98, per additional 0.5 log cpm
[3] Maximum VL during low-level viremia: 615 vs 150 cpm, p= .001
[4] High magnitude pLLV defined as >400 cpm (no defined upper limit)
[5] Based upon lack of published studies demonstrating DRM evolution when pVL<50 cpm
Abbreviations: LLV: low level viremia; cpm: copies/mL

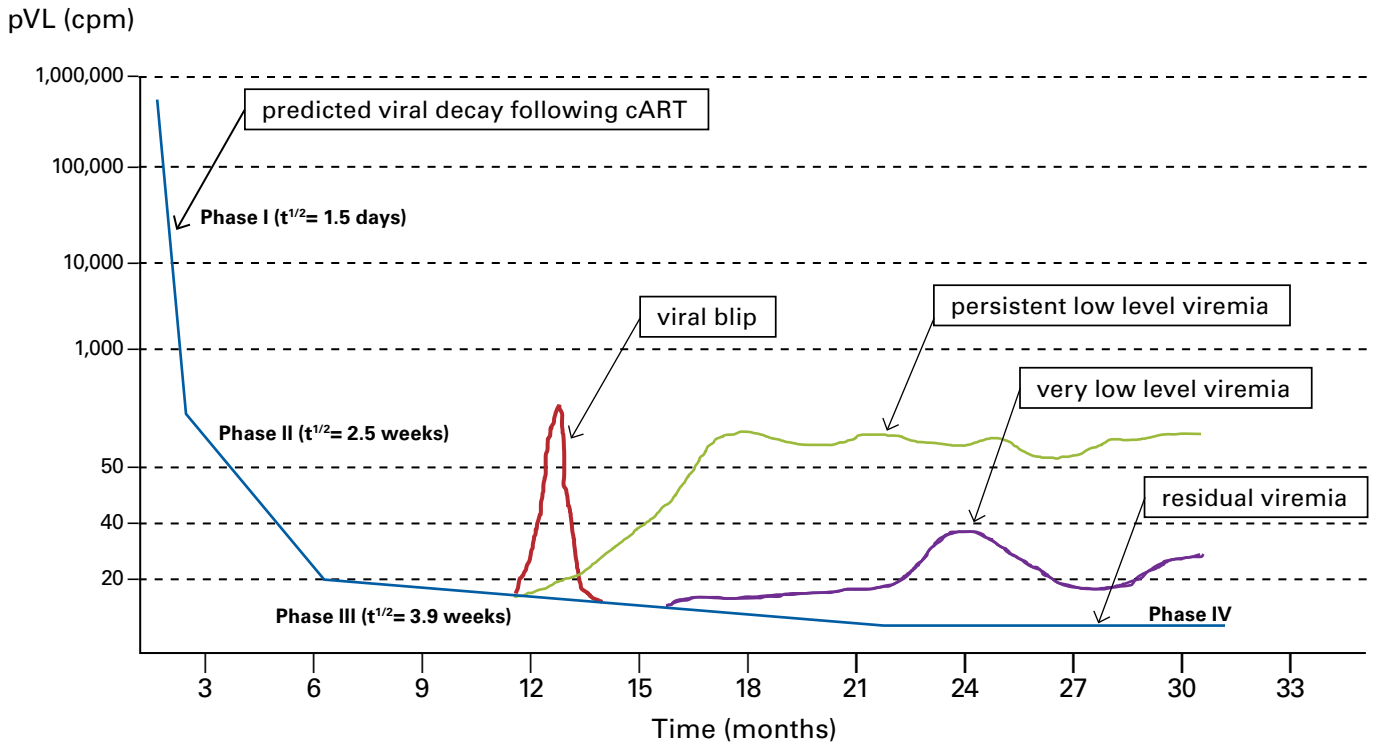
pVL and an upward trajectory in LLV magnitude over time. When modifying the regimen without genotype results, the clinician should consider the patient's treatment history and prior drug resistance. There are new concerns surrounding optimal management of patients with pVL of 50–200 cpm in light of evidence that even this range of viremia may be associated with increased risk of virologic failure later on. The DHHS currently defines virologic failure as persistent pVL >200 cpm, but this may change with time.

C. Very low-level viremia and residual viremia in patients with pVL < 50 cpm

i. Incidence and risk factors

The majority of patients will achieve pVL <50 cpm by the end of six months of effective cART. There are two categories of viremia that may be present in patients with pVL <50 cpm. The first is VLLV of 20–48 cpm, which can be detected with commercially available assays that have detection limits lower than 50 cpm. Sometimes, the assays simply report VLLV as presence of HIV RNA using qualitative methods. The other category is residual viremia of approximately 1–10 cpm (average of around 2–3 cpm) that can only be detected (for now) using even more sensitive research assays. It takes longer than 6 months for most patients to reach this residual viremia plateau.[9,53] The key feature of residual viremia is that it is present in most patients and cannot be eliminated by cART, no matter how intensive the cART is. Risk factors for detectable viremia after suppressing below 50 cpm may include correlates of HIV disease stage prior to cART (including pre-cART HIV RNA, CD4 count), duration of cART, cART adherence, and specific ARVs. In particular, NNRTI, as compared to PI-based cART, has been associated with lower

Figure 1: Patterns of HIV-1 virologic decay following cART initiation[1,2]



rates of this level of viremia, though the mechanism underlying this difference is not well-established.[12,54-56]

ii. Clinical significance

Several studies have examined the risk of virologic rebound among those with evidence of viremia <50 cpm. Many of these studies lumped together patients with VLLV and those with residual viremia, reflecting the lack of consensus definitions (Table 3). Unfortunately, these studies differed in terms of patient population, duration of suppressive cART and follow up, and pVL assay platforms used. The largest of such studies found an increased risk of viral rebound (to levels >50 cpm) among those with evidence of viremia <50 cpm.[13,54,57,58] Further, there may be a linear relationship between the magnitude of viremia <50 cpm and risk of viral rebound13, although three smaller studies found no association of presence of viremia <50 cpm with virologic rebound.[12,56,59] Despite limitations due to discrepancies in study design, patient population and results in some cases, the accrued literature suggests an increased risk of virologic rebound to levels >50 cpm in patients with evidence of viremia <50 cpm using newer assays compared with those who have no evidence of viremia whatsoever with these more sensitive assays. It is uncertain how much of this risk is driven by cART adherence and duration. Re-suppression sometimes occurs without a change in treatment.[57] There has been no documented evolution of viral resistance when pVL is suppressed below 50 cpm and no consistent evidence of an increase in markers of immune activation and/or inflammation.[49,60–63]

iii. Management

Given known patterns of viral decay following cART initiation, presence of VLLV should not cause concern in the first 12 months on cART. Such patients can continue to have routine pVL monitoring (e.g. every 12–24 weeks). Some experts advocate that patients with VLLV while on stable, long term (e.g. >12 months) should have an ARV adherence assessment performed and addressed, and perhaps be observed at closer intervals with repeat pVL testing using the same HIV PCR assay. This is not a consensus view, as other experts consider it unnecessary to implement any changes in patients who have any degree of viremia under 50 cpm. At present, there is insufficient evidence to support cART change or treatment intensification in patients with VLLV. HIV

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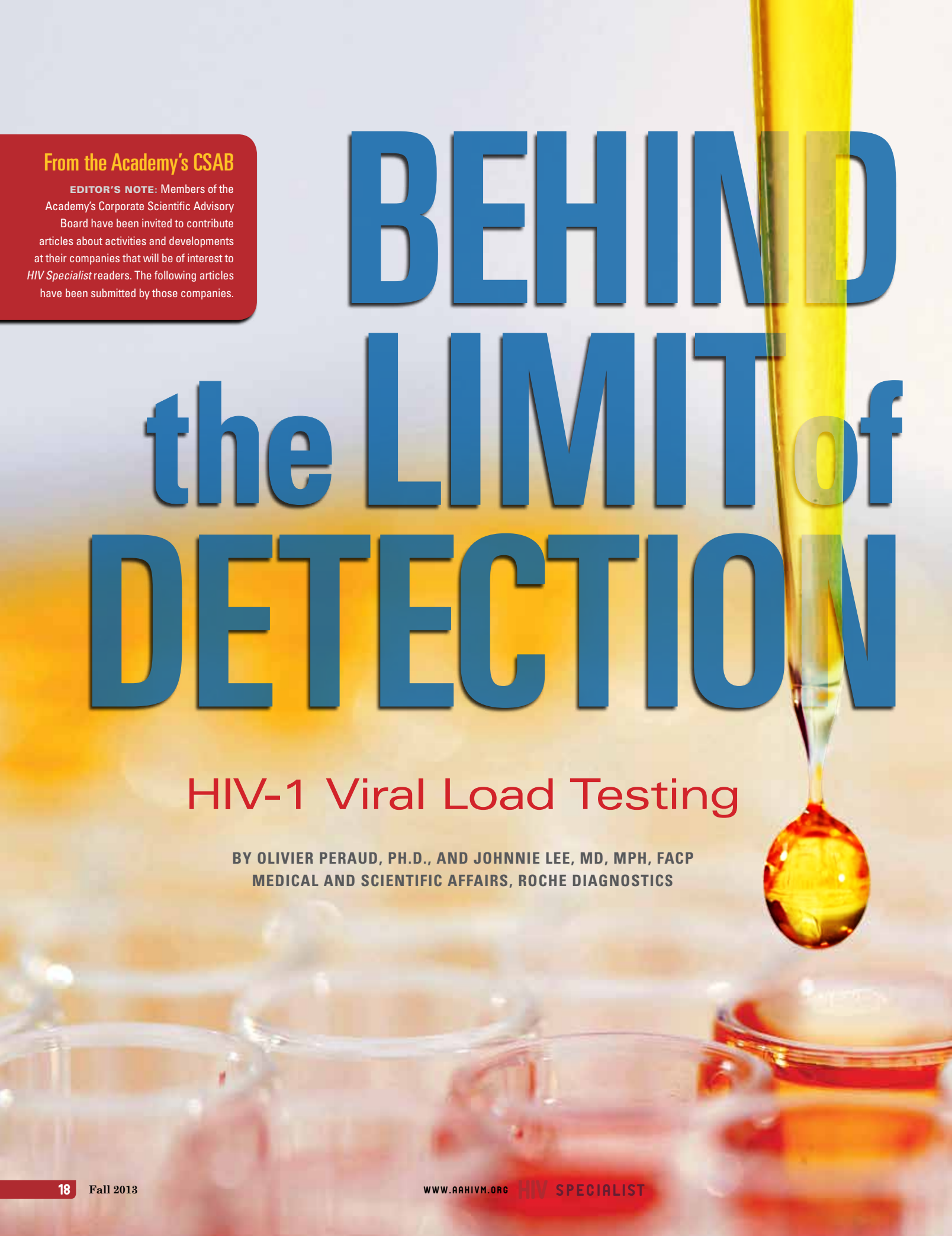
From the Academy's CSAB

EDITOR'S NOTE: Members of the Academy's Corporate Scientific Advisory Board have been invited to contribute articles about activities and developments at their companies that will be of interest to *HIV Specialist* readers. The following articles have been submitted by those companies.

