THE AMERICAN ACADEMY OF HIV MEDICINE www.aahivm.org OCTOBER 2017
Patient Care, Practice Management & Professional Development Information for HIV Care Providers

HIV Specialist

HIV By the Numbers

See the video series and gain access to resources & tools at:

HELPSTOPTHEVIRUSPRO.COM

GILEAD

THE AMERICAN ACADEMY OF HIV MEDICINE

HIV Specialist

Patient Care, Practice Management & Professional Development Information for HIV Care Providers

PUBLISHER
The American Academy of HIV Medicine
1705 DeSales St., NW, Suite 700
Washington, D.C. 20036
202-659-0699 • 202-659-0976
info@aahivm.org • www.aahivm.org

CONTENTS

October 2017 | Volume 9, No. 3 | **www.aahivm.org**

FEATURES

DEPARTMENTS

COVER:STOCK

BY JAMES M. FRIEDMAN, MHA
Executive Director, AAHIVM

My Lucky Number


James M. Friedman

THIS ISSUE OF *HIV SPECIALIST* FOCUSES ON HIV BY THE NUMBERS. Well, I have a number for you. I recently celebrated my tenth anniversary as the Executive Director of the Academy. And that anniversary reminded me how fortunate I have been to have worked with a group of smart, dedicated, hardworking, healthcare professionals—our members.

From day one, I recognized how special you are. You work exceptionally hard to stay up-to-date on the best therapies for your patients. You find resources to care for patients who have none. You care not only for your patients, but also for one another. Many of you find time to volunteer in your community and to the Academy, and for that, I am especially grateful.

Let me give you just one recent example. In mid-September, the United States was hit with two mammoth hurricanes, Harvey in Texas and Louisiana, and Irma in Florida. Our Deputy, Bruce Packett, suggested we reach out to our members in those states to determine whether some needed help to care for their patients and if others could provide help to those displaced. I was gratified to see how many of you volunteered to provide assistance.

And then, a couple of weeks later, Puerto Rico and the U.S. Virgin Islands were hit hard by Hurricane Maria. With many of the islands virtually destroyed, we made a plea to our members and others to help support our colleagues by financially donating to the HIV care community in the hardest hit areas. To date, we've raised nearly $5,000.

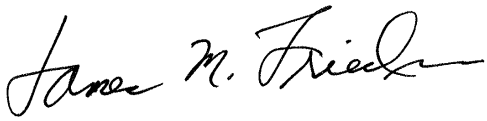
I am also full of gratitude to see how many of you volunteer to serve on AAHIVM chapter, programmatic and departmental committees, as well as on our national board. Simply put, our members are number one.

This issue of *HIV Specialist* includes many interesting articles focused on important numbers. Gary Spinner, Secretary of our National Board, has written an updated look on the new numbers released on the treatment cascade. Two very interesting articles on PrEP by Dr. Phillip Bolduc and Dr. John Scheider appear in this issue. Both articles recognize that we need to get our PrEP subscription numbers up. And Emily McCloskey of the National Association of State and Territorial AIDS Directors (NASTAD) has provided a Federal funding landscape, numbers that keep us guessing and keep changing.

Jeff Kirchner, our Chief Medical Officer, has provided a summary of new numbers from studies released at the recent IAS meeting. And finally, Carl Schmidt, Deputy Director of The AIDS Institute and Tyler Andrew TerMeer, Executive Director of Cascade AIDS Project, shine a spotlight on the number of patients that are discriminated against in regards to their HIV care.

I'm especially pleased to see an article in this issue on the Los Angeles HIV Public Health Fellowship Program. The goal of this fellowship is to grow the number of HIV care providers in the future.

All of these numbers are critical to providing quality HIV care to the millions of people living with HIV. HIV



In the NEWS

Study: Tick Saliva May Help HIV Patients with Heart Disease

A STUDY PUBLISHED IN *SCIENCE TRANSLATIONAL MEDICINE* found that treatment with a compound isolated from tick saliva, ixolaris, can stem some of the side effects of chronic infection in HIV patients with cardiovascular or neurological complications.

The risk of heart attack and stroke is nearly double that of the general population, according to a study at Northwestern Medicine (https://news.northwestern.edu/stories/2016/12/hiv-patients-have-nearly-twice-the-heart-attack-risk/), including people whose virus was undetectable.

Chronic inflammation is suspected as the cause of cardiovascular disease, and the research team for the study reported in *Science Translational Medicine* found that people with HIV share an elevated number of immune cells that continue to express a protein that triggers blood clotting and inflammation even when HIV is under control.

In that study, human blood samples were exposed to ixolaris, a synthetic version of the small molecule found in the saliva of the Ixodes scapularis tick, and researchers found that the protein activity was blocked. A small group of lab monkeys with an early infection of SIV, the primate form of HIV, were treated with ixolaris. Levels of inflammatory proteins were lowered with the treatment.

Ixodes scapularis tick

Published August 30, 2017, the study can be found at http://stm.sciencemag.org/content/9/405/eaam5441.

New Survey Ranks Diarrhea as Top Gastrointestinal Complaint of HIV Patients

A NEW SURVEY BY NAPO PHARMACEUTICALS, INC., a human health company developing and commercializing novel gastrointestinal prescription products from plants used traditionally in rainforest areas, concludes that the number one gastrointestinal (GI) complaint for people living with HIV/AIDS is diarrhea.

The study of 271 U.S. board certified gastroenterologists was conducted for Napo by Schlesinger Associates, a leading global data collection provider specializing in online surveys.

"While it's typically not the main reason patients come to see me, frequently my patients with HIV inform me that they suffer from chronic diarrhea. Worth noting, diarrhea appears to be more common in patients who have been HIV-positive for several years; this is most likely due to HIV enteropathy, which is the effect of the virus on the lining of the intestine," said Dr. Maurizio Bonacini, associate professor of clinical medicine at the University of California, San Francisco. "Diarrhea is a significant problem in many HIV patients, and unfortunately, they think there is nothing they can do and that they just have to live with it."

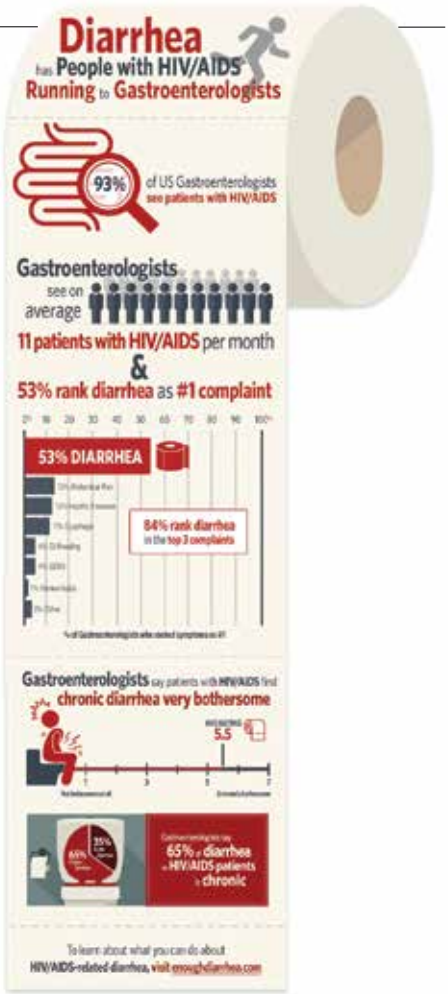
Highlights of the survey of U.S. board certified gastroenterologists include:

- 93 percent of U.S. gastroenterologists see patients with HIV/AIDS in their practice.
- 84 percent rank diarrhea in the top three complaints of HIV/AIDS patients.
- 53 percent indicated diarrhea is the number one complaint in HIV/AIDS patients.
- 65 percent of diarrhea in HIV/AIDS patients is chronic.

Only 53 percent of gastroenterologists were aware of Mytesi® (crofelemer), the only drug that has been specifically studied in and FDA-approved for use in managing diarrhea in people living with HIV.

Launched by Napo in October 2016, Mytesi® is the only antidiarrheal studied in and U.S. FDA-approved for the symptomatic relief of noninfectious diarrhea in adults living with HIV/AIDS on antiretroviral therapy (ART).

For more information, please visit www.mytesi.com.



In the NEWS

Gilead Awards $7.5 Million in Grants for HIV Cure Research

GILEAD SCIENCES, INC. has announced the second round of recipients of its HIV cure grants program, providing $7.5 million to support five additional HIV cure research initiatives led by top academic institutions and focused on translational research and efficacy studies in preclinical models.

"Finding a cure for HIV is a formidable challenge to the scientific community. Together with our newest grant recipients, all of whom have a record of excellence in their research, we can take collective steps to help end this devastating epidemic," said William Lee, Ph.D., executive vice president, research, Gilead Sciences.

The following organizations and corresponding projects will receive grants from Gilead to help fund their activities:

- University of California, San Francisco, School of Medicine, Microbiology and Immunology, Chan Zuckerberg Biohub—Alexander Marson, M.D., Ph.D.—*An Integrated CRISPR Platform to Discover Regulators of HIV Latency in Primary Human T Cells*
- Institute of Human Genetics, French National Center for Scientific Research (CNRS) and University of Montpellier—Monsef Benkirane, Ph.D.—*Paving the Way Towards Elimination of HIV Persistent CD4T Cell In Vivo*
- University of Massachusetts Medical School—Abraham L. Brass, M.D., Ph.D.—*A CRISPR/Cas9 Screen to Discover HIV-1 Latency Factors*
- Frederick National Laboratory for Cancer Research, AIDS and Cancer Virus Program—Jeffrey D. Lifson, M.D.—*TLR Ligand Augmented, Tissue Homing AIDS Virus-Specific Adoptive Cell Therapy to Target Viral Reservoirs*
- Dana-Farber Cancer Institute—Joseph G. Sodroski, M.D.—*Unlocking HIV-1 Env to Deplete Viral Reservoirs*

The initial round of Gilead's giving program awarded $22 million to 12 projects in January 2017.

Chronic Pain Common in People Living with HIV

BECAUSE ONGOING PAIN IS A SIGNIFICANT PROBLEM that affects 39 to 85% of people living with HIV, everyone with the infection should be assessed for chronic pain, recommend guidelines released by the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA) and published in the journal *Clinical Infectious Diseases*.

Those who screen positive should be offered a variety of options for managing pain, starting with non-drug treatment such as cognitive behavioral therapy, yoga and physical therapy, suggest the first comprehensive guidelines on HIV and chronic pain.

"Because HIV clinicians typically are not experts in pain management, they should work closely with others, such as pain specialists, psychiatrists and physical therapists to help alleviate their patients' pain," said Douglas Bruce, MD, MA, MS, lead author of the guidelines, chief of medicine at Cornell Scott-Hill Health Center, and associate clinical professor of medicine at Yale University, New Haven, Conn.

"These comprehensive guidelines provide the tools and resources HIV specialists need to treat these often-complex patients, many of whom struggle with depression, substance use disorders, and have other health conditions such as diabetes."

The guidelines recommend all people with HIV be screened for chronic pain using a few simple questions:

- How much bodily pain have you had during the week?
- Do you have bodily pain that has lasted more than three months?

Those that screen positive should undergo comprehensive evaluation, including a physical exam, psychosocial evaluation and diagnostic testing. Nearly half of chronic pain in people with HIV is neuropathic (nerve pain), likely due to inflammation or injury to the central or peripheral nervous system caused by the infection. Non-neuropathic pain typically is musculoskeletal, such as low-back pain and osteoarthritis in the joints.

HIV specialists should work with an interdisciplinary team to offer multi-modal treatment, according to the guidelines, which recommend offering alternative, non-pharmacological therapies first, including cognitive behavioral therapy, yoga, physical and occupational therapy, hypnosis and acupuncture. If medication is needed, the guidelines recommend beginning with non-opioids, such as gabapentin (anti-seizure medicine) and capsaicin (topical pain reliever made from chili peppers), both of which help with nerve pain.

The online version of the guidelines includes an extensive list of resources for physicians to reference to help them treat the patients comprehensively.

In addition to Dr. Bruce, the guidelines panel includes: Jessica Merlin, Paula J. Lum, Ebtesam Ahmed, Carla Alexander, Amanda H. Corbett, Kathleen Foley, Kate Leonard, Glenn Jordan Treisman and Peter Selwyn.

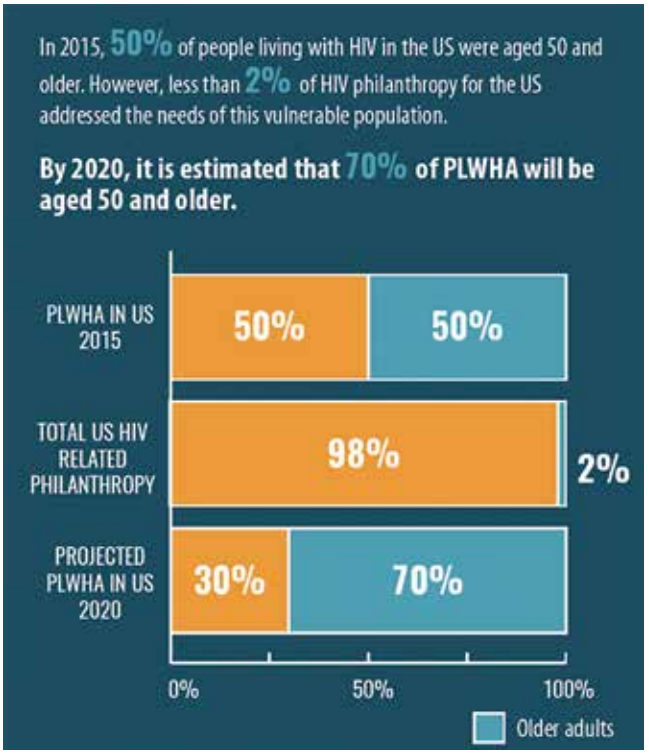
The full guidelines are available free on the IDSA website at www.idsociety.org.

HIV-focused Giving Fails to Address Needs of Over-50 PLWH

PHILANTHROPIC DATA SHOWS AN "ALARMING GAP" in resources devoted to the needs of people living with HIV (PLWH) who are age 50 and older, according to Funders Concerned About AIDS (FCAA).

In a report presented at the annual AIDS Philanthropy Summit, FCAA said that while fully half of PLWH are 50 or older, only 2% of the country's HIV-focused philanthropy addressed the needs of this growing group.

"Due to enormous advances in treatment, people are able to live far longer; so much so that by the year 2020, 70 percent of those living with HIV in the US will be over the age of 50," said John Barnes, FCAA executive director.



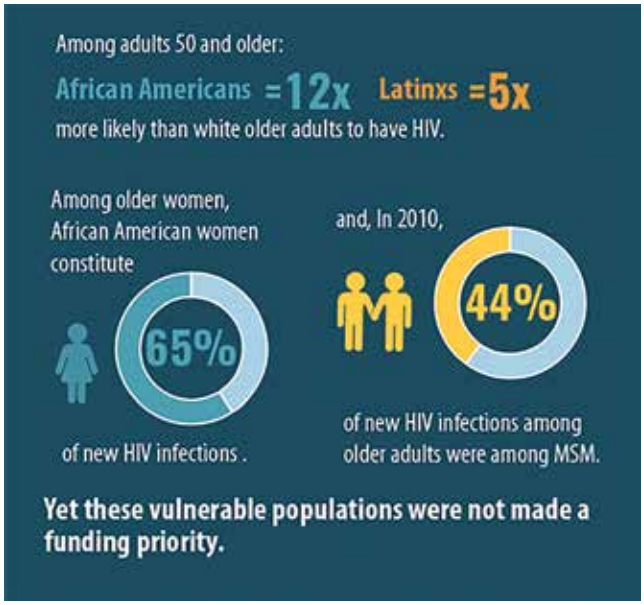
"This is good news, but it brings with it unique complexities. Philanthropic funding is a critical source of support and is essential to ensuring that we adequately address the needs of older HIV-positive adults."

Other key findings from FCAA's report include:

- Nearly $5 million in HIV-related philanthropy addressed the needs of older adults living with HIV/AIDS. Though impressive, that is only 2% of total U.S. HIV-related philanthropy.
- According to the CDC, older adults account for 17% of new HIV infections, yet only 7% of HIV philanthropy addressed prevention for this population.
- Economically disadvantaged/homeless and transgender people received the largest percentage of philanthropic funding (10% each).
- Philanthropic funding was used to provide social services (30%), treatment (26%) and research (15%).

"Supporting an aging HIV positive population is, in many ways, uncharted territory," said Barnes. "Conquering new frontiers requires resources. The philanthropic sector has a long history of helping to bridge such gaps in the past; we are calling upon the sector to do so now and help us adequately support older individuals living with HIV and AIDS."

The complete study can be found here: http://www.fcaaids.org/wp-content/uploads/2017/09/agingInforgraphic2017-FINAL.pdf.



In the NEWS

Janssen Announces Pivotal Phase 3 Study Results for Investigational Darunavir-Based Single-Tablet Regimen

JANSSEN PHARMACEUTICA ANNOUNCED RESULTS from the pivotal Phase 3 EMERALD study which were published online in *The Lancet HIV* and presented at IDWeek 2017 in San Diego. The study demonstrated that switching to the investigational single-tablet regimen (STR) containing darunavir 800 mg, cobicistat 150 mg, emtricitabine 200 mg and tenofovir alafenamide 10 mg (D/C/F/TAF) was non-inferior to continuing treatment with a boosted protease inhibitor (PI) plus emtricitabine and tenofovir disoproxil fumarate in human immunodeficiency virus type 1 (HIV-1) positive, virologically suppressed adults.

There were no observed resistance associated mutations (RAMs) to study drugs through 48 weeks. If approved in the U.S., D/C/F/TAF would be the only complete regimen that may deliver the potential adherence benefit of a once-daily STR with the durability and high genetic barrier to resistance of darunavir and the demonstrated bone and renal safety profile of TAF.

"When people who are diagnosed with HIV don't adhere to their treatment regimen, they can build up drug resistance, which can render their treatment–and even an entire class of treatments—ineffective," said Joseph Eron, MD, professor of medicine and director, clinical core, University of North Carolina Center for AIDS Research, Chapel Hill, NC.

"The findings from the EMERALD study bring us one step closer to being able to offer those who live with HIV and struggle with adherence an option that combines the efficacy and high genetic barrier to resistance of darunavir with the demonstrated safety profile of tenofovir alafenamide into a single tablet."

Study investigators did not observe any resistance-associated mutations related to any study drug.

About the EMERALD clinical trial

The Phase 3 EMERALD study is a randomized (2:1), open-label, international, multi-center, parallel-group, non-inferiority, 48-week study evaluating the efficacy and safety of switching to D/C/F/TAF versus continuing with a boosted PI (lopinavir/ritonavir, atazanavir or darunavir boosted by either ritonavir or cobicistat) plus emtricitabine/tenofovir disoproxil fumarate in adult HIV-1 infected patients who are virologically suppressed (viral load [VL] <50c/mL for ≥2 months and had no more than one VL ≥50c/mL and <200 c/mL allowed within 12 months before screening).

The FDA-stipulated primary endpoint of the trial is the proportion of patients with virologic rebound (confirmed VL≥50c/mL or premature discontinuations with last VL≥50c/mL) cumulative through week 48 (non-inferiority margin=4%). 1,141 patients were randomized and treated as follows: D/C/F/TAF (n=763); control (n=378). Inclusion criteria to be enrolled in the trial included absence of history of virologic failure on darunavir, and if historical genotype was available, absence of darunavir RAMs.

Through 48 weeks, cumulative virologic rebound was 2.5% (D/C/F/TAF, n=19) vs. 2.1% (control, n=8) with 12/19 in D/C/F/TAF and 4/8 in the control group re-suppressed (<50 c/mL) by the end of the evaluation period. Additionally, at week 48, virologic suppression was 94.9% (D/C/F/TAF) and 93.7% (control), and virologic failure occurred in 0.8% and 0.5%, respectively, with no discontinuations for virologic failure and no observed RAMs to any study drug through 48 weeks.

D/C/F/TAF also demonstrated similar safety versus control group through 48 weeks. Rates of discontinuations due to adverse events (AEs) were 1.4% (D/C/F/TAF) vs. 1.3% (control); Grade 3-4 AEs were 6.8% (D/C/F/TAF) vs. 8.2% (control); and serious AEs were 4.6% (D/C/F/TAF) vs. 4.8% (control). There were no deaths in either arm of the study. The most common AEs were nasopharyngitis (D/C/F/TAF 10.6% vs. control 10.3%), upper respiratory tract infection (10.6% vs. 10.3%), and diarrhea (7.9% vs. 4.2%).

On September 25, 2017, the European Commission approved the use of D/C/F/TAF for the treatment of HIV-1 infection in adults and adolescents aged 12 years and older with body weight of at least 40 kg. This approval allows Janssen to market D/C/F/TAF in all member states of the European Union and the European Economic Area.