BEHIND the LIMIT of DETECTION

HIV-1 Viral Load Testing

BY OLIVIER PERAUD, PH.D., AND JOHNNIE LEE, MD, MPH, FACP
MEDICAL AND SCIENTIFIC AFFAIRS, ROCHE DIAGNOSTICS



HIV-1 VIRAL LOAD TESTING provides essential information to guide clinicians in making treatment decisions. Over the past two decades, testing has evolved to provide increased assay sensitivity and more actionable results for clinicians. Today, a viral load result is a routine barometer of an HIV-1 patient's health and is typically used by physicians to monitor a patient's response to therapy.

Treatment guidelines for HIV patients recommend plasma HIV RNA (viral load) testing at the first patient assessment visit and every three to six months before and during antiretroviral therapy (Table 1).[1] Viral load testing is based on polymerase chain reaction, or PCR, technology, which has dramatically changed the field of molecular pathology by providing tests with high sensitivity and specificity. PCR tests can take one HIV-1 virus particle and exponentially amplify a piece of its genome so it can be detected and quantified.[2]

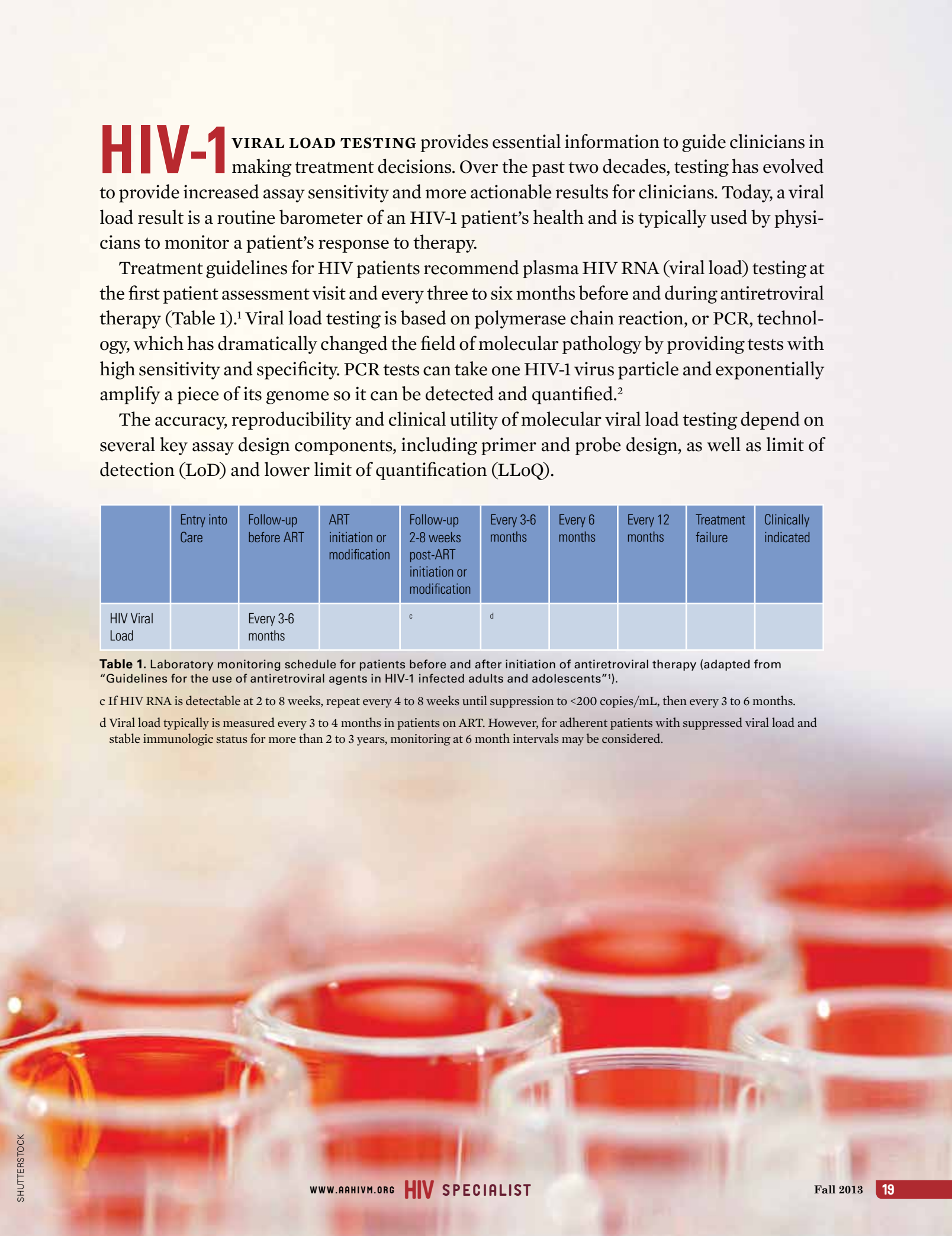
The accuracy, reproducibility and clinical utility of molecular viral load testing depend on several key assay design components, including primer and probe design, as well as limit of detection (LoD) and lower limit of quantification (LLoQ).

	Entry into Care	Follow-up before ART	ART initiation or modification	Follow-up 2-8 weeks post-ART initiation or modification	Every 3-6 months	Every 6 months	Every 12 months	Treatment failure	Clinically indicated
HIV Viral Load		Every 3-6 months		[c]	[d]				

Table 1. Laboratory monitoring schedule for patients before and after initiation of antiretroviral therapy (adapted from "Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents"[1]).

c If HIV RNA is detectable at 2 to 8 weeks, repeat every 4 to 8 weeks until suppression to <200 copies/mL, then every 3 to 6 months.

d Viral load typically is measured every 3 to 4 months in patients on ART. However, for adherent patients with suppressed viral load and stable immunologic status for more than 2 to 3 years, monitoring at 6 month intervals may be considered.



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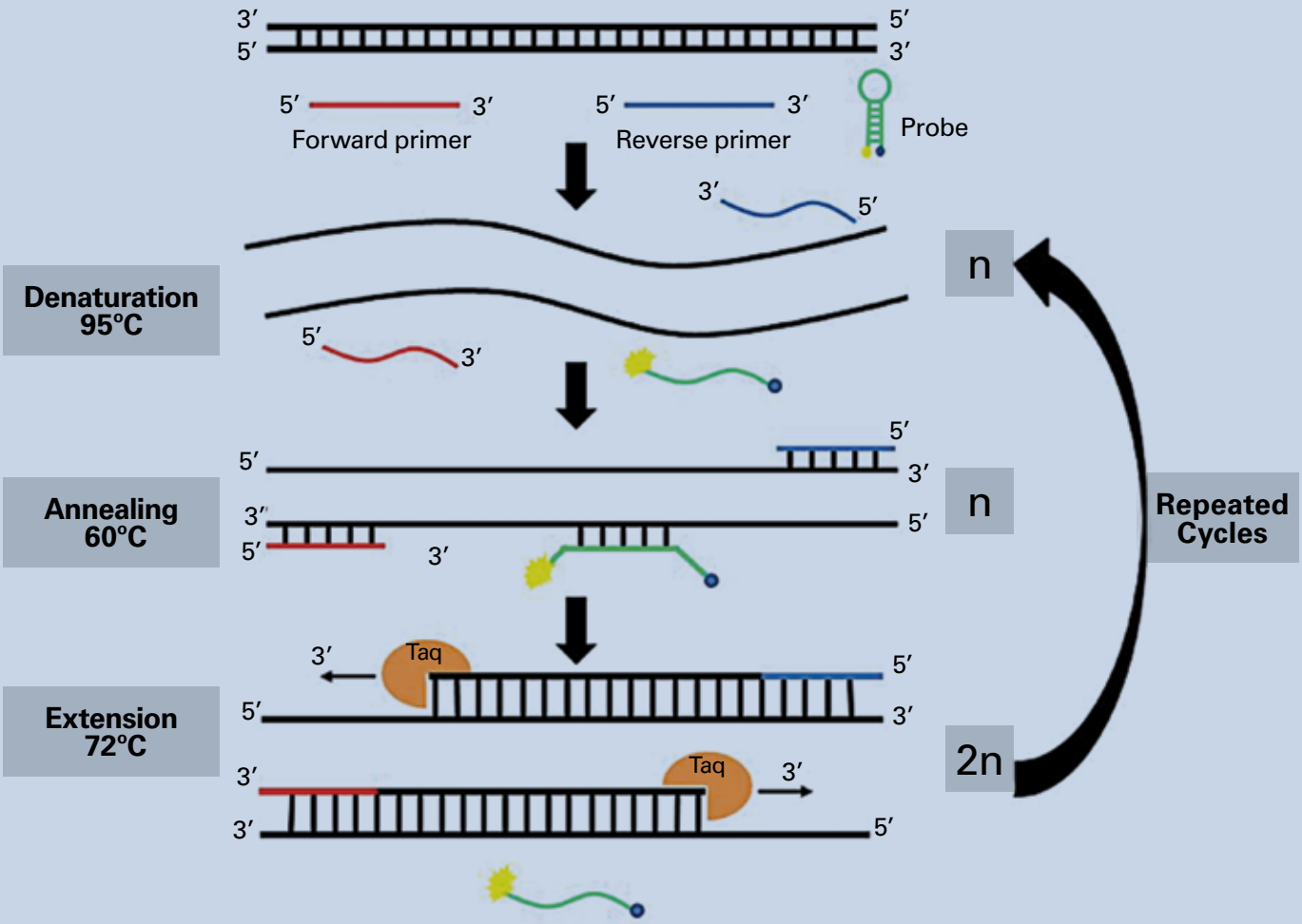

Figure 1. Example of amplification and detection of target nucleic acid by real-time PCR.

Primer and Probe Design

The efficacy of a molecular assay is only as good as its genomic target and this is why primer design and the selection of the target region are critical. Primers are nucleic acid sequences matching the flanking region of the virus target region and signal to the polymerase enzyme where the amplification should start (Fig. 1). Probes are nucleic acid sequences labeled with a fluorescent reporter for the detection of the amplification. The primer/probe selection plays a key role in the effectiveness of HIV-1 viral load testing because of the high variability of the virus genome and the added pressure of selection from antiretroviral drugs such as integrase inhibitors (Fig. 2).[3]

HIV-1 produces 10 billion virions per day and creates a genome sequence polymorphism every 2000-5000 nucleotides.[4] A naturally occurring mutation event or the increased pressure of selection from antiretroviral therapy drugs can alter the target sequence of primers and probes and result in reduced efficiency or the assay not being able to detect HIV-1 viruses.