In the U.S., D/C/F/TAF is an investigational product. A new drug application (NDA) was filed on September 22, 2017 to the U.S. Food and Drug Administration (FDA), and is currently awaiting approval. The NDA was filed for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older and was based on the results from two pivotal Phase 3 studies, EMERALD and AMBER. AMBER is a 48-week, double-blind, non-inferiority study evaluating the efficacy and safety of D/C/F/TAF in antiretroviral therapy (ART) treatment-naïve patients. Phase 3 AMBER data through 48 weeks will be presented at the upcoming European AIDS Conference, October 25-27, 2017 in Milan, Italy.

For more information on the clinical trials please visit: www.clinicaltrials.gov.

48-Week Efficacy and Safety Results Presented for Ibalizumab

THERATECHNOLOGIES INC. HAS ANNOUNCED 48-week efficacy and safety results for ibalizumab in patients infected with multidrug resistant HIV-1 who completed the 24-week Phase III study (TMB-301) and continued treatment in the Expanded Access Program study (TMB-311). These data were presented at IDWeek 2017™ in San Diego (abstract #1686) Oct. 4.

Of the 27 patients who completed the 24-week treatment period of TMB-301 in the U.S., all entered TMB-311, where patients continued to receive ibalizumab at 800 mg every 2 weeks for up to 48 weeks. The virologic suppression observed at week 24 was sustained through week 48; median viral load reduction from baseline was 2.5log10 at weeks 24 and 48. In TMB-311, all 15 patients with an undetectable viral load at week 24 maintained suppression to week 48. Another patient in TMB-311 reached less than 50 copies/mL at week 48 after having a detectable viral load at week 24. A total of 17 patients (63%) achieved a viral load less than 200 copies/mL.

In TMB-311, ibalizumab plus optimized background regimen (OBR) was well tolerated; of the 27 patients in the study, 24 (89%) continued to receive treatment until week 48 and 3 patients discontinued early due to non ibalizumab-related reasons. No new or unexpected safety concerns emerged between weeks 24 and 48. The most common adverse reactions were diarrhea, dizziness, nausea and rash.

"The participants enrolled in the Phase III study were highly treatment experienced with limited antiretroviral options due to drug resistance. As clinicians treating these patients, having access to an agent with a novel mechanism of action was critical," said Dr. Brinda Emu, assistant professor of medicine, iInfectious diseases, Yale School of Medicine, New Haven, CT. "Seeing sustained virologic response out to 48 weeks is heartening and emphasizes the potential benefit that ibalizumab may bring to HIV patients in need of new treatment options."

About Study TMB-311

Of the 27 patients who completed the 24-week treatment period in TMB-301 in the U.S., 27 entered TMB-311, the ibalizumab Expanded Access Program, where patients continued to receive ibalizumab at 800 mg every 2 weeks for up to 48 weeks. Additionally, 59% and 33% of the patients in the study had exhausted at least three or four antiretroviral (ARV) classes, respectively, and 15% had HIV-1 resistant to all approved ARVs.

The Expanded Access Program is ongoing and enrolling patients. For more information about TMB-311 (NCT02707861), please refer to the ClinicalTrials.gov website (www.clinicaltrials.gov) or the study website (www.ibalizumab-eap.com).

Study: Smoking for PLWH More Likely Cause of Death than AIDS

A NEW MODELING ANALYSIS LOOKING AT THE RISK OF LUNG CANCER DEATH due to smoking for a person living with HIV concluded that "for people living with HIV who adhere to antiretroviral therapy (ART), smoking is a much greater threat to their health than HIV itself," reports HIV.gov.

In fact, those who continued to smoke were six to 13 times more likely to die from lung cancer than from traditional AIDS-related causes, depending on how much they smoked and their gender.

Today, people living with HIV (PLWH) who are diagnosed early, start HIV medical care and treatment, and achieve and maintain viral suppression are expected to live nearly as long as their HIV-negative peers. As a result, the causes of death among people living with HIV have shifted from AIDS-related to non-AIDS-related causes.

Over 40% of PLWH in the United States smoke cigarettes, according to several estimates, a rate two to three times greater than the general population. This risk reflects the fact that some groups of people who are at increased risk for HIV infection, such as gay and bisexual men and people who inject drugs, are more likely to smoke.

Combining their model-generated estimates with published epidemiological data on the number of people living with HIV in care in the United States, the authors project nearly 60,000 of the people will die from lung cancer deaths if smoking habits do not change. However, if just 20% of the current smokers quit, not only would their lung cancer risk decrease, but nearly 7,000 lung cancer deaths could be averted.

The NIH-supported study, "Lung Cancer Mortality Associated With Smoking and Smoking Cessation Among People Living With HIV in the United States," was led by Krishna P. Reddy, M.D., of the Massachusetts General Hospital and was published online in *JAMA Internal Medicine.*

BY JEFFREY T. KIRCHNER, DO, FAAFP, AAHIVS

Future Paradigm Shift in our Treatment of HIV Disease?

Updates from the 9th International AIDS Society Conference—Paris 2017

SINCE THE MID TO LATE 1990s, the standard of care for treating HIV disease with combination ART has included three agents—usually consisting of dual nucleoside reverse transcriptase inhibitors (NRTIs) with a boosted protease inhibitor (PI) or NNRTI. Over the past few years, integrase strand inhibitors (ISI) have become the recommended first-line treatment per the DHHS guidelines due to their excellent potency, tolerability, and in the case of dolutegravir—a high genetic barrier to resistance. Although there have been several small clinical trials using PI monotherapy or a boosted-PI and lamivudine, these have not been part of the DHHS HIV treatment guidelines. At the recent IAS Conference in Paris, data from several clinical trials were presented that likely will impact the future treatment of patients with HIV disease.

ANDES Study (Dual therapy versus Triple therapy with a boosted PI)

This is a randomized, open-label, phase IV study that compares darunavir/ritonavir (DRV/RTC) plus lamivudine (3TC) with DRV/RTV plus tenofovir/lamivudine in treatment-naïve patients. There were 145 patients enrolled who received either dual or triple therapy. The median CD4 cell count was 383 cells/mm3 and about 25% had viral loads >100,000 copies/ml. **At week 24, 94.7% of patients receiving dual therapy and 97% receiving triple therapy achieved viral loads of < 400 copies/mL.** Of note, those with high baseline viral loads (>100,000 copies) had a 100% response in both arms. The mean CD4+ increases were similar in both groups (206 vs 204 cells/mm3). This study preliminary shows that a combination of DRV/RTV in fixed-dose plus 3TC appears to be non-inferior to a standard three-drug regimen. The second phase of this study will include 190 additional participants, all who will be followed for at least 48 weeks. If confirmed, these data will provide further evidence supporting the efficacy of dual therapy using 3TC and a drug with a high genetic barrier to resistance such as darunavir.

Sued O, et al. Dual therapy with darunavir/ritonavir plus lamivudine for HIV-1 treatment initiation: week 24 results of the randomized ANDES study. J Int AIDS Soc. 2017; 20(suppl 5):104. Abstract MOAB0106LB.

PADDLE Trial (Dolutegravir plus lamivudine as initial therapy)

Figueroa presented 96-week data from the PADDLE trial done in Argentina. This is a proof of concept study that evaluated the efficacy, safety and tolerability of a dual-therapy regimen with dolutegravir plus lamivudine given once daily to treatment-naïve patients. Previous 48-week data presented in 2016 found that 90% (18/20) of patients reached the primary study endpoint of a viral load of <50 copies/mL. The 18 patients who completed the first part of the PADDLE study were included in this extension phase of an additional 48 weeks. **At week-96, 100% of patients maintained a plasma HIV-1 RNA below 50 copies/mL.** The mean CD4+ increase from baseline was 271 cell/mm^3, although there was no significant change in CD4 counts after 48 weeks. There were no new virologic failures, AIDS defining illnesses, or serious adverse events observed among the participants. Two large clinical trials are now underway to study this two-drug strategy. (see below).

M.I. Figueroa et al. Dolutegravir-Lamivudine as initial therapy in HIV-1 infected, ARV-naïve patients: 96 week results of the PADDLE trial. MOPED0287

ACTG A5353 (Dolutegravir plus Lamivudine in Treatment-Naïve Patients)

This is a phase 2, single-arm, study of dolutegravir and lamivudine in treatment-naïve HIV-patients. Entry criteria included a viral of ≥1000 but <500,000 copies/mL. There were 120 patients in this study of whom 87% were male. Baseline CD4 counts ranged from 350 to 413 and viral loads from 4.2 to 5.2 log10 copies/mL. **At 24 weeks, 90% of patients achieved HIV RNA <50 copies/mL regardless of baseline HIV RNA level.** Virologic failure (n=3) was uncommon and associated with suboptimal adherence. There were no discontinuations due to adverse events. The study will continue for 52 weeks. Two larger RCTs (GEMINI-1 and -2) are underway and should provide more data on the efficacy and resistance barrier to dolutegravir + lamivudine. If successful, estimates are that this two-drug combination could save between $500 million and 3 billion dollars in drug costs in the U.S. over five years.

Taiwo BO, et al. ACTG A5353: a pilot study of dolutegravir (DTG) + lamivudine (3TC) for initial treatment of HIV-1-infected participants with HIV-1 RNA <500,000 copies/mL. J Int AIDS Soc. 2017; 20(suppl 5). Abstract MOAB0107LB.

A Phase III, Randomised, Double-blind, Multicenter, Parallel-group, Non-inferiority Study Evaluating the Efficacy, Safety, and Tolerability of Dolutegravir Plus Lamivudine Compared to Dolutegravir Plus Tenofovir/Emtricitabine in HIV-1-infected Treatment-naïve Adults. (Gemini 1) NCT02831673 and (Gemini 2) NCT02831764

EMERALD Study (Single-tablet regimen of D/C/F/TAF)

This is an open-label, phase 3, non-inferiority trial that is evaluating switching to single-tablet fixed-dose darunavir/cobicistat/emtricitabine/tenofovir alafenamide versus continuing on a boosted PI (lopinavir, atazanavir, or darunavir) + FTC/TDF in patients with HIV RNA <50 copies/mL for at least two months. The study included 1,141 participants of whom 80% were men. Median duration of HIV disease was nine years and median CD4 count was 630 cells/mm3. **At Week 24, an FDA snapshot analysis showed virologic suppression was approximately 96% in both arms.** Virologic failure occurred in only 0.5% and 0.8% in the D/C/F/TAF and boosted PI arms + FTC/TDF arms respectively. Reported side-effects and treatment discontinuations were infrequent (~3% each arm). Drug-related grade 3-4 adverse events only occurred in 1% of patients in either group. There were slight increases in bone mineral density at the hip and spine with patients who were switched to the TAF regimen. The 48-week data will hopefully further confirm these findings. There is also a phase-3 trial with single-tablet D/C/F/TAF in treatment naïve patients that is ongoing.

Molina JM, Efficacy and *safety of switching from boosted protease inhibitor plus emtricitabine/tenofovir disoproxil fumarate regimens to single-tablet darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) in virologically suppressed, HIV-1-infected adults through 24 weeks: EMERALD study. J Int AIDS Soc. 2017; 20(suppl 5):28. Abstract TUAB0101.*

Clinicaltrials.gov A study to evaluate efficacy and safety of D/C/F/TAF fixed dose combination versus a regimen consisting of darunavir/cobicistat with FTC/TDF. NCT02431247

LATTE-2 Trial- 96 week data (Cabotegravir and rilpivirine as long-acting injectable therapies)

The LATTE-2 study evaluated cabotegravir plus rilpivirine for maintenance of HIV-1 viral suppression. The 48-week results were presented in 2016 in Durban, South Africa. This phase 2b, open-label study, included treatment-naive adults (n=286) who initially received oral cabotegravir plus abacavir-lamivudine once daily for a 20-week induction period. After viral suppression (VL <50 copies) was attained, patients were randomly assigned (2:2:1) to intramuscular long-acting cabotegravir plus rilpivirine at 4-week intervals (400mg cabotegravir plus 600mg of rilpivirine 600 as two 2 mL injections) or 8-week intervals (600mg cabotegravir 600 mg plus 900 mg rilpivirine as two injections) or continued on oral therapy.

At week 96, viral suppression was maintained in 47 (84%) of 56 patients receiving oral treatment, 100 (87%) of 115 patients in the 4-week group, and 108 (94%) of 115 patients in the 8-week group. Three patients (1%) experienced protocol-defined virological failure (two in the 8-week group; one in the oral group). Injection-site reactions were very common but "mild" [84%] or "moderate" [15%] in intensity and rarely resulted in discontinuation (<1% patients). Most frequently reported was injection-site pain. Serious adverse events were reported in 10% of patients in the IM groups and 13% patients in the oral treatment group but none were drug-related. The two-drug combination of IM cabotegravir plus rilpivirine every 4 weeks or every 8 weeks was as effective as daily three-drug oral therapy at maintaining viral suppression through 96 weeks and was well accepted and tolerated by patients. The ATLAS Studies are ongoing registrational trials looking at this regimen given every 4 weeks for maintenance therapy in virologically suppressed individuals. These tails should better define the overall safety, efficacy and acceptability of this regimen. There is also ongoing discussion regarding initiation of an every 8-week trial.

Eron J et al. Safety and efficacy of long-acting cabotegravir and rilpivirine as two drug maintainece therapy: LATTE-2 96 week results. MOAX0205LB.

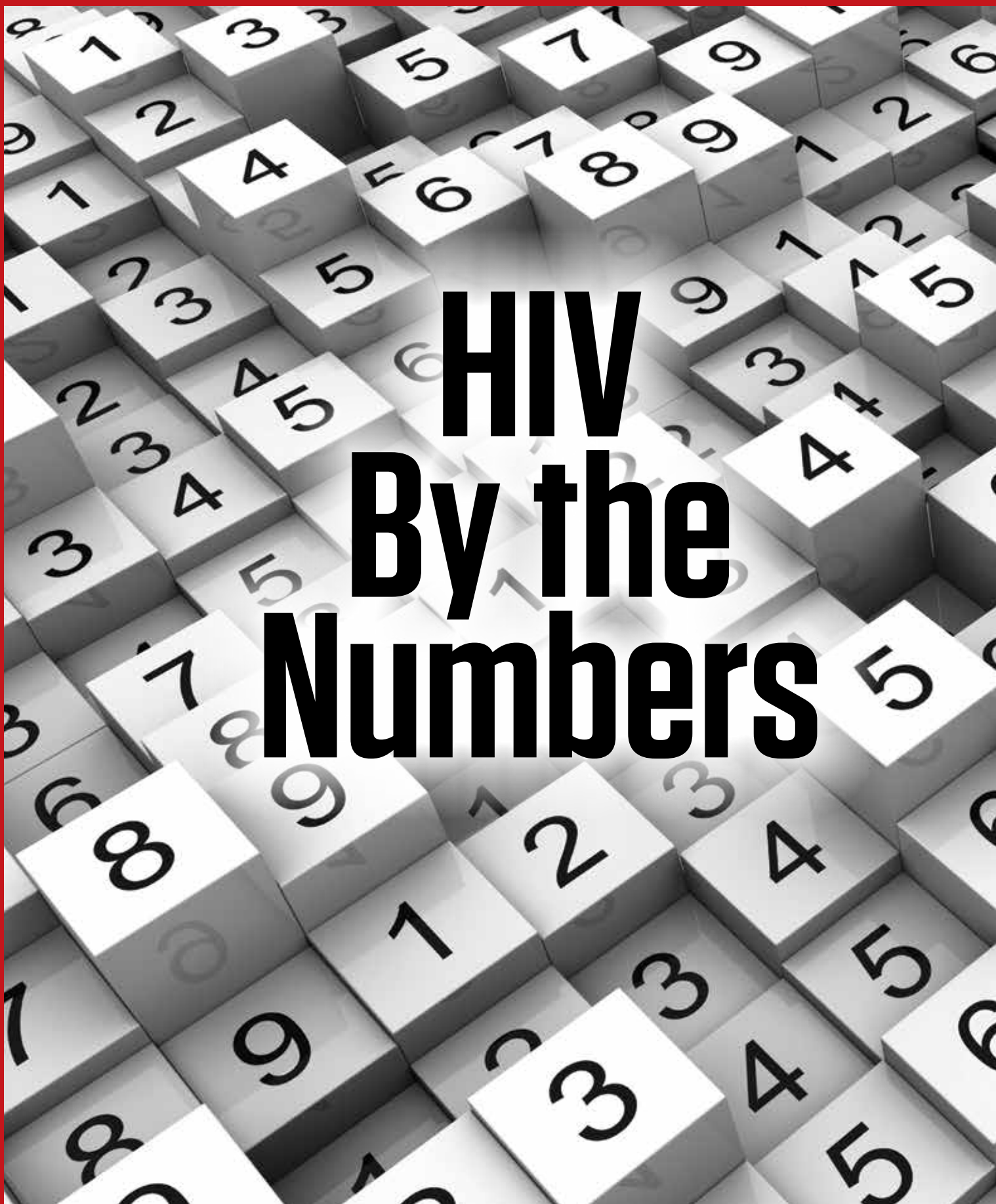
Margolis B et al. Lancet. 2017 Sep 23; 390):1499-1510.

A Phase III, Randomized, Multicenter, Parallel-group, Non-inferiority, Open-label Study Evaluating the Efficacy, Safety, and Tolerability of Switching to Long-acting Cabotegravir Plus Long-acting Rilpivirine From Current INI- NNRTI-, or PI-based Antiretroviral Regimen in HIV-1-infected Adults Who Are Virologically Suppressed. ClinicalTrials.gov NCT02951052

HIV

ABOUT THE AUTHOR

Jeffrey T. Kirchner, DO, FAAFP, AAHIVS, is Medical Director at Penn Medicine/LGHP Comprehensive Care at Lancaster General Hospital, Lancaster, PA. He chairs the *HIV Specialist* Editorial Advisory Group.



HIV By the Numbers

We know that some 1.2 million people in the U.S. still are infected with HIV, including many who have not yet been diagnosed. But within that number, how many have achieved viral suppression? What progress has been made in the effort to decrease the number of new infections?

For instance, the numbers tell us that new infections have declined dramatically in recent years in most categories, but not among men who have sex with men (MSM). Why is that?

Further, according to the Centers for Disease Control and Prevention (CDC), 90% of new HIV infections are transmitted by people who have not yet been diagnosed or who are not in care, emphasizing the absolute necessity of increasing diagnoses and keeping people in care.

And what about prevention? In only the last few years, PrEP has been introduced as a powerful tool for stopping transmission. However, the numbers tell us that it is not being widely prescribed. And with an Administration in the White House calling for a dramatic cut in HIV prevention funding, we are more challenged than ever to stop new infections.

Are we ever going to get to zero? This issue of *HIV Specialist* helps to answer some of these questions.

Certainly, the numbers tell us that much progress has been made. But they also tell us that there is much left to be achieved, and they point the way to a path to further progress.

The HIV Care Continuum

How It Can Inform Clinical Practice

BY GARY F. SPINNER, PA, MPH, AAHIVS

THOSE CARING FOR PATIENTS WITH HIV DISEASE should become familiar with the HIV Care Continuum as it provides data on the strengths and weaknesses of our system of care to patients with HIV. It also allows providers to measure the effectiveness of care in their individual clinics and practices against a national standard.

The HIV Care Continuum, also often referred to as the "HIV Cascade of Care," is a model created by the Centers For Disease Control and Prevention (CDC) to track sequential steps one must go through from the time of initial diagnosis of HIV until attaining viral suppression.

Since viral suppression reduces HIV morbidity, mortality, and HIV transmission to others, the care continuum allows us to track the effectiveness of reaching this goal with the estimated 1.2 million people in the United States infected with HIV. It shows the proportion of individuals with HIV at each stage of the continuum—including HIV-infected but not yet diagnosed, those diagnosed but not yet linked to care, patients engaged or retained in care, as well as prescribed antiviral medication and finally, the key goal of achieving viral suppression.[1]

This model is a quality improvement tool for policy makers and providers of care to identify gaps and opportunities at each stage of the continuum. It helps identify where barriers that prevent attainment of complete viral suppression for people with HIV may exist. It identifies populations, and regions in the care continuum in which resources and improved strategies may need to be directed to more fully achieve viral suppression of people with HIV and to monitor progress in doing so.

The CDC uses two different methods in calculating the care cascade. The first is a prevalence-based model that quantifies the number of people at each step of the continuum using the denominator of the entire population of people living with HIV, whether or not they have been diagnosed. The second is a diagnosis-based model in which the denominator is only those people who have been tested and diagnosed as having HIV. It does not include an estimate of individuals with HIV disease, but who have not yet been tested and diagnosed.