One strategy to mitigate the effect of mutation-induced changes in HIV-1 nucleic acid sequence is to design HIV-1 viral load assays to target conserved regions of the virus genome. For example, a recently developed assay from Roche, the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, v2.0, includes two targets in the LTR and GAG regions. These are outside of any current target regions for therapeutic drugs, including integrase inhibitors, which target the POL region (Fig. 2).[5] This dual target approach is designed to add redundancy to the test and minimize the potential for mismatches and under-quantification of the virus.[6]

Limit of Detection (LoD) and Lower Limit of Quantification (LLoQ)

For highly active antiretroviral therapy (HAART) naïve patients, the treatment goal is to have an undetectable viral load within 12–24 weeks of the onset of therapy.[1] It is therefore important for clinicians to use an assay sensitive enough to detect HIV-1 at very low levels so they can monitor the patient's response to therapy and adapt the therapeutic regimen accordingly.

For an HIV-1 viral load assay, limit of detection (LoD) and lower limit of quantification (LLoQ) define the analytical

DREAMSTIME

Some recent HIV-1 studies have suggested that there is clinical value in detecting very low-level viremia in HAART patients.

sensitivity of the test. The LoD is the lowest concentration of analyte that can be consistently detected, typically in ≥95% of samples tested. The LLoQ is the lowest amount of analyte in a sample that can be quantitatively determined with stated acceptable precision and trueness, under stated experimental conditions. The LoD and LLoQ values can be the same, but the LLoQ will never be lower than the LoD. Current FDA-approved HIV-1 viral load tests have LLoQs that range from 20 cp/mL to 75 cp/mL (Table 2).

A "Target not detected" or "Undetectable" result for any real-time PCR test is directly linked to the LoD of the assay. The result could mean that HIV-1 is not present in the sample, but it could also mean the target is present but at a level below the LoD. For example, the Roche test mentioned earlier has an LoL/LLoQ of 20 copies/mL with >95% detectability.[5] However, the test is able to detect concentrations lower than the LoD with lower positivity rates (i.e., 8.0 copies/mL with 53% positivity rate for plasma).[5] This means that when a patient's sample at an 8.0 copies/mL concentration is tested 10 times, it will generate a detectable result five times and an undetectable or "target not detected" result five times.

Some recent HIV-1 studies have suggested that there is clinical value in detecting very low-level viremia in HAART patients.[7,8,9] Doyle et al. reported that for patients with a viral load <50 cp/mL, HIV-1 RNA detection below this threshold predicted a risk of rebound greater than 50 and 400 cp/mL

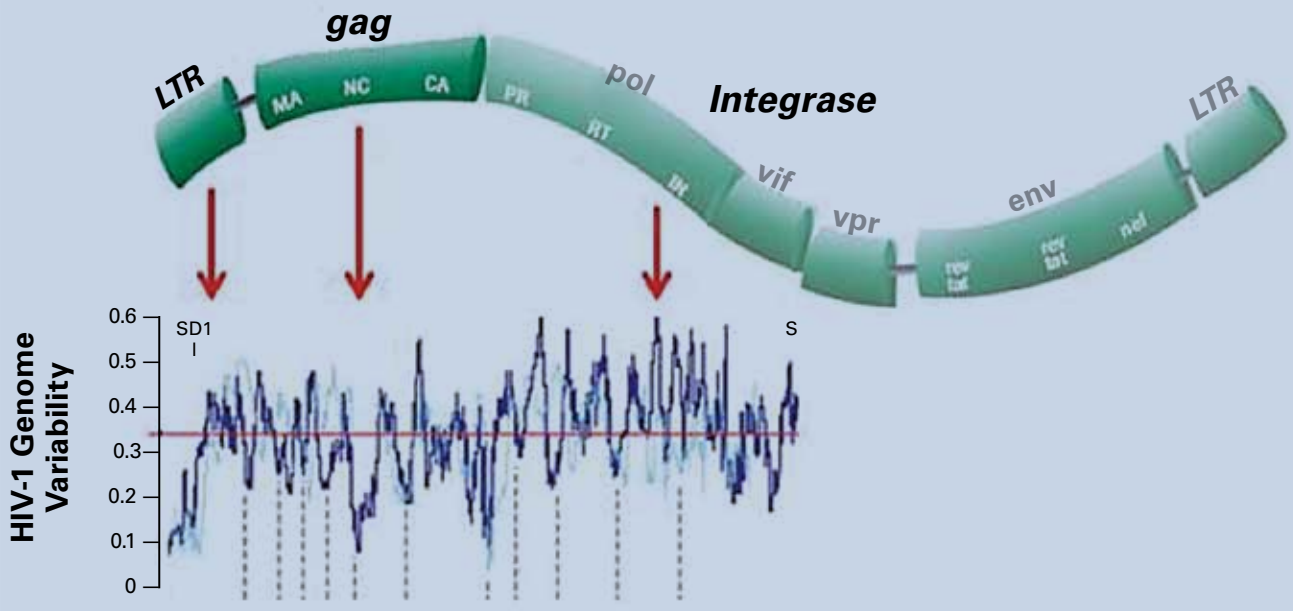

Figure 2. HIV-1 genome variability (adapted from: JM Watts et al. Nature. 2009;460: 711-716).

Manufacturer	Assay Name	Target Region	LoD (cp/mL)	LLoQ (cp/mL)	*Linear Range (cp/mL)*
Roche	COBAS® AmpliPrep/ COBAS® TaqMan® HIV-1 Test v2.0	gag and ltr	20[a]	20[a]	20-10 million[a]
Abbott	RealTime HIV-1 assay	pol	40[b]	40[b]	40 –10 million[b]
Bayer HealthCare	Versant® HIV-1 RNA 3.0 assay	pol	68[c]	75[c]	75 – 500,000[c]

Table 2. LoD and target regions of FDA-approved HIV-1 viral load assays.

[a]Roche COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, v2.0, U.S. IVD package insert

[b] Abbott RealTime HIV-1, U.S. IVD package insert

[c] Versant® HIV-1 RNA 3.0 assay (bDNA)
http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/UCM091276.pdf

during follow-up. In another study, Álvarez et al. stratified patients into three groups: <20 cp/ml, 20-39 cp/ml and 40-49 cp/ml.[9] The results indicated that time to virologic failure was significantly shorter for patients with a viral load of 20-39 cp/mL and 40-49 cp/mL when compared to patients with a baseline viral load of <20 cp/mL.

Evolving with the Virus

As HIV evolves and mutates, it is essential to stay one step ahead in both therapeutic regimens and viral load monitoring. A better understanding of the biology of the virus has led to the development of integrase inhibitors, a new class of efficient antiretroviral drugs. In particular, raltegravir is being used successfully for the first line of therapy in combination with tenofovir.[1,10] Additional integrase inhibitors, such as evitegravir and dolutegravir, are now available and more compounds in this class are being developed.

In viral load monitoring, the ability to detect low levels of HIV-1 remains paramount, as there is growing evidence of its clinical utility and connection to outcomes. Another key factor driving long-term clinical utility is the capability of assays and specifically primer/probe designs to withstand the constant genomic changes the virus undergoes.

It is an exciting time for the HIV field as cures have been reported, new drugs are being developed and novel technology delivers more robust and sensitive viral load assays.[11,12] Clinicians are now better equipped to make the therapeutic decisions that will most benefit their patients. HIV

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ViiV Healthcare

IN MEMORIAM

Dr. James Goodrich

IT IS WITH SADNESS that ViiV Healthcare reports the death of Dr. James Goodrich in early June 2013. Jim leaves behind his wife, Carolyn, and two daughters.

Jim had a distinguished career as a physician, both in the clinical and basic science realms. He received a Ph.D. in Virology from the University of Wisconsin and a M.D from Rush Medical College in Chicago. Following an internal medicine residency at the University of Texas Southwestern/ Parkland Hospital in Dallas, Jim completed an Infectious Disease fellowship at the Fred Hutchinson Cancer Research Center in Seattle, Washington. While at "the Hutch," Jim performed groundbreaking research on the use of ganciclovir for the prevention of CMV disease in bone marrow transplant patients. The seminal article describing this work was published in the New England Journal of Medicine, of which Jim was the first author. This was one of many articles published by Jim on the infectious complications of bone marrow transplant patients.

Following his academic career, Jim joined the infectious disease group at Pfizer where he was part of the development team for maraviroc as well as other earlier stage anti HIV medications. Jim moved to North Carolina and became the Vice President for Global Medical Strategy for ViiV Healthcare when the company was formed. He was instrumental in the formation of the R&D group in ViiV and made important contributions to the development of all the ViiV compounds, including dolutegravir.

Jim will truly be missed. He will be most remembered for is his unwavering devotion to medical excellence and the care of patients.

Dolutegravir

TIVICAY® (dolutegravir) 50-mg tablets was approved by the Food and Drug Administration (FDA) in August for use in the U.S. Tivicay is an integrase inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 in adults and children aged 12 years and older weighing at least 40 kg (approx. 88 lbs).

The indication is based on data from four pivotal Phase III clinical trials that treated 2,557 adults (who received at least one dose of study medication) with HIV across the treatment spectrum; it also included data in children aged 12 years and older.

This Phase III program included two trials in treatment-naïve patients: one where a once-daily Tivicay-based regimen was compared to twice-daily raltegravir and another where the regimen of once-daily Tivicay and abacavir/ lamivudine was compared to once-daily Atripla® (efavirenz/emtricitabine/tenofovir disoproxil fumarate). It also included treatment-experienced patients who had not previously been treated with an integrase inhibitor, where a once-daily, Tivicay-based regimen was compared to twice-daily raltegravir. The fourth trial studied treatment-experienced patients with resistance to multiple classes of HIV medicines, including resistance to integrase inhibitors, where the effectiveness of twice-daily Tivicay on viral load was evaluated.

Please visit www.us.tivicay.com for the full U.S. prescribing and patient information. HIV

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Screening and Prevention More Important Than Ever

Emerging Sexually Transmitted Infection *Superbugs* Impacting HIV Care

The Centers for Disease Control and Prevention (CDC) estimates that there are approximately 700,000 cases of gonorrhea and 100,000 cases of primary and secondary syphilis diagnosed each year in the US.[1] Gonorrhea and syphilis are most prevalent among men, especially men who have sex with men (MSM), ethnic minorities, especially African Americans, and the urban underserved.

We are also observing a spike in all sexually transmitted infections (STIs) within the HIV-infected population, particularly among MSM.[2] Most worrisome has been the parallel increase in resistance of *Neisseria gonorrhoeae* and *Treponema pallidum* to antibiotics.[3-5]

Although the rise in antibiotic resistant gonorrhea and syphilis is not unique to HIV-infected persons, this population represents a critical driver of STI transmission.[2,6,7] People with STIs are at increased risk for acquiring and transmitting HIV, and conversely, HIV-infected persons have a higher risk of acquiring and transmitting STIs (Figure 1).[7,8] HIV focused clinicians can help prevent the transmission of resistant gonorrhea and syphilis by regularly screening their sexually active HIV patients for STIs, providing primary prevention messages at every visit, implementing routine brief risk-reduction counseling, providing prompt and effective antibiotic treatment, and initiating earlier antiretroviral therapy.[2,9]

HIV focused clinicians can help prevent the transmission of resistant gonorrhea and syphilis by regularly screening their sexually active HIV patients for STIs, providing primary prevention messages at every visit, implementing routine brief risk-reduction counseling, providing prompt and effective antibiotic treatment, and initiating earlier antiretroviral therapy.