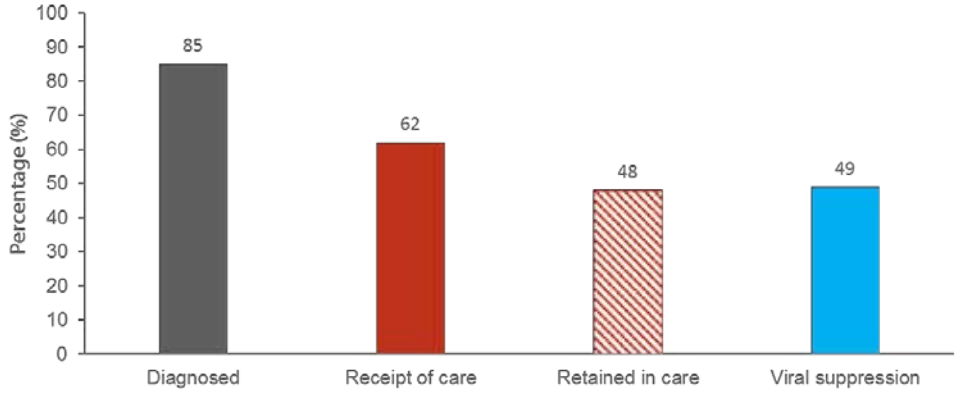
According to the CDC's most recent report using prevalence data through the end of 2014, 85% of the 1.1 million people in the United States living with HIV were diagnosed and knew they had HIV.[2,3] Sixty-two percent of people living with HIV were then linked to care. Forty-eight percent were retained in care and 49% achieved viral suppression. That nearly half of all patients in the U.S. with HIV have achieved viral suppression was a significant improvement. This number is likely due to revised treatment guidelines in 2012 recommending that all persons with HIV be treated with ART, as well as expanded availability of testing and treatment.

Significant progress in prevention was noted by the decrease in new HIV infections in 2014 to 37,600 new infections from a previous number of about 50,000, an 18% decline in new infections from 2008 to 2014. Looking at new HIV infections by risk category reveals the steepest decline in persons who inject drugs, which decreased by 31% since 2010. Heterosexual transmission was down by 24%, and men who have sex with men (MSM) who also inject drugs declined by 24%.

Of greatest concern however are the two-thirds of new HIV infections that occur in the MSM population. This group has shown no significant decline. Moreover, the number of

FIGURE 1

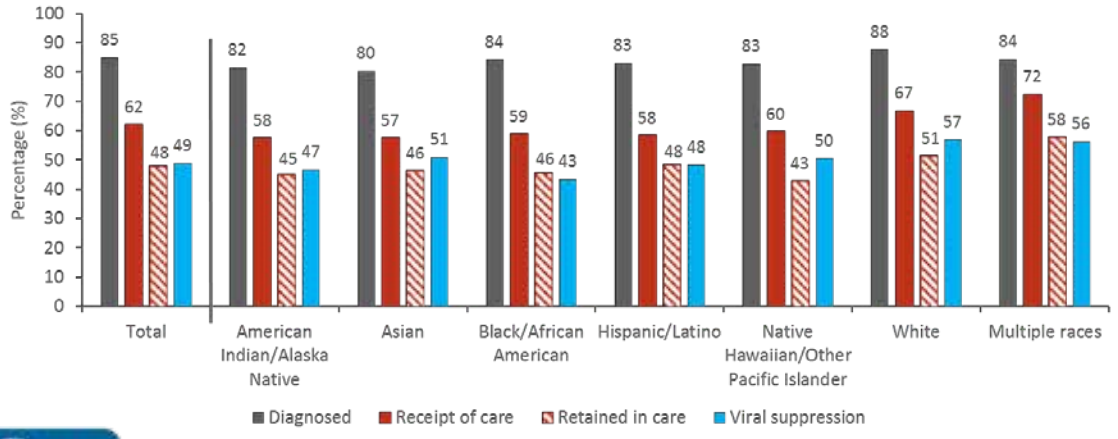
Persons Living with Diagnosed or Undiagnosed HIV Infection
HIV Care Continuum Outcomes, 2014—United States



Note. Receipt of medical care was defined as ≥1 test (CD4 or VL) in 2014. Retained in continuous medical care was defined as ≥2 tests (CD4 or VL) ≥3 months apart in 2014. Viral suppression was defined as <200 copies/mL on the most recent VL test in 2014.

FIGURE 2

Persons Living with Diagnosed or Undiagnosed HIV Infection
HIV Care Continuum Outcomes, by Race/Ethnicity, 2014—United States



Note. Receipt of medical care was defined as ≥1 test (CD4 or VL) in 2014. Retained in continuous medical care was defined as ≥2 tests (CD4 or VL) ≥3 months apart in 2014. Viral suppression was defined as <200 copies/mL on the most recent VL test in 2014. Asian includes Asian/Pacific Islander legacy cases. Hispanics/Latinos can be of any race.

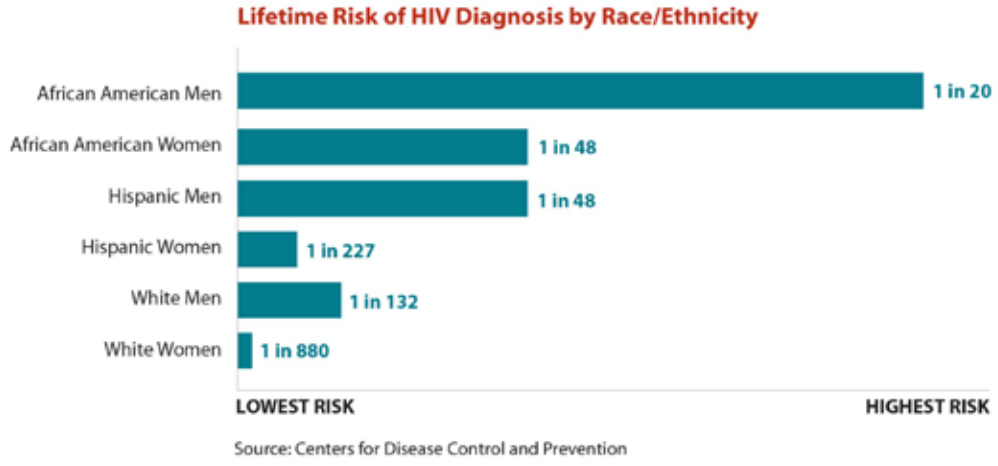
new infections in MSM actually increased in this population among those ages 25–34 years old.

The CDC data reveal that 90% of new HIV infections are transmitted by either people not diagnosed or not in care. A prior CDC analysis (Skarbinski, 2015) estimated that patients with previously diagnosed HIV infection, but not linked to care, were responsible for 61% of new HIV infections in the U.S.[4] Further, a statewide study from North Carolina (Cope 2015) that analyzed patients with acute HIV infection found that most transmission events (77%) were attributable to partners with previously diagnosed infection, of whom only 23% were reportedly in care and were taking antiviral medication within the time that transmission was likely to have occurred.[5]

While the recent CDC report reflected significant progress, with almost half of Americans with HIV now virally suppressed, it also underscores the fact that the other half of individuals with HIV are not in care and are the major source of new HIV infections. An analysis of high-risk groups, and the demographics of those with the highest

FIGURE 3

Lifetime Risk of HIV by Race/ Ethnicity



prevalence of HIV infection by race, ethnicity and age, along with a regional analysis of HIV prevalence in the United States can help us to understand where the most effort is needed to achieve viral suppression and reduce HIV transmission.

Racial and Ethnic Disparities

Racial and ethnic disparities in both HIV prevalence and viral suppression continue to be of significant concern as seen in Figure 2.[6] African-Americans bear the greatest burden of HIV infection, followed by Hispanics. Figure 3 shows the lifetime risk of HIV infection in black men is one in 20, black women one in 48, Hispanic men one in 48, compared to one in 132 for white men, and one in 880 for white women. MSM have the overall highest lifetime risk of HIV, at one in six. The disparity by race and ethnicity amongst MSM (Figure 4) reveals black MSM having a lifetime risk of HIV infection of one in two, Hispanic MSM a risk of one in six, compared to whites at one in 11.

Regional and Urban Disparities

Analysis of the data by region shows that persons living in the 16 Southern states and the District of Columbia have the greatest lifetime risk of HIV (Figure 5).[7,8] Half of new HIV infections in 2014 occurred in the southern United States.

It should be noted that many Southern states rejected Medicaid expansion, which limits healthcare access to the poor. Furthermore, within Medicaid, there is state level variation in reimbursement services for routine HIV testing, with only 34 states providing reimbursement for routine HIV screening.

Some regions and urban sub-populations in the U.S. have HIV prevalence rates that compare with some Sub-Saharan African countries. For example, while the overall HIV prevalence rate in the U.S. is 0.4, in Washington, D.C. it is 2.5 overall, similar to Rwanda at 2.9%.[9,10,11] And black men in Washington, D.C. have a prevalence of 4.6%, comparing closely with the prevalence rate of Tanzania at 4.7%.[12] These figures factor in the significant 10% per year decrease in HIV prevalence in the U.S. capital, according to CDC 2014 data. In a positive trend, the CDC data showed annual infections decreasing or remaining stable in each of the 35 states and Washington, D.C. from which data is reported.

Risk of HIV Infection by Age

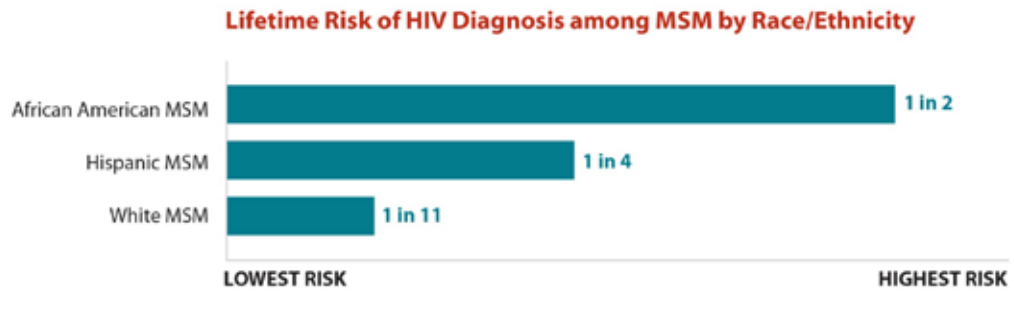
CDC data reveal that among youth ages 13–24, there is the lowest rate of diagnoses, and lowest rates of viral suppression. Similarly, persons ages 25–34 are also underdiagnosed, and have low rates of viral suppression among those in care (Figure 6).[13]

Improving Outcomes at Each Stage of Diagnosis

The CDC estimates that 85% of persons living with HIV are aware of their status. Although guidelines published in

FIGURE 4

Lifetime Risk for MSM by Race/ Ethnicity



2006 recommended that everyone age 13–64 be tested for HIV. They also recommended that all persons likely to be at high risk for HIV infection, including MSM, be tested at least annually. Although now supported by most major medical organizations (ACP, AAFP) the implementation of these guidelines in clinical practice in the U.S. is still lacking. Primary care providers (PCP) should be consistently encouraged to adopt routine opt-out HIV testing in their clinical practices. Some electronic health records do include routine HIV screening on their maintenance "dashboard" as a reminder to clinicians. Since 67% of new HIV infections in 2014 occurred in MSM, more needs to be done to encourage PCPs to take a sexual history for all patients during an initial visit, at routine preventive visits, and when a patient presents with signs of symptoms of a sexually transmitted infection.

Linkage to Care

The HIV Care Cascade is a series of successive steps that must be reached to achieve the final goal of viral suppression. Gonsalves, et.al. present the CDC data in a "queuing model" that correlates the waiting times that HIV-infected individuals spend in each stage of the care continuum, both for those who remain engaged in care and those who drop out.[14]

In their model, they estimate that people newly diagnosed with HIV spend an average of 3.1 months before they become engaged in care. It has not been uncommon for someone testing positive for HIV to wait for an appointment and perhaps have multiple visits for counseling, and laboratory testing before ultimately being offered antiviral therapy.

Given the high attrition that may occur from testing to start of treatment, offering ART on the day of diagnosis may promote engagement and retention in care. The Rapid Initiative at San Francisco General Hospital led to a high rate of treatment initiation and more rapid viral suppression compared to standard practice.[15] A recent study from Haiti showed improved retention in care with virologic suppression and decreased mortality in same day of diagnosis and start of antiviral treatment.[16]

Retention in Care

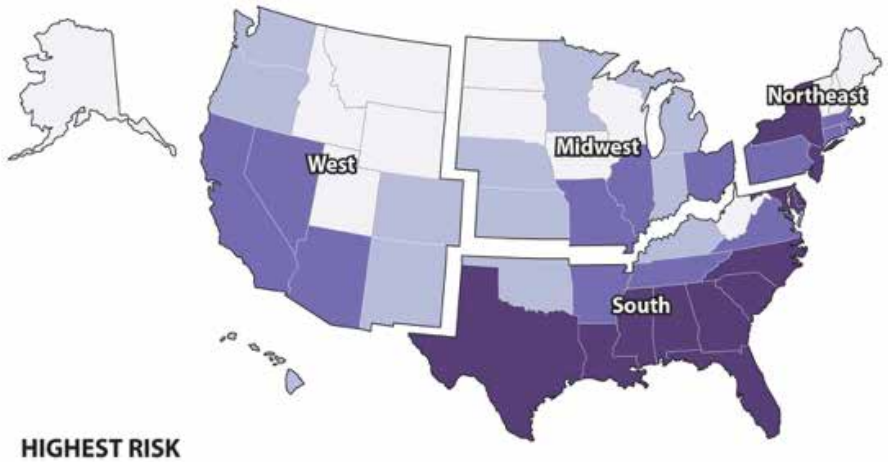
Improving retention in care is perhaps the most difficult challenge in achieving a high rate of viral suppression in the HIV Care Continuum. Several evidence-based strategies have been employed to retain patients in care. These include the provision of co-located care and ancillary services, identification of each patient's barriers to care and helping to address them, and the use of data to identify and make contact with patients who are out of care.[17]

PrEP—Reducing New HIV Infections

With 67% of new HIV infections in men who have sex with men, the failure of health care providers to take an adequate sexual history prevents many patients from disclosing to their health care providers. This will preclude the appropriate sexually transmitted infection screening, treatment, and access to Pre-exposure Prophylaxis (PrEP), all of which can greatly reduce new HIV infections.

FIGURE 5

Lifetime Risk of HIV Diagnosis by State



HIGHEST RISK **LOWEST RISK**

State	One in "n"	State	One in "n"	State	One in "n"	State	One in "n"
District of Columbia	13	Nevada	98	Michigan	167	West Virginia	302
Maryland	49	Illinois	101	Oklahoma	168	Wisconsin	307
Georgia	51	California	102	Kentucky	173	Iowa	342
Florida	54	Tennessee	103	Indiana	183	Utah	366
Louisiana	56	Pennsylvania	115	Washington	185	Maine	373
New York	69	Virginia	115	Colorado	191	Alaska	384
Texas	81	Massachusetts	121	New Mexico	196	South Dakota	402
New Jersey	84	Arizona	138	Hawaii	202	New Hampshire	411
Mississippi	85	Connecticut	139	Oregon	214	Wyoming	481
South Carolina	86	Rhode Island	143	Minnesota	216	Vermont	527
North Carolina	93	Ohio	150	Kansas	262	Idaho	547
Delaware	96	Missouri	155	Nebraska	264	Montana	578
Alabama	97	Arkansas	159			North Dakota	670

Source: Centers for Disease Control and Prevention

One Practitioner at a Time

It is clear when analyzing the data from the Care Continuum that in spite of the progress being made, much work needs to be done to address the 51% of persons with HIV who are not virally suppressed. While individual clinicians might think this is a job for policymakers, I will share a few personal experiences, which have improved the Care Cascade at Southwest Community Health Center where I care for patients.

Through data collection, we are able to identify which groups of patients are not adequately being tested, and which providers are not ordering HIV tests in accordance with CDC guidelines, thus enabling interventions to address these deficiencies. Patients who test positive are immediately referred to our HIV program staff, and newly infected patients are linked to care with an HIV specialist usually within 1–2 days, and sometimes the same day as their diagnosis.

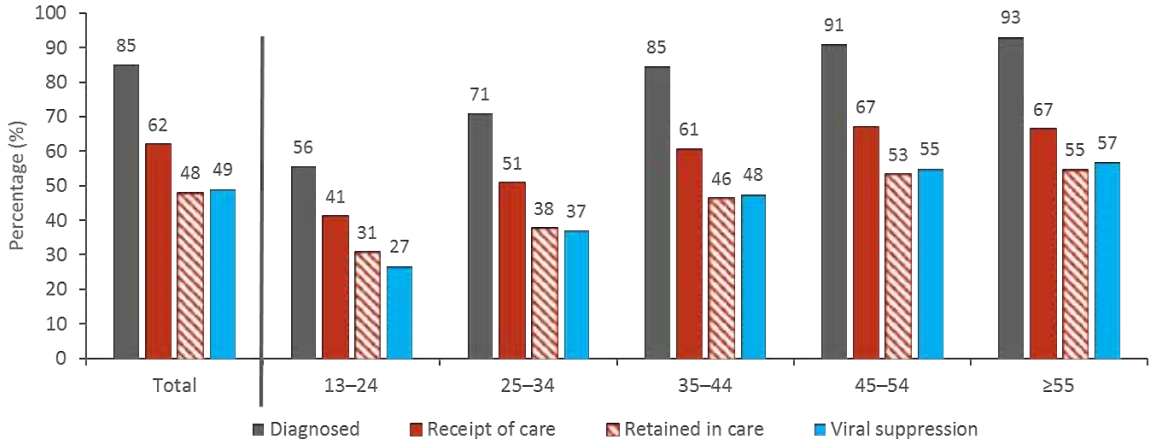
My two most recent newly infected patients were started on ART on the day of diagnosis. As in most clinics, retention in care remains problematic. I have had some success with personally calling patients who miss an appointment to get them in. Patients are always happy to hear directly from me and more likely to come in for an appointment. Direct handoffs of patients to a mental health clinician embedded in our department helps connect patients who have behavioral health problems to appropriate care. The involvement of a case management team, and sending outreach staff to a patient's home often helps reconnect these patients who have dropped out of care.

While there are varied and individual reasons that patients drop out of care, the failure to understand the important cultural context from which a patient interacts with the health care system often leads to poor ART adherence and loss of retention in care.

How health care providers interact with their patients, attempt to understand their racially and ethnically diverse cultures, and develop a relationship built on trust and free of personal bias is essential to keep patients engaged in and retained in care.

FIGURE 6

Persons Living with Diagnosed or Undiagnosed HIV Infection HIV Care Continuum Outcomes, by Age, 2014—United States



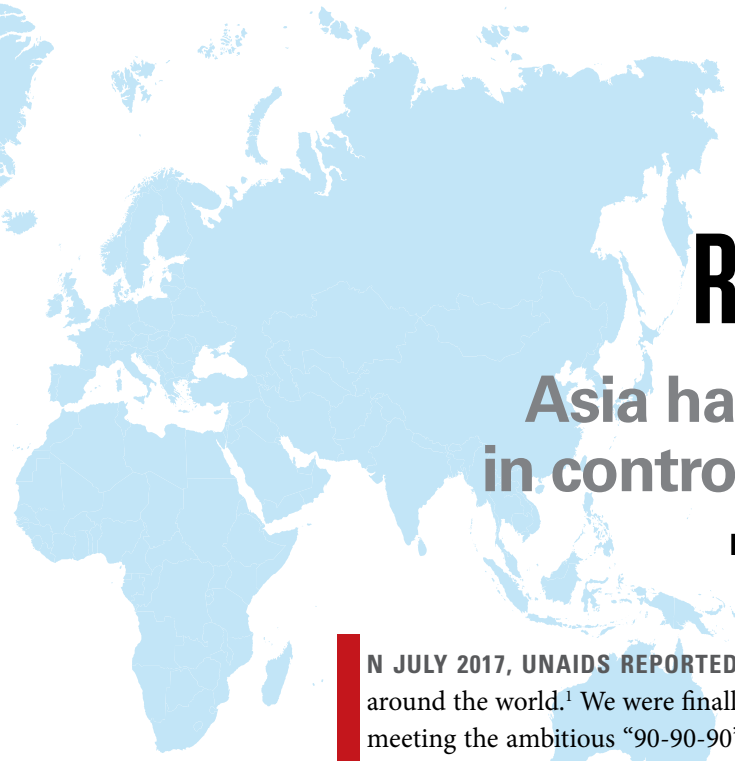
Note. Receipt of medical care was defined as ≥1 test (CD4 or VL) in 2014. Retained in continuous medical care was defined as ≥2 tests (CD4 or VL) ≥3 months apart in 2014. Viral suppression was defined as <200 copies/mL on the most recent VL test in 2014.