Decreased Effectiveness of Antibiotic Therapy for Gonorrhea and Syphilis

CDC's Gonococcal Isolate Surveillance Project (GISP) first reported gonococcal resistance to fluoroquinolones.[10] By 2007, the prevalence of fluoroquinolone-resistant *N gonorrhoeae* represented >5 percent of isolates, prompting the CDC to no longer recommend the use of fluoroquinolones for empiric treatment.

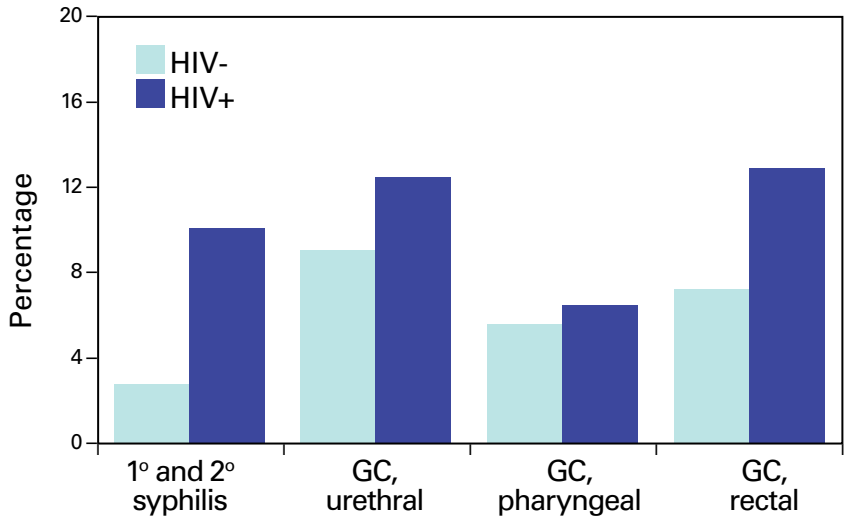
Consequently, only one class of antimicrobials, the cephalosporins, was available for the treatment of gonorrhea in the US. But, by the early 2000's, the first cases of gonococcal resistance to cefixime emerged in the US; the percentage of isolates with elevated MICs to cefixime (≥0.25 µg/mL) increased 14-fold from 0.1 percent in 2006 to 1.4 percent in 2011 (Figure 2).[10]

Fluoroquinolones and cefixime had been the most active oral agents for the treatment of gonorrhea. Now, the only remaining reliably effective antibiotic to treat gonorrhea is ceftriaxone, which must be administered by injection. However, the recent emergence of a highly ceftriaxone-resistant gonococcal strain (H041) was reported in Japan in 2011. Current reports have identified H041 resistant isolates in other countries and the US, primarily among MSM in California, New York City, and Chicago (Figure 2).[3,11-13] These also represent individuals at the highest risk of sexually acquiring and transmitting HIV.

In September 2013, the CDC released a new report that outlined all critical drug-resistant threats and also prioritized bacteria into three categories by level of concern: urgent, serious, and concerning.[14]

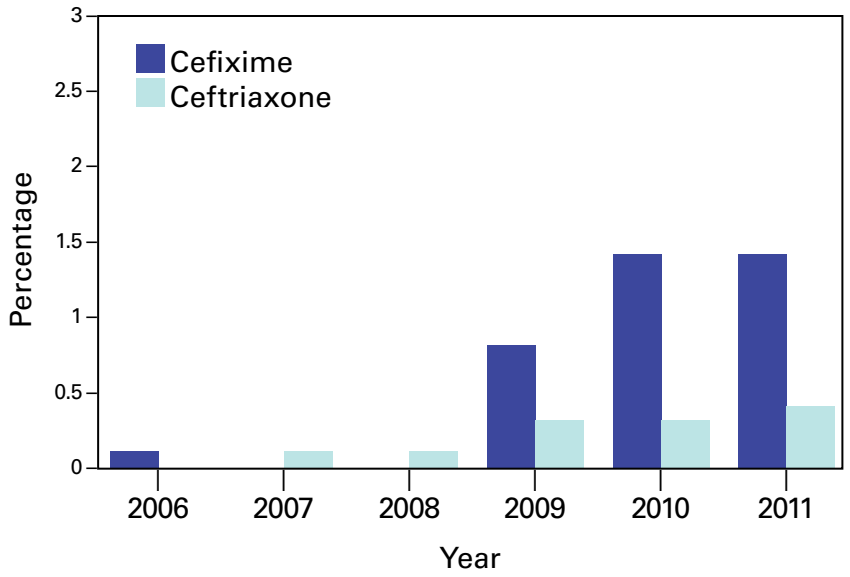
Not only is drug-resistant *N. gonorrhoeae* included in this report, but it is prioritized as an urgent threat. *N. gonorrhoeae* has among the highest morbidity of critical antibiotic-resistant infections, with an estimated 250,000 annual drug resistant cases. According to this report, if drug-resistant gonorrhea

Figure 1. Proportion of MSM Attending STI Clinics with Syphilis or Gonorrhea by HIV Status.[7]



MSM = men who have sex with men. GC = gonorrhea.
STD Surveillance Network (SSuN), 2011.

Figure 2. Percentage of Urethral N. gonorrhoeae Isolates with Elevated MICs to Cefixime (³0.25 mg/mL) and Ceftriaxone (³0.125 mg/mL) During 2006-2011.[10]



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becomes widespread, public health impact during a 10-year period is estimated to be 75,000 additional cases of pelvic inflammatory disease (a major cause of infertility), 15,000 cases of epididymitis, and hundreds of additional HIV cases.

Although we haven't yet isolated these "superbugs" where I practice in Wisconsin, recent US surveillance reports represent just the tip of the iceberg. This is an urgent issue and suggests that *N. gonorrhoeae* at some point may become resistant to essentially all currently recommended antibiotics, leading to cases with no proven effective treatment.

State and local surveillance for antimicrobial resistance is crucial for guiding local therapeutic recommendations. GISP, which samples approximately 3 percent of all U.S. men who have gonococcal infections, is a mainstay of this surveillance.[1]

However, surveillance by front-line clinicians is also critical. Clinicians who diagnose *N. gonorrhoeae* infection in a patient with suspected cephalosporin treatment failure must perform culture and susceptibility testing of all relevant clinical specimens, consult a specialist for guidance in clinical management, and report the case to state and local public health authorities. Without a robust clinician-driven public health effort, resistant isolates will continue to spread throughout the US.

Fortunately, penicillin is still effective for the treatment of syphilis. Parenteral administered penicillin G, is the preferred drug for treating all stages of syphilis. However, syphilis resistance has emerged to macrolide antibiotics, which are the primary alternative to penicillin.[4] *T. pallidum* chromosomal mutations associated with azithromycin resistance and treatment failures have been documented in several communities in the US. As such, the use of azithromycin should only be used under rare circumstances and with caution when treatment with penicillin or doxycycline is not feasible.[1] Likewise, azithromycin should not be used in MSM or pregnant women.

HIV focused clinicians can help by eliciting sexual histories, regularly screening sexually active patients who engage in risky behavior, providing prevention counseling, and appropriately treating STIs.

How Do STIs Increase the Risk of HIV Transmission?

Persons with an active STI are at least two to five times more likely to acquire HIV infection through sexual exposure.[1] In addition, an HIV-infected person with an STI is more likely to sexually transmit HIV to a partner.[1]

STIs increase acquisition of HIV infection by mucosal disruption leading to direct viral entry, and by mobilizing greater concentrations of CD4+ lymphocytes into genital secretions, thereby providing numerous targets to facilitate HIV transmission.

STIs increase HIV viral shedding in genital secretions with a tenfold higher median concentration of HIV in the semen of men with active gonorrhea and HIV coinfection. People with active syphilis and HIV co-infection have higher serum HIV viral loads and significantly reduced CD4+ cell counts.[14, 15]

Conversely, treatment of syphilis leads to lower serum HIV viral loads, increases in CD4+ cell counts, and reduced genital HIV shedding.[15,16] These findings underscore the importance of primary prevention, regular screening, and prompt treatment of gonorrhea, syphilis, and all potential STIs in HIV-infected persons.

Current CDC Recommendations for Treating STIs in HIV-Infected Persons

The development and spread of cephalosporin-resistant *N. gonorrhoeae* complicates treatment efforts, and new antimicrobial options are needed.[10] Until then, the CDC currently recommends combination therapy for the treatment of uncomplicated urogenital, anorectal, and oropharyngeal gonorrhea, with a single IM dose of ceftriaxone 250 mg plus either a single dose of azithromycin 1 g orally or doxycycline 100 mg orally twice daily for 7 days.[17]

Patients infected with *N. gonorrhoeae* frequently are coinfected with *Chlamydia trachomatis*; this finding has led to the recommendation that patients treated for gonococcal infection also be treated routinely with the above regimen, effective against uncomplicated genital chlamydia infection. Patients diagnosed with uncomplicated gonorrhea who are treated with this recommended regimen do not need a test-of-cure (i.e., repeat testing 3–4 weeks after completing therapy). Likewise, there is no specific modification to this regimen for the treatment of gonorrhea in HIV-infected patients.

Similarly, clinical studies have not led to a modified antimicrobial regimen for treating syphilis in HIV-infected patients.[18] Thus, the CDC recommends benzathine penicillin G, 2.4 million units IM in a single dose for an early syphilis infection (primary, secondary, and early latent) regardless of HIV status.[1] HIV-infected persons, however, should be evaluated clinically and serologically for treatment failure at 3, 6, 9, 12, and 24 months after therapy.

What Can Clinicians Do?

HIV focused clinicians can help by eliciting sexual histories, regularly screening sexually active patients who engage in risky behavior, providing prevention counseling, and appropriately treating STIs.[2]

Clinicians should routinely screen for STIs in sexually active HIV-infected persons long before patients present with symptoms, and not just during a regional spike in cases.[1,19] STI screening should include separate tests for urogenital, anorectal, and oropharyngeal infections, especially among MSM. Retesting several months after the diagnosis and treatment of an STI (i.e., chlamydia or gonorrhea) should be considered in order to detect repeat infection and potentially enhance population-based prevention.[20]

Clinicians have a unique opportunity to provide education and counseling to their patients to avoid STIs through encouraged changes in sexual behaviors and the use of recommended prevention services. Although brief clinician-administered behavioral interventions have been shown to reduce risky sexual behaviors in HIV-infected persons, this requires additional clinician time and training for effective implementation.[9]

Fortunately, a number of organizations, including AAHIVM and the AIDS Education & Training Centers (AETCs) provide clinician training and technical assistance regarding best practice implementation models. These clinic focused models address a number of evidence-based prevention efforts including Partner Services to patients to help them confidentially notify sexual partners at risk after an STI or HIV infection is diagnosed.[21]

The timely treatment of recent sex partners is essential to prevent reinfection and curtail further transmission. These recommendations underscore the vital role clinicians play in the comprehensive care of their patients and the health of their communities. HIV

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What Clinicians Can Do

- Take a detailed sexual history to identify behaviors that promote HIV and STI transmission, and regularly screen sexually active, HIV-infected persons for syphilis, gonorrhea, and chlamydia at least annually.
- Additionally, screen women for trichomoniasis and obtain a cervical PAP smear annually.
- Screen HIV-infected persons more frequently for STIs (i.e., at 3-month intervals) if they have numerous and/or anonymous partners or live in geographic areas with a higher relative number of STI cases.
- Offer HIV-infected patients brief prevention counseling at every visit to reduce the risk of STI acquisition.
- Include topics such as how to practice safer sex, how to discuss sex with partners, how to negotiate condom use, and consistent and correct condom use with each sexual encounter.