Additional research on why patients drop out of care and better interventions to bring them back is needed. Further progress in the HIV Care Continuum will require continued progress in all HIV clinics to reduce new infections. This includes, but is not limited to, patient education, increasing HIV testing, the delivery of PrEP, more rapid access from testing to treatment, and a greater effort to keep our patients better engaged in the care we provide. With continued vigilance in these efforts, future success in achieving the goals of the National HIV/AIDS Strategy is attainable. HIV

ABOUT THE AUTHOR:
Gary Spinner, PA, MPH, AAHIVS, is with the Southwest Community Health Center in New Haven, Connecticut. He also serves a Secretary on the AAHIVM Board of Directors.

REFERENCES

1. Health Resources and Services Administration, About the Ryan White HIV/AIDS Program, HIV Care Continuum, accessed August 30, 2017.
2. CDC, HIV Continuum of Care, U.S. 2014, https://www.cdc.gov/nchhstp/newsroom/2017/HIV-Continuum-of-Care.html, accessed September 3, 2017.
3. Centers for Disease Control and Prevention, More people with HIV have the virus under control, Press Release, July 27, 2017.
4. Skarbinski J, Rosenberg E et al. Human immunodeficiency virus transmission at each step of the care continuum in the United States. JAMA Intern Med 2015; 175 (4) 596-597.
5. Cope AB, Power KA, et al. Ongoing HIV transmission and the HIV care continuum in North Carolina. PLoS One. 2015; 10(6):e0127950
6. CDC, HIV Continuum of Care, U.S., 2014, overall and by Age, Race/Ethnicity, Transmission Route and Sex, https://www.cdc.gov/nchhstp/newsroom/2017/HIV-Continuum-of-Care.html, July 27, 2017, accessed September 3, 2017.
7. CDC, https://www.cdc.gov/nchhstp/newsroom/2016/croi-2016.html#Graphics2, accessed September 4, 2017.
8. Hess K, et al. CROI 2016. Boston, MA. #52. Adapted from CDC at https://www.cdc.gov/nchhstp/newsroom/2016/croi-2016.html#Graphics2. Accessed
9. Centers for Disease Control and Prevention. HIV Surveillance Report, 2014; vol. 26. http://www.cdc.gov/hiv/library/reports/surveillance/ Published November 2015 accessed September 2, 2017.
10. Annual Epidemiology and Surveillance Reports for the District of Columbia. HIV/AIDS, Hepatitis, STD and TB Administration (HAHSTA) Annual Report 2016;accessed September 2, 2017
11. Prevalence of HIV, World Bank Group. http://data.worldbank.org/indicator/SH.DYN.AIDS.ZS. Accessed September 2, 2017.
12. Prevalence of HIV, World Bank Group. http://data.worldbank.org/indicator/SH.DYN.AIDS.ZS. Accessed September 3, 2017.
13. CDC, https://www.cdc.gov/nchhstp/newsroom/2016/croi-2016.html#Graphics2, accessed September 4, 2017.
14. Gonsalves, GS, Paltiel, A.D., Cleary, PD et.al, A Flow-based model of the HIV Care Continuum in the United States, J Acquir Immune Defic Syndr. 2017 Aug 15; 75(5):548-553.
15. Pilcher CD, Ospina-Norvell C, Dasgupta A et al. J Acquir Immune Defic Syndr. 2017 Jan 1; 74(1):44-51.
16. Koenig,SP, Dorvil,N, Devieuz,JG et al, Same-day HIV testing with initiation of antiretroviral therapy versus standard care for persons living with HIV: A randomized unblended trial. Plos Medicine July 25, 2017.
17. International Advisory Panel on HIV Care Continuum Optimization. J Int Assoc Provid AIDS Care. 2015; 14(suppl 1):S3-S34.



Reality Check

Asia has fallen behind Africa in controlling the HIV epidemic

BY ANNETTE SOHN, M.D.

IN JULY 2017, UNAIDS REPORTED that 19.5 million people were accessing antiretroviral therapy (ART) around the world.[1] We were finally halfway to achieving full treatment coverage, and well on our way to meeting the ambitious "90-90-90" targets by 2020.[2] Reaching the "90-90-90" goals set forth in 2014 has become the primary objective of global HIV programs and donors, and the measure of success for national HIV programs. Overall, UNAIDS estimates that in 2016, 77% of people with HIV who knew their status were on ART, and 82% of those on treatment were virally suppressed. This was a reflection of how countries in the poorest regions of the world were finally achieving what was once thought impossible, and collectively moving us closer to ending AIDS.

Unfortunately, these achievements have been widely inconsistent in the Asia-Pacific region. Although Thailand achieved elimination of mother-to-child HIV transmission and congenital syphilis in 2016, it is one of the few success stories in a region that includes some disappointing low HIV testing and treatment coverage rates.[3] To illustrate how far we have yet to go, amfAR compared overall Asia-Pacific HIV program metrics to the region hardest hit by HIV—East and Southern Africa.[4]

Using the most recent data from UNAIDS, treatment coverage in adults in Asia was just 47% compared to 61% in East and Southern Africa, and 40% in children under 15 years compared to 51%. Even worse was the 48% of pregnant women receiving ART to prevent mother-to-child transmission, which is about half the 89% coverage in East and Southern Africa.

If we dig into country-specific details, UNAIDS reports that India has the largest epidemic in the region, with 2.1 million people living with HIV. Of these, 77% know their HIV status, and 49% were on treatment in 2016. At the same time, Indonesia has 620,000 people living with HIV, but only 35% of them know their status, and 13% are on treatment. Neither country has sufficient HIV viral load testing available to estimate their levels of viral suppression.

Given that the Asia-Pacific region is a mix of low-, middle-, and high-income countries, why haven't we seen greater progress towards the global 90-90-90 targets? Insufficient political will, inadequate financial resources, and limited access to lowest-cost generic antiretroviral treatment have all been cited as the more obvious contributing reasons.[5,6] Less easily measured are the stigma and discrimination that directly and indirectly fuel the stagnation in the regional response. National epidemics are frequently concentrated among high-risk key populations—including men who have sex with men (MSM), migrants, people who inject drugs, prisoners, sex workers, and transgender people. Preventing new infections requires needle and syringe exchange programs and opioid substitution therapy, promotion of condom use, and implementation of human rights protections for these groups—interventions that have been blocked by some funders and under-prioritized by local governments.

The consequences of failing to implement strategies to prevent and treat HIV in the region are clear—it results in new infections and poor treatment coverage. However, by admitting that "AIDS is not over," and being more transparent about the scope of local epidemics, we can begin working towards closing these gaps in care. The Philippines is an example of a national health program openly sharing its surveillance data to improve understanding of the impact of HIV among policymakers and the community as a way to promote prevention and testing.

Between 2010 and 2016, their annual rate of new infections

FIGURE 1. Treatment and prevention coverage in East and Southern Africa compared to the Asia-Pacific, UNAIDS 2016 data

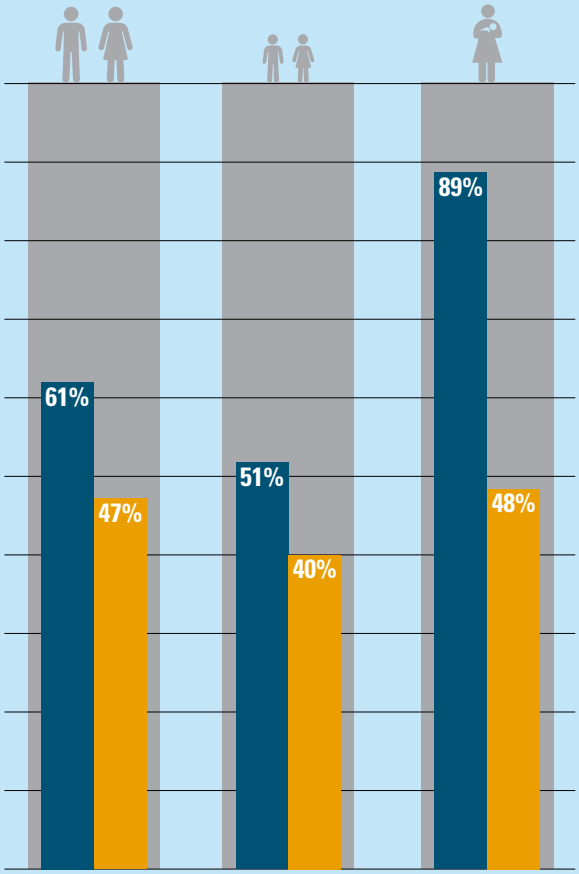
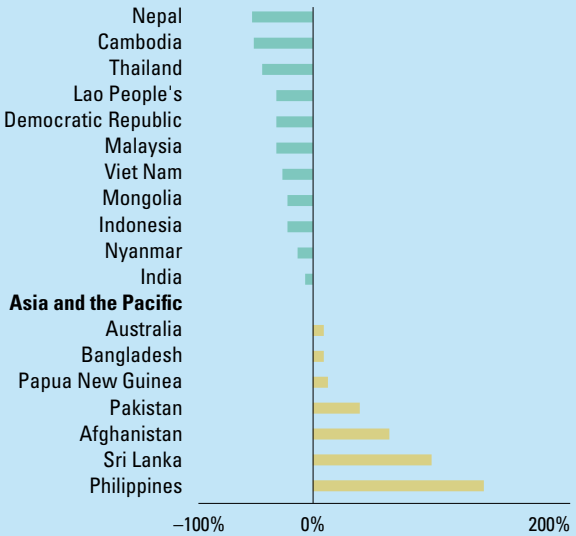


FIGURE 2. Percent change in new HIV infections, by country, Asia and the Pacific, from 2010 to 2016
Source: UNAIDS 2017 estimates[7] [they are actually 2016 data but in the 2017 report]



The consequences of failing to implement strategies to prevent and treat HIV in the region are clear—it results in new infections and poor treatment coverage.

in the Philippines increased by 141%—designating the country as having the fastest-growing epidemic in the region.[7] As part of its response, the Philippines Department of Health has been regularly and publicly reporting new infections, treatment coverage, and AIDS-related deaths in detail, including disaggregating data by sex, age, and key populations.[8] This practice engages clinicians and civil society to know their epidemic, and is a model for other countries.

The World Health Organization and UNAIDS have admitted that many countries in the Asia-Pacific are not on track to reach the targets by 2020, let alone to end AIDS by 2030. The reality is that we need to remind governments, donors, and ourselves that HIV is still a serious problem in the region, and that greater investments in people and programs to implement solutions are required, if we hope to control it. HIV

ABOUT THE AUTHOR:
Dr. Annette Sohn joined amfAR's staff as vice president and director of TREAT Asia in September 2008. In this capacity, she leads a staff of 20 based in amfAR's Bangkok, Thailand, office. Dr. Sohn is a highly regarded pediatrician and researcher with extensive experience treating HIV/AIDS among children in Southeast Asia. She was on faculty in the Division of Pediatric Infectious Diseases and is currently assistant clinical professor in the Department of Pediatrics at the University of California, San Francisco (UCSF), and was the Vietnam country representative for the UCSF Institute for Global Health.