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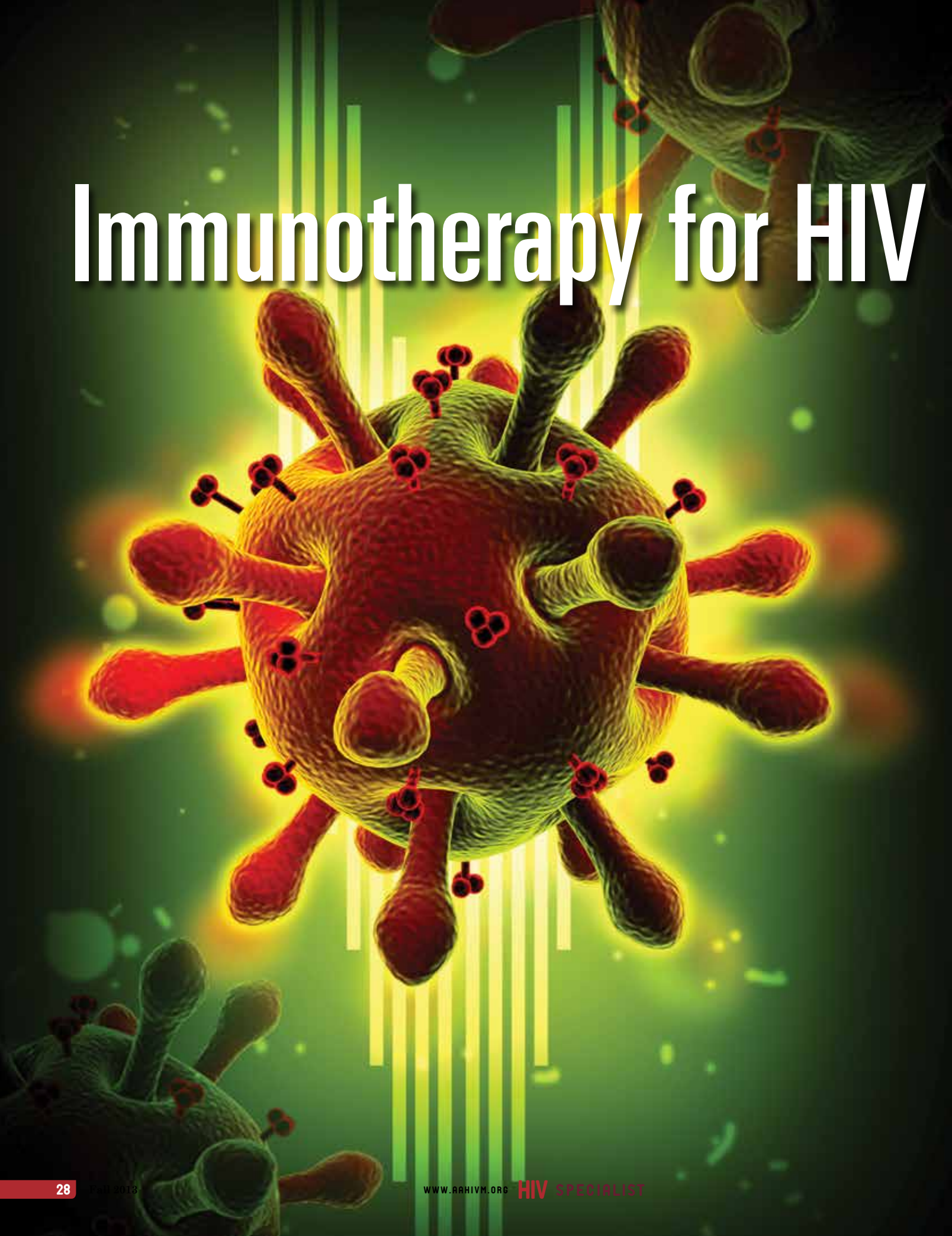
Immunotherapy for HIV



Past, Present and Future

NOVEL APPROACHES NEEDED

BY IRINA Y. TCHEREPANOVA AND CHARLES A. NICOLETTE

ANTIRETROVIRAL THERAPY (ART) in HIV-infected patients decreases levels of HIV in the blood below the limits of detection (<50 copies/mL) of standard clinical viral load assays, and also increases quality of life and life expectancy. However, residual virus persists in latently infected cells, and after cessation of ART, virus replication invariably reinitiates from those reservoirs. Neither prolonged ART treatment nor intensification of ART regimens can eliminate the latent reservoir[1].

Residual low-level viremia causes T cells to remain chronically activated, even in ART-suppressed patients. It has been reported that CD4+ T cell loss, a hallmark of disease progression, can be predicted by high levels of immune activation, independent of HIV blood levels[2]. This generalized immune activation is a major contributor to HIV pathogenesis[3] and is associated with increased mortality[4]. In addition, up to 30% of patients receiving ART fail to achieve normal CD4+ T-cell counts [5]. Because of this and the limited ability of ART to eliminate residual viral replication, latent reservoirs and inflammation, novel approaches are greatly needed for better management of HIV infected patients.

Therapeutic vaccines designed to augment antiviral immunity in patients already infected are a promising adjunct to currently available treatments. These experimental immunotherapies attempt to induce anti-HIV CD8+ T cells with the goal of replicating the type of immune responses observed in long-term non-progressors (LTNP) and elite controllers (EC), which are rare individuals that have the natural ability to control HIV replication without therapy. The EC's are the best testament to the possibility for success with immunotherapeutic intervention. These patients possess large numbers of central and effector memory CD8+ T cells with low levels of activation markers and exhibit low levels of systemic inflammation. It has been reported that transmission of HIV from a patient with progressive disease to an EC resulted in efficient control of the infection, providing further support that it is the patient's immune system rather than an attenuated virus strain which resulted in viral load control[6].

An effective immunotherapy would induce immune control over the virus via formation of HIV-specific CD8+ T cells. These cells would produce multiple cytokines and effector molecules and possess long-term proliferative capacity with broad antiviral antigen specificity, leaving little opportunity for immune escape[7,8]. Importantly, these CD8+ T cells would also possess a high-avidity cytolytic potential against infected cells[9] and have the capacity to suppress viral replication[10,11]. These considerations provide a rationale for the development of therapeutic vaccines that enhances immune control of HIV[12]. Therapeutic vaccination would be administered to HIV infected patients to reprogram and equip the immune system to combat the virus.

Challenges Ahead

The development of successful immunotherapies for HIV faces many challenges. Particularly confounding is the abnormal immune functionality of HIV-infected individuals where naturally occurring productive cell mediated anti-HIV responses decrease during progression of HIV infection[13].

DREAMSTIME

This dysfunction extends to CD8+ and CD4+ T cells as well as antigen presenting cells, such as Dendritic cells (DC), whose function is to 'educate' the T cells to seek out and destroy HIV-infected cells. DCs resident in the mucosal tissues are among the first cells to encounter the virus at the time of infection and are targets for HIV infection. This results in abnormal differentiation and function required for productive CD8+ T cell responses[14, 15]. In fact, we discovered that the HIV protein, Vpr, renders DC incapable of generating memory CD8+ T cell responses by blocking IL-12 secretion[16].

Therefore, immunization strategies that do not rely on endogenous mechanisms of antigen presentation in an infected individual are desirable. Another challenge to vaccine design is the large sequence diversity that exists within an infected individual and these viral 'swarms' vary from individual to individual. In our opinion, this situation demands an autologous approach where the antigens used for immunization are matched to each patient's pool of unique virus mutations.

Indeed, clinical studies that attempted therapeutic vaccination using a variety of HIV immunogens based on defined sequences failed to demonstrate virological benefit.

ALVAC, a Canarypox virus expressing the HIV genes *env* and *gag*, is one of the most clinically studied therapeutic vaccines. Although immune responses to env and gag could be detected after vaccination, this did not lead to viral control. In one of these studies, vaccination did not provide for any benefit after discontinuation of ART[17] and in a second study it led to a shorter time to resume ART, and even higher viral rebound[18].

The VRC DNA vaccine, which used DNA plasmids encoding a Gag-Pol-Nef fusion protein, resulted in broader anti-HIV immune responses but no viral control after ART interruption[19]. Studies employing Remune, an inactivated HIV, failed to demonstrate significant differences with respect to changes in HIV levels between the vaccine and placebo groups[20]. Combining Remune with ALVAC resulted in a delay of viral rebound during ART interruption of 11 days compared to placebo group, [21] but overall did not lead to a better viral control after ART interruption[21,17].

These clinical trials and others that utilized classical approaches to induce productive immune responses did not overcome the challenges associated with HIV immunotherapy described above. Solving these challenges clearly requires a more complex approach.

EVEN WITH THE UNRELENTING DRIVE IN THE GLOBAL SCIENTIFIC COMMUNITY TO ERADICATE HIV FROM INFECTED INDIVIDUALS, SUCCESS IS STILL MANY YEARS AWAY. HOWEVER, WE EXPECT THAT NEARER TERM PARTIAL SUCCESSES COULD PROVIDE NEW TOOLS FOR TREATING PHYSICIANS TO DEPLOY.

Clinical data suggest that DC-based vaccines may be effective in HIV infected patients. One advantage of this approach is that generating DCs *ex vivo* provides an environment that is devoid of HIV and its negative effects on DC biology and DC maturation in this highly controlled environment results in optimal phenotype and function.

Also, DCs can be modified to express antigens using a variety of approaches that can include autologous HIV quasispecies. To date, 13 DC-based trials in HIV infected patients have been reported[22] with excellent safety profiles. Among the studies that evaluated viral impact, those that led to decreased virus combined both *ex vivo* matured DCs and autologous HIV antigens. HIV antigen was generated using chemically or heat inactivated autologous HIV particles [23-26] or through the expression of amplified RNAs encoding autologous HIV antigens[27].

In a randomized, placebo-controlled study reported by Garcia *et. al.*, after ART interruption, median decrease of plasma viral load setpoint of ≥1 log was observed in 12 of 22 (55 percent) versus 1 of 11 (9 percent) and in 7 of 20 (35 percent) versus 0 of 10 (0 percent) patients in the DC–HIV-1 and DC-control groups, respectively[26]. In a single arm open label clinical study reported by Routy *et. al.*, a decrease of mean viral load set point of 1.21 log was observed in 16 out of 24 patients (67 percent) responding to the treatment after ART interruption[27]. In this study, the DCs were 'programmed' with amplified RNA encoding Gag, Nef, Vpr and Rev, including the unique patient-specific quasispecies of each antigen. These data suggest that DC-based therapeutic vaccines directed against autologous viral antigens can impact viral loads.

These early successes represent proof of concept for immune augmentation to decrease viral load and the goal of functional cures in the form of durable viral control or complete virus eradication.

Outlook

The ultimate objective of virus eradication is unlikely to be achieved with therapeutic vaccines alone since the HIV latent reservoir, which serves as a source for low level virus replication and viral rebound in the absence of ART, is poorly visible to the immune system due to a

low level or lack of expression of HIV antigens.

An area of active research in the HIV field is the development of drugs that activate the latently infected cells, resulting in increased viral antigen expression, making them vulnerable to elimination via the immune system. It is feasible that combining DC-based autologous therapeutic vaccination with latency reversing drugs could lead to activation of antigen expression from dormant cells, allowing their complete eradication. We and others are planning clinical studies to test this hypothesis.

Advances in the field of therapeutic vaccines and a more detailed understanding of HIV biology have provided new avenues for experimental therapeutic intervention. Even with the unrelenting drive in the global scientific community to eradicate HIV from infected individuals, success is still many years away. However, we expect that nearer term partial successes could provide new tools for treating physicians to deploy.

For example, even if therapeutic vaccination cannot fully eradicate the virus, it may provide a safety net for poorly compliant patients or offer the opportunity for ART interruption in patients experiencing intolerable side effects. Lastly, therapeutic vaccination may offer incremental benefit in pediatric HIV patients that initiated ART therapy at birth or shortly thereafter. These patients typically have very small latent reservoirs which may become overwhelmed after optimal anti-viral immunity is established. HIV

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Managing Occupational Exposure to HIV

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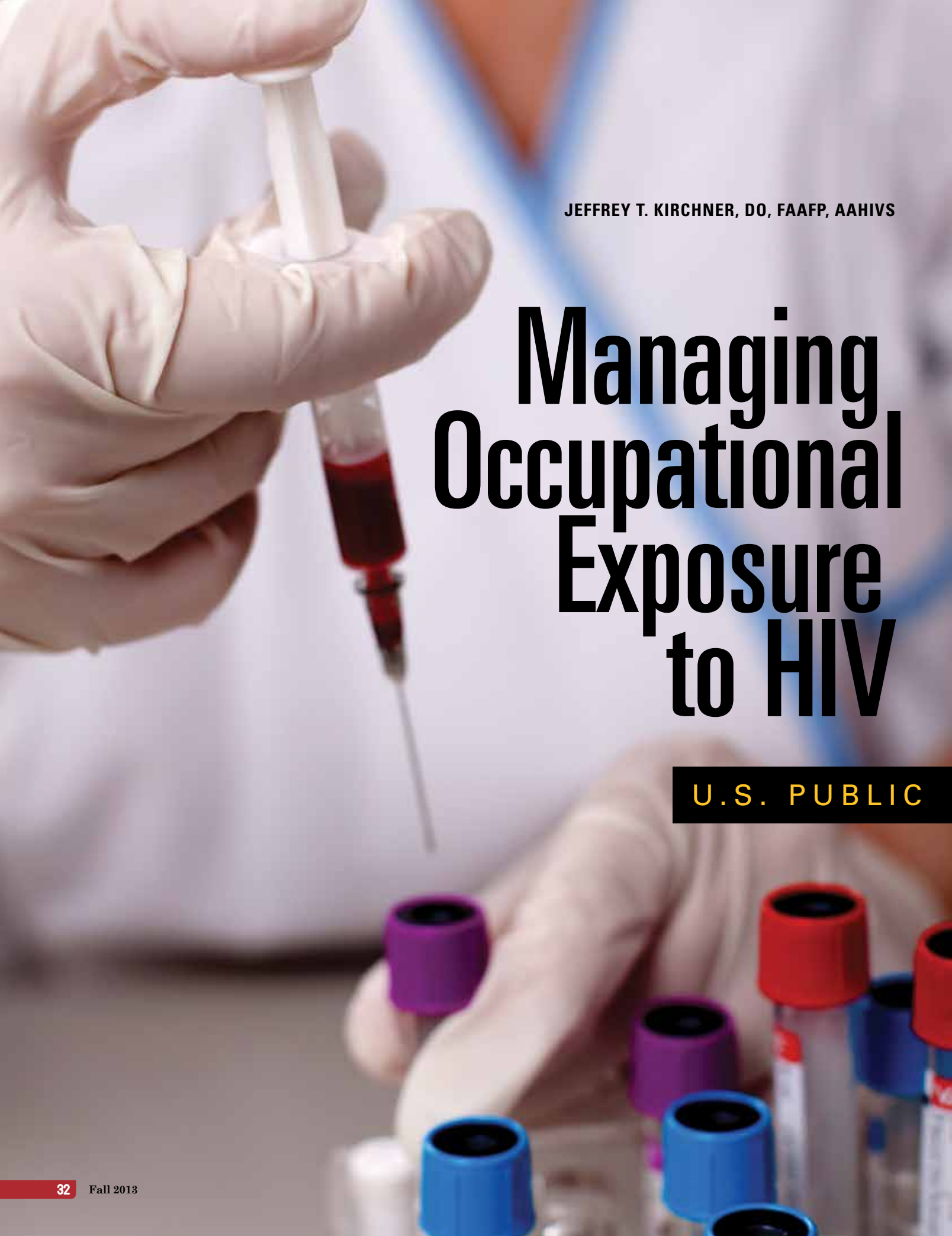

HEALTH SERVICE UPDATES GUIDELINES

THE U.S. PUBLIC HEALTH SERVICE (PHS), with the guidance of representatives from the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the Health Resources and Services Administration (HRSA), recently updated recommendations for the management of healthcare personnel (HCP) who experience exposure to blood or other body fluids that may contain human immunodeficiency virus (HIV).[1]

The use of antiretrovirals as post-exposure prophylaxis (PEP) was first noted by the CDC in 1990 and the first formal guidelines were issued in 1996. Recommendations were periodically updated; however, this is the first revision since 2005.[2]

The previous guidelines were challenging to apply as they emphasized determining the level of risk for infection based on exposure. The number of drugs recommended was based on the level of risk. The new guidelines have simplified the approach to PEP and recommend medication regimens that contain three antiretroviral drugs. A "hierarchy" of specific drugs was selected based on safety, tolerability, toxicity, frequency of dosing and pill burden.

Definition of HCP and Exposure Risk

The definition of HCPs has not changed since the prior updates. It applies to persons working in healthcare settings with potential exposure to infectious materials including blood, tissue, and specific body fluids. A HCP includes (but is not limited to) emergency services personnel, laboratory personnel, physicians, nurses, nurses' assistants, therapists, technicians, pharmacists, autopsy personnel, dental personnel, students, and trainees.

An exposure that may place a HCP at risk for HIV infection is defined as a percutaneous injury such as a needle stick or cut with a sharp object. It also may include contact of mucous membrane or non-intact skin with blood, tissue, or other body fluids that are potentially infectious. The risks of HIV infection vary with the type and severity of exposure.

Whenever possible, the HIV status of the source patient should be determined. If the status of the source patient is unknown, rapid HIV testing facilitates decision making regarding the need for PEP. Exposure to a known HIV-positive patient with an undetectable viral load does not eliminate the need for PEP and follow-up testing. While the risk is very low, PEP should still be offered as plasma viral load reflects only the level of cell-free virus in peripheral blood and persistence of HIV in latently infected cells which are potential infectious has been demonstrated.

Selection and Duration of Antiviral Agents for PEP

A regimen containing three (or more) antiretroviral drugs is recommended routinely for all occupational exposures to HIV. **The favored initial regimen consists of tenofovir and emtricitabine with raltegravir**. Other agents are recommended in the guidelines as secondary choices if the above three drugs are contraindicated, note tolerated, or cause toxicity. None of the antiretroviral agents has an FDA-approved indication for PEP.

Persons eligible for PEP should start treatment as soon as possible after exposure and continue for four weeks. The guidelines also address special situations where expert consultation should be used. These include delayed exposure reported beyond 72 hours, known or suspect drug resistance in the source patient, or if the exposed individual is pregnant or breast-feeding.

Follow-up

HCP who experience occupational exposure to HIV should receive close follow-up, counseling, and testing regardless of whether they take PEP. A follow-up visit should occur within 72 hours which provides an opportunity to address questions, reassess need for PEP, discuss medication adherence, manage any drug-related symptoms, and improve the likelihood for follow-up serologic testing.

If PEP is started and the source patient is ultimately determined to be HIV negative then the drugs can be stopped and no further testing is needed. If PEP is maintained, a CBC and hepatic and renal function should be checked at baseline and again two weeks after starting. Along with baseline testing, repeat HIV testing should be done at 6 weeks, 12 weeks, and 6 months after exposure. If a newer 4th generation HIV Ag/Ab assay is used, testing can be stopped at four months post-exposure. HIV

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SHUTTERSTOCK

Prevention with Positives

Where We Are Now

THE DECLINING death rate from HIV over the last 10 years[1] and the relatively unchanged annual rate of new infections have contributed to the increasing number of people living with HIV (PLWH).[2]

In the face of this challenge, HIV providers are increasingly incorporating prevention into the clinical care of their patients to reduce their risk of transmitting HIV, and help them live healthier and longer lives. These benefits frequently overlap because interventions that reduce HIV transmission risk also improve the health and longevity of PLWH.

For example, in 2009 for PLWH the NA-ACCORD, a randomized controlled trial, showed that early intervention with antiretroviral therapy (ART) before the CD4+ count fell below 2 pre-specified thresholds (<350 and <500) significantly improved survival compared with deferred therapy.[3]

As a result, the Department of Health and Human Services (DHHS) HIV guidelines recommended earlier treatment for HIV-infected persons. NA-ACCORD also reported a reduction of HIV-associated inflammation in virtually all organ systems, which, in turn, increased the possibility of improved quality and quantity of life.

Rationale for Prevention

ART is allowing persons to live longer with HIV; in fact, individuals who attain viral suppression and a CD4 count >350 cells/mm^3 within 1 year of initiating ART now have a normal life expectancy.[4] Prevention efforts have helped keep the rate of new infections stable in recent years, but continued growth in the number of PLWH ultimately may lead to more new infections if prevention, care, and treatment efforts are not targeted toward those at greatest risk to reduce community viral load (CVL).[5-9]

An early adopter of this concept was the San Francisco Department of Health. Using the San Francisco HIV/AIDS surveillance system to examine trends in CVL, they were one of the first to show that identifying those at risk earlier and treating earlier would decrease CVL, which is associated with decreases in HIV infection.[10]

Early ART Reduces HIV Transmission

The most recent DHHS guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents strongly recommend prevention of HIV transmission as a key component of the management of HIV-infected persons.[11]

These recommendations were strengthened substantially by the HPTN 052 study of over 1,700 serodiscordant couples, which found a 96 percent reduction in HIV transmission when the infected partner was started on suppressive ART based on the CD4 count at baseline (plus condom use).[12] Previous observational studies suggested that early initiation of ART could reduce the risk of HIV transmission,[13-16] but HPTN 052 was the first randomized, controlled trial to confirm the benefits of early ART on sexual transmission of HIV (**Figure 1**). HPTN 052 also provided support for revising the DHHS guidelines, which were updated in 2012 and now recommend offering ART to all HIV-infected persons regardless of CD4 count.[11]

After the results of HPTN 052 were reported, 484 HIV-infected participants in the delayed-treatment arm who had not initiated ART were offered the opportunity to begin treatment; 387 accepted.[17] ART must be accepted by as many HIV-infected persons as possible to achieve its potential preventive impact.[18]

The follow-up results of HPTN 052 indicate that some HIV-infected persons will decline ART despite their awareness of its benefits, at least with respect to the reduced risk of viral transmission to an uninfected partner.

HPTN 052 has encouraged other studies of early ART. For example, the Strategic Timing of Antiretroviral Treatment (START) trial is currently recruiting participants to determine the medical benefits of starting ART when the CD4 count is >500 cells/mm^3 in HIV-infected persons.[19]

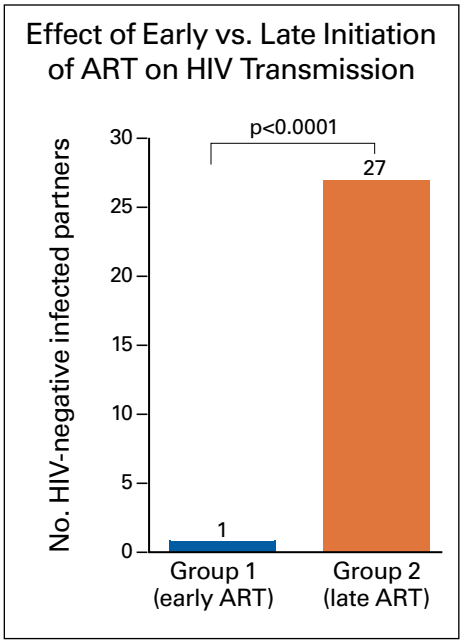

Figure 1. ART initiation substantially protected HIV-negative sexual partners from acquiring HIV infection (Group 1: early treatment group—only 1 partner infected, with a 96% reduction in risk of HIV infection; Group 2: late treatment group—27 partners infected by the HIV-infected participant). The difference was statistically significant (P<0.0001). (Adapted from Cohen 2011)

ART for all HIV-infected persons appears to represent a paradigm shift in thinking about HIV treatment. Historically, we have treated infectious diseases when they are diagnosed. HIV was an exception because of initially limited therapeutic options, drug toxicities and side effect profiles, pill burden, and rapidly developing resistance. However, these areas have improved substantially, and HIV treatment should be initiated as early after diagnosis as feasible.

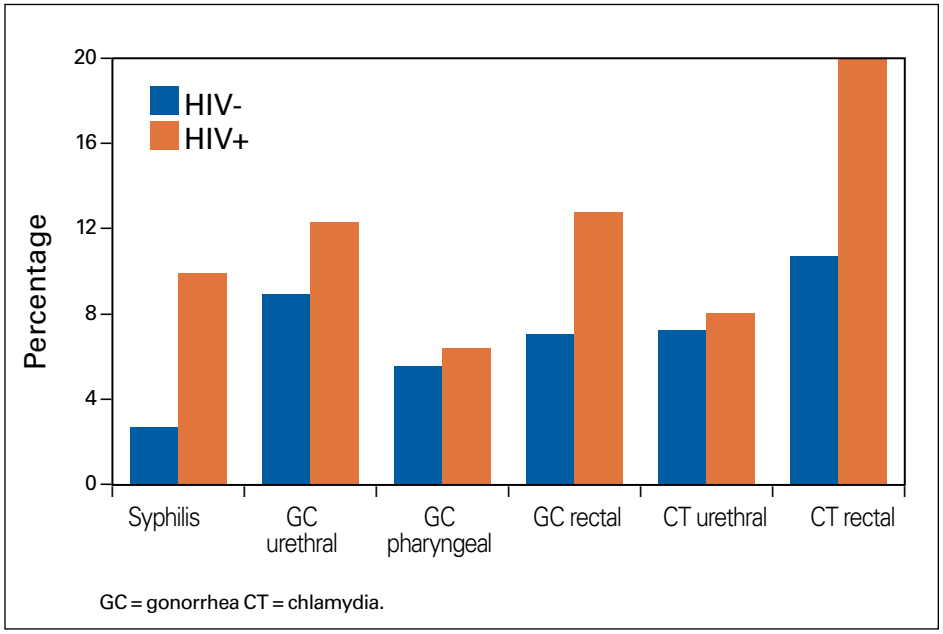

Figure 2. HIV-infected MSM: higher proportion of all STDs vs. HIV-uninfected MSM. (Source: STD Surveillance Network [SSuN], 2011)

Other HIV Transmission Interventions

ART initiation is only one component of HIV care. HIV care also includes early diagnosis, linkage to care, adherence to ART, and retention in care.[20] For these goals to be achieved, we must first communicate clearly with our patients, helping assure a safe, wellness-oriented, and caring environment from the day of diagnosis.

We must also work with other care providers (mental health workers, addiction specialists, registered dieticians, and other specialists) to offer patients a more holistic approach and ensure the best outcome.

In 2012, the International Association of Physicians in AIDS Care (IAPAC) published guidelines for improving and monitoring ART adherence and entry into and retention in care.[21] IAPAC added the cautionary note that retaining patients in care is essential to providing all HIV-infected persons with ongoing treatment, including those not yet on ART, and poor retention in care is associated with decreased likelihood of receiving ART, high rates of ART failure, increased risky behavior facilitating HIV transmission, increased rates of hospitalization, and decreased survival.[22]

Several tools and interventions for improving ART adherence and retention in care currently are under development,[23,24] including interactive text messaging and online peer-to-peer social support.[25,26]

Although we are primarily discussing prevention of transmission by focusing on the HIV-infected person, it should be mentioned that, under appropriate circumstances, HIV-negative persons at risk for an acute infection of HIV should have the option of post-exposure prophylaxis (PEP) with currently recommended antiretroviral agents. Pre-exposure prophylaxis (PrEP) may be an option for HIV-negative persons who are at ongoing, increased risk for HIV acquisition.

STD Screening

Equally important is the need to screen sexually active HIV-infected patients regularly for sexually transmitted diseases (STDs), which increase the risk of transmitting HIV directly and are associated with risky sexual behaviors that contribute to HIV transmission (**Figure 2**). We review the medical records of our new patients to identify prior morbidity indicators including signs of risky sexual behavior such as previously diagnosed STDs. This is particularly important because syphilis and antibiotic-resistant gonorrhea are increasing, especially among HIV-infected men who have sex with men (MSM).[27-30]

Ongoing Risk-Reduction Discussions

HIV providers should:

- Offer brief prevention messages at every visit.
- Create a safe environment for patients to discuss intimate sexual and other risk behavior; without this information we cannot assess actual risk.
- Provide an interaction in which, in addition to medical co-morbidities, we are able to address co-morbid factors affecting adherence such as mental and behavioral health issues, substance abuse, social and economic challenges, and other personal obstacles (utilizing other care providers and case management can be crucial here).
- Help patients disclose information we may not consider or know to ask about, but which, nevertheless, is affecting patients' ability to maintain adherence and goals by asking open-ended questions about issues that are known to increase the risk of HIV transmission such as drug use.
- Maintain continuity of care so that, when changes in status occur (medication change, new co-morbid diagnosis, life stressor, etc.), the change doesn't compromise care or increase risk profile.
- Educate patients about the effects of STDs on their health status and potential for transmission of HIV to their partners.

Conclusion

Preventing new HIV infections is a primary goal of the US National HIV/AIDS Strategy. Clinicians should proactively incorporate into their practices the additional tools and interventions provided by new research, continue to search for innovative and interactive ways to reach out to communities at high risk for HIV acquisition, and optimize the care we currently provide those who are already infected to achieve this important goal. HIV

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Screen All Baby Boomers for Hepatitis C

BY JULIE STOLTEY, M.D., M.P.H, RACHEL MCLEAN, M.P.H, AND KYLE RIZZO

THE UNITED STATES PREVENTIVE SERVICES TASK FORCE (USPSTF) published its final hepatitis C virus (HCV) testing guidelines in June 2013 and issued a grade B recommendation in support of one-time, universal HCV screening for all individuals born during 1945-1965.[1]

The "baby boomers" members of this birth cohort account for 76 percent of all HCV cases nationally and 60 percent of newly reported HCV infections in California.[2, 3] HCV is the most common reason for liver transplantation and the leading cause of hepatocellular carcinoma in the United States.[4] In California, HCV-related hospitalization charges have increased from $1.6 billion in 2007 to $2.3 billion in 2011.[5] Nationally, HCV-related deaths have now surpassed deaths related to HIV.[6]

Approximately 25 percent of those infected with HIV are co-infected with HCV. HIV infection can lead to more rapid liver disease progression and higher risk of cirrhosis, end-stage liver disease, liver cancer, and liver-related death in co-infected people.

The USPSTF also has issued a grade B recommendation for clinicians to provide HCV screening to persons at risk of HCV infection, including persons with a history of blood transfusions prior to 1992, and to provide periodic screening to persons with continued HCV risk, such as injection drug users.[1]

Of particular interest to patients, clinicians, and health plans, the Patient Protection and Affordable Care Act requires health plans to cover preventive services with a USPSTF grade 'A' and 'B' without patient cost-sharing.

The Centers for Disease Control and Prevention (CDC) published updated HCV testing guidelines in August 2012, also recommending one-time, universal screening for HCV among persons born during 1945-1965.[2] The new CDC guidelines supplement prior guidelines, which recommend HCV testing in the following groups:[2, 7]

- Persons with behavioral risk factors, including those who ever injected illegal drugs, including just once many years ago;
- Individuals with selected medical conditions, including those with unexplained persistently elevated alanine aminotransferase (ALT) levels; those who ever received long-term hemodialysis; recipients of transfusions or organ transplants before 1992 or clotting factor concentrates made before 1987; and HIV-positive individuals;
- Individuals with a recognized exposure, such as children born to HCV-positive mothers or healthcare workers who have sustained needle sticks involving known HCV-positive blood.

The updated USPSTF and CDC recommendations have important clinical and public health implications, including the potential to increase the proportion of persons with HCV who are aware of their infection and may be linked to care.

In clinical settings, a testing recommendation based on date of birth could facilitate the incorporation of automated HCV antibody testing prompts into electronic health records. Likewise, risk-based screening could improve access to testing and linkages to care for underserved populations, including injection drug users.

While beyond the scope of the CDC and USPSTF recommendations, future interferon-sparing treatment regimens may make HCV easier to treat—and cure—in a primary care setting.[8] However, the potential for increased HCV screening, diagnosis, and linkages to care can only be realized if these recommendations are widely adopted in clinical settings.

The California Department of Public Health encourages primary care providers and other clinicians in California to implement USPSTF and CDC screening guidelines for one-time HCV screening for persons born during 1945-1965 and routine HCV screening for other persons at increased risk for HCV infection, including injection drug users. HCV testing should also be offered to all people with HIV infection.

For more information on HIV and HCV co-infection, including clinical management guidelines, visit the CDPH, Office of Viral Hepatitis Prevention, Viral Hepatitis Prevention and Control Guidelines web page: http://www.cdph.ca.gov/programs/Pages/ViralHepatitisPreventionControlGuidelines.aspx. HIV

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BY HOLLY KILNESS PACKETT, MA

Health Reform & My Patients

How to talk with your patients about changes in care and help them choose the right option

STARTING IN 2014, many of your patients will have new options to receive health coverage through new systems in their state. To make sure your patients do not have interruptions in care, or lose access to you as their provider, here are steps that HIV providers should take over the coming months.

What is changing for your patients?

If your patients already have health insurance coverage that fulfills the individual mandate requirement, then they do not need to obtain additional insurance or change insurance coverage. If they do not have insurance and live in a state that is expanding Medicaid, they may be newly qualified for the state Medicaid program, or for Medicaid managed care programs in the state. If they do not have health insurance coverage, and do not qualify for Medicaid, they may be able to purchase health insurance in the new State Insurance Exchanges Marketplaces.

Connecting Your Practice

HIV care providers will need to make an effort to connect to the new systems of care in their state as fully as possible to retain access to their patients after January 1, 2014.

In all states, it is especially important for HIV providers to be fully connected to the Medicaid program in his or her state.

Connecting to Medicaid

In states that are expanding Medicaid, a large portion of the HIV patient population will likely gain new access to the state Medicaid program through the expansion and become Medicaid patients. Even in states that are not yet expanding Medicaid, some new eligible beneficiaries are likely to be identified during the enrollment processes.

It is vital that HIV providers contact their state or local Medicaid office and make sure they have current contact information, as well as accurate information on type of provider, specialty, certifications, medical facility, patient population served, etc. This is to ensure that appropriate referrals are made within the program and patient access to their preferred provider is maintained during the transition period.

Many states are initiating or expanding enrollment of Medicaid beneficiaries in prepaid managed care plans. In states where this is occurring, it is important for health care providers to consider contracting with each Medicaid managed care plan operating in their service area to be included in their provider network and continue to access to their patients enrolling in those plans.

Connecting to State Insurance Exchanges

Starting in 2014, every state will have a new State Insurance Exchange (Marketplace) where individuals who lack insurance can purchase new Qualified Health Plans (QHPs). Some states have established their own state-run exchange, some are partnering with the federal government, and some will have a federally-facilitated exchange. Each state's exchange will be different, so it is important to learn about the specific insurers and plans operating in your state.

Health care providers will need to contract with each insurer offering plans in the exchange separately to be included in their provider network. This process is similar to contracting with private employer-based health plans prior to the Affordable Care Act.

Plans in the exchanges are required to demonstrate provider network sufficiency by contracting with at least one of each type of "Essential Community Provider" (ECP) in their geographical area, and at least 20 percent of all the ECPs in a county. An ECP is defined as a providers with experience caring for medically underserved populations or low-income populations. A list of automatically designated ECPS is available from CMS, but includes Ryan White HIV/AIDS providers, FQHCs, and safety net hospitals among others.

Inform Your Patients about Your Network

It is essential for HIV providers to inform patients about which networks they are included in – both for insurance plans offered in the exchanges and Medicaid Managed Care plans. Otherwise, patients with new coverage options may unintentionally select an option where their preferred provider is not in-network.

Helping Your Patients Enroll

Many systems have been set up to help with patient enrollment nationwide. Patients can take advantage of a single-form application to determine what programs and assistance they qualify for under health reform. Enrollment will be available by phone, Internet, and in-person. Patient Navigators and Certified Enrollment Counselors are available in every state to help patients enroll in both the health insurance plans offered in the state Insurance Exchanges or in the Medicaid program. HIV providers may want to consider designating a member of the care team as a patient enrollment counselor and take advantage of training on enrollment offered by HHS.

However, it is important to exercise caution in urging patient enrollment in new coverage options. HIV patients should thoroughly review the details of different options and plans to determine which is best for their individual health needs.

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What Plan is Best for Your Patients

Patients are also likely to ask their providers which plan is best for them. Providers can offer their patients key guidance on this subject. Some basic considerations providers may wish to discuss with their patients who are selecting new coverage are:

1.Does your HIV provider participate in a health plan available to you?

Many HIV positive patients consider their relationship with their HIV provider to be critical in ensuring access to high quality HIV care. If a provider does not participate in a selected private insurance plan, patients must pay additional out-of-pocket costs for going "out of network" to receive services from that provider.

Also, some HIV providers are considered "specialists" within some plan networks, and patients may have to obtain a referral or get authorization from the insurer before specialist services are authorized. Plans may put limits on the number of visits that can be made to a specialist.

2. What are the limitations and cost-sharing for office visits?

HIV patients must see their provider regularly to maintain regular care, receive prescriptions for HIV and other medications, and monitor their disease and treatments. Patients should consider the limits placed by insurers on the numbers of medical visits that can be made per month or year. They should also consider the cost–sharing requirements such as co-pays and deductibles, on office visits.

3. What are the limitations and cost-sharing requirements for lab tests?

HIV care commonly involves regular laboratory monitoring to assess the effect of antiretroviral medications on CD4 count and viral load, check for drug resistance, and monitor other changes in disease progression. Patients should determine if an insurer limits or excludes lab procedures for HIV-related tests, including CD4, viral load, genotyping, and phenotyping. Patients should also familiarize themselves with cost–sharing requirements, such as co-pays and deductibles on lab tests.

4. Are my medications on the plan's prescription drug formulary?

HIV positive patients should identify whether their particular drug treatment regimen is covered by a plan. They should also identify cost-sharing requirements such as co-pays, or deductibles associated with their medications. Patients should also be aware of requirements for prior authorization or generic drug substitutions.

5. Will the insurance plan cover my other medical conditions?

Some HIV positive patients have other medical conditions that have particular requirements in terms of care or treatments. Patients should seek advice from their provider on any other considerations they may need to take into account when selecting a health insurance plan. HIV

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BY SUSAN LeLACHEUR, PA

Why My Work Matters

IN 1987, "TOMMY" WAS 21 YEARS OLD AND HAD JUST BECOME A PARTICIPANT in a new research study to see if the combination of AZT plus acyclovir was better than AZT alone in slowing the progression of AIDS in patients with a history of opportunistic infection or a CD4 of ≤200 cells/cm².

As clinicians, we were not too surprised when, within two weeks of starting the medication, he came down with PCP (then *pneumocystis carinii*, now *pneumocystis jiroveci*). We were able to keep him on his medication during his hospital stay, and he recovered and remained a participant in the study. This was particularly important because the study offered patients free access to otherwise costly medication, and that meant a lot to Tommy.

But research studies also have been known as a source of inequity and abuse, particularly towards African-Americans, a community of which Tommy was a member.

On his first clinic visit after the hospitalization, I welcomed his mother and two brothers into my office. I let them vent their fear and anger related to the study, and when they were done, let them know that he was receiving the only medicine we currently had for HIV: AZT with no placebo. Only the acyclovir component might be placebo.

I acknowledged that only 15 years earlier, in 1972, the atrocity of the Tuskegee syphilis study came to light and its impact was still a reality. I assured them that I would personally guarantee that Tommy would always be treated with the very best care we had to offer as long as I had anything to say about his treatment. They must have believed me, because Tommy remained on that study and continued to participate in other studies as new medications came along.

As a physician assistant (PA), I was initially hired to help with clinical research work because PAs have clinical acumen, but also a comprehensive approach to collecting and documenting patient history and physical examination. My physician supervisors were excellent clinicians, but lacked the time for the comprehensive evaluation and documentation required by the research studies. In those days, medications available through research trials were much sought after as so little was available otherwise, so mine was a prime position from which to observe the unfolding science of HIV and its treatment.

I saw Tommy last week in clinic; it was all I could do to hold back tears of joy. For me, he is a walking, talking, smiling reminder of what has been accomplished in HIV treatment, and why my work matters.

PAs across the country have been caring for patients with HIV since the beginning of the epidemic. We work in community clinics, prisons, public health clinics, academic medical centers and private practices.

With my PA colleagues at Whitman Walker Health in Washington, DC, I practice as a team with our supervising physicians, as well as with nursing, adherence counselors, pharmacy, dental, mental health and often legal services. HIV care is an area where the team approach has taken hold, often because of the complexities of our patient population. Like Tommy's family, many people may be distrustful of the healthcare system. They may need frequent visits at the outset of care and during other times of increased need. Working in a PA/physician team can allow a physician to extend his or her ability to provide the level of care these complex patients require.

I saw Tommy last week in clinic, and as usual each time I see him, it was all I could do to hold back tears of joy. For me, he is a walking, talking, smiling reminder of what has been accomplished in HIV treatment, and why my work matters. I wonder what might have happened if his clinician that first day had reacted differently to his family. He, like many others, might have run off feeling frightened.

There are many reasons patients are lost to follow-up, but I hope that a good PA may sometimes be one reason they come back. HIV

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AAHIVM Health Reform Resource Center for HIV Providers Now Available!

THE RESOURCE CENTER assists practitioners in learning about the specific developments in the health care systems in their state including:

- **Information on State Insurance Exchanges (Marketplaces)**
- **Summary on Medicaid Managed Care plans offered in the states**
- **Update on Medicaid Expansion Options**
- **Complete list of Qualified Health Plans, such as Plan Premiums Pricing, and the Tax Credits available**
- **Find out about the Essential Health Benefits covered for beneficiaries**
- **Learn about Patient Enrollment efforts in your region, and how the Patient Navigators in your state can help.**

Visit **www.aahivm.org/healthreformresourceforproviders**.

IS YOUR PRACTICE TECH SAVVY?

Apply for the 2014 AAHIVM/Institute for Technology in Health Care HIV Practice Award!

For the third year, the American Academy of HIV Medicine is proud to announce the opportunity for HIV practices using innovative models of technology to apply for two $10,000 unrestricted awards.

Last year's award recipients were Dr. Melissa Badowski of the University of Illinois Medical Center for her provision of direct patient care to incarcerated patients through an HIV telemedicine clinic, and to Dr. Nadia Dowshen of the Children's Hospital of Philadelphia for her prototype of a smart phone-based application to improve medication adherence among youth living with HIV/AIDS.

The award criteria, as well as an application form, will be on the Academy website (www.aahivm.org) during the application enrollment period from October 15 to December 1.

This award is supported by a grant from The Institute for Technology in HealthCare. It is a non-profit organization, located in Washington, DC. The Institute for Technology in HealthCare is concerned with the use of technology to benefit health care. For more information about ITHC, please visit the website at www.ithcawards.org

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