REFERENCES

1. UNAIDS, Ending AIDS, Progress towards the 90-90-90 targets, July 2017. http://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf
2. UNAIDS, 90-90-90 An ambitious treatment target to help end the AIDS epidemic, October 2014. http://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf
3. UNAIDS, Press release: Thailand is first country in Asia to eliminate mother-to-child transmission of HIV and syphilis, June 2016. http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2016/june/20160607_Thailand
4. UNAIDS, UNAIDS data 2017, July 2017. http://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf
5. Singh PK, What needs to be done in South East Asia to End AIDS? J Virus Erad 2016;2 (Supplement 4): iv. Available at: http://www.searo.who.int/entity/hiv/data/si-hivaids.pdf?ua=1 or http://viruseradication.com/supplement-details/The_HIV_epidemic_in_South-east_Asia:_initial_responses_towards_the_UNAIDS_90%E2%80%9390%E2%80%9390_goal/
6. Pendse R, Gupta S, Yu D, Sarkar S. HIV/AIDS in the South-East Asia region: progress and challenges. J Virus Erad 2016;2 (Supplement 4):1-6. Available at: http://www.searo.who.int/entity/hiv/data/si-hivaids.pdf?ua=1 or http://viruseradication.com/supplement-details/The_HIV_epidemic_in_South-east_Asia:_initial_responses_towards_the_UNAIDS_90%E2%80%9390%E2%80%9390_goal/
7. UNAIDS, Ending AIDS, Progress towards the 90-90-90 targets, July 2017. http://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf
8. HIV/AIDS and ART Registry of the Philippines (HARP), Department of Health, Epidemiology Bureau, May 2017. Available at: http://www.doh.gov.ph/sites/default/files/statistics/DOH_EB_HIV_May-AIDSreg.pdf

HIV by the Budget Numbers

BY EMILY MCCLOSKEY

THE FEDERAL GOVERNMENT'S ANNUAL APPROPRIATIONS PROCESS is in full swing for the fiscal year 2018 (FY2018) that started October 1. Although complex, this process is important to understand because many HIV prevention, care, research, and housing programs HIV community advocates have fought for are funded through this annual process.

The process goes like this:

1. **The President submits a budget request. This indicates the President's priorities, but does not have the rule of law.**
2. **Congress responds to this request by passing budget resolutions, which sets the top-line spending levels across the entire federal government.**
3. **The House and Senate Appropriations Committees then allocate funding separately at programmatic levels and later negotiate through a process called "a conference" to establish a final funding allocation.**

This article will highlight some of the historical funding trends and successes of several HIV prevention and care programs and how they could be impacted in the FY2018 appropriation process.

CDC's HIV Prevention Program

The Centers for Disease Control and Prevention (CDC)'s HIV Prevention Program funds health departments and community-based organizations throughout the U.S. to implement high impact HIV prevention programs. The Program is currently funded at $788.7 million, an increase of nearly $100 million since the beginning of the early 2000s. During the Obama Administration, funding for HIV prevention grew about 14%. From 2008 to 2014, new HIV infections in the United States fell by 18% to about 37,600 new infections a year. While there are many factors that contribute to this drop in new infections, prevention funding is critical to address the nation's HIV epidemic. Sustained investment in these programs makes possible the implementation of new, scientifically-based prevention tools, while ensuring that funding is reaching the most impacted populations in the most impacted areas of the U.S.

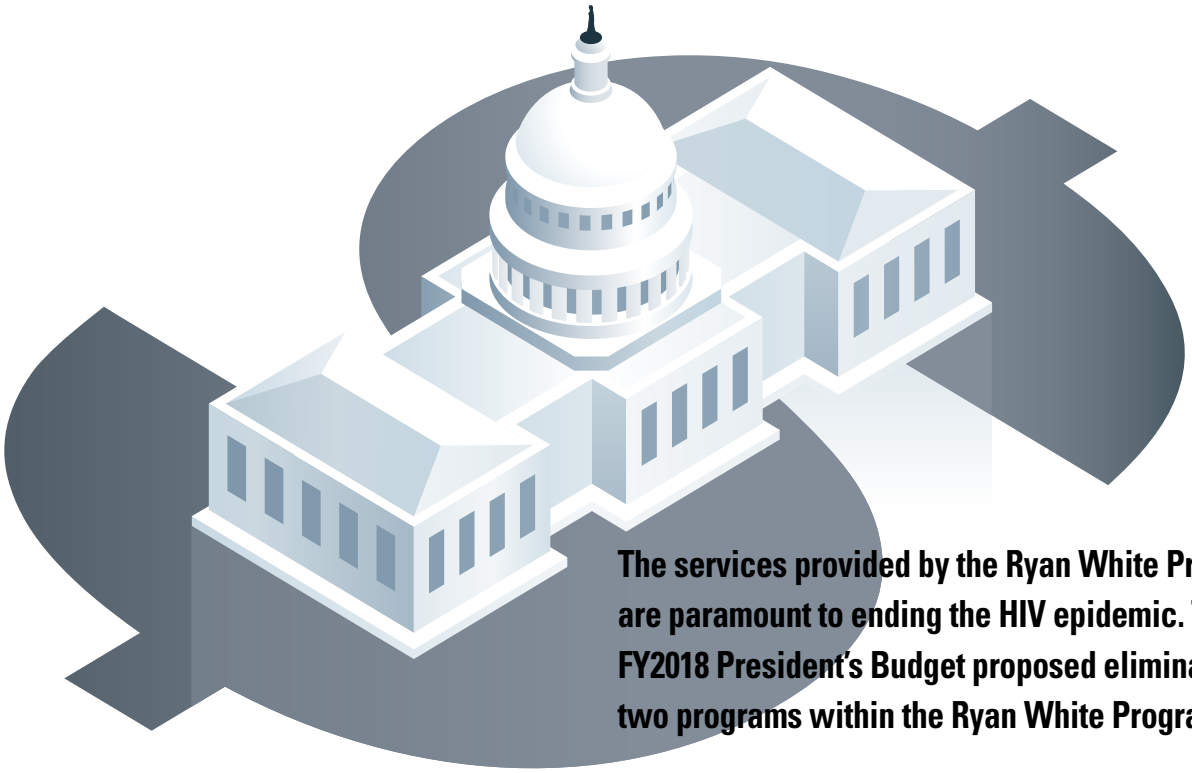
In the FY2018 President's budget request, the Administration requested a $148.6 million cut for HIV Prevention Program. The budget states that at "the FY2018 requested amount, CDC will reduce activities around testing, support services for persons living with HIV, and prevention services. In addition, CDC's ability to implement innovative demonstration projects or research examining strategies related to high impact prevention and new tools supporting HIV prevention will be reduced."

Luckily, both the House and the Senate rejected this proposal and instead included flat funding for HIV prevention. While funding is not yet finalized for FY2018, it is likely the program will be funded at $788.7 million.

The Ryan White Program

The Ryan White Program serves more than 500,000 people — over half of the people living with HIV (PLWH) in the United States who have been diagnosed. The Ryan White Program is crucial to meet the health care needs of PLWH and improve health outcomes. In FY2007, the Ryan White Program was funded at $2.1 billion. Over the decade, the program has grown to a funding level of $2.3 billion. The Ryan White Program's comprehensive system of care includes access to primary care, medication, and supportive services that keep PLWH engaged in care by funding cities, states, community based organizations, and clinics, as well as other stakeholders.

The services provided by the Ryan White Program are paramount to ending the HIV epidemic. For example, there



The services provided by the Ryan White Program are paramount to ending the HIV epidemic. The FY2018 President's Budget proposed eliminating two programs within the Ryan White Program.

is conclusive scientific evidence that a person living with HIV who is on antiretroviral therapy (ART) and is durably virally suppressed (defined as having a consistent viral load of less than <200 copies/ml) does not sexually transmit HIV. In 2015, 83% of Ryan White Program clients had reached viral suppression. Most recent data show that only about 49% of PLWH in the United States have achieved viral suppression. This demonstrates the unique success of Ryan White in accelerating health outcomes for disproportionately impacted populations.

The FY2018 President's Budget proposed eliminating two programs within the Ryan White Program—AIDS Education and Training Centers (AETCs) and Special Projects of National Significance (SPNS).

- AETCs "are the only nationally coordinated network of leading HIV experts able to provide local, community-based, interprofessional education and training programs to healthcare teams and systems," states the National Alliance for HIV Education and Workforce Development. This network focuses on workforce development, capacity building, and addressing inequities within the epidemic.
- According to the President's Budget, SPNS "supports the development, evaluation, and dissemination of innovative models of HIV care to improve the retention and health outcomes of RWHAP clients." The 64 grantees throughout the country implement innovative programs to advance the end of the HIV epidemic.

Again, the House and Senate rejected these devastating eliminations, flat funding both programs in their respective funding bills. It is expected that these funding levels will remain the same during the conference process and AETCs and SPNS will retain their funding.

The Secretary's Minority AIDS Initiative Fund

The Secretary's Minority AIDS Initiative Fund (SMAIF) works across government agencies to implement innovative programs that are focused on improving HIV prevention and care for racial and ethnic minorities living with HIV or at increased risk for infection. SMAIF currently funds 31 projects across the country, which have demonstrated success in project and health outcomes.

The President's Budget proposes eliminating SMAIF. The budget also requests a cut to Minority AIDS Initiative (MAI) funding at the Substance Abuse and Mental Health Services Administration (SAMHSA). Unfortunately, the House Appropriations matched this request and included the elimination of SMAIF and the cut to the SAMHSA MAI funding in their appropriations bill. However, the Senate flat funded both programs. The House and Senate will have to negotiate the final funding amount. However, the fate of SMAIF and SAMHSA MAI funding is currently unclear.

Next Steps

While FY 2018 began on October 1, Congress has funded the government through a continuing resolution until mid-December. Many health advocates hope that Congress will reach a budget deal to raise overall funding levels, which would allow for increased funding for many programs and alleviate sequestration. However, Congress has not cited this as a priority for the coming months. The House and Senate will work together on funding legislation that will determine final funding levels for FY2018 before mid-December. Between now and then, the HIV community will continue to advocate on behalf of the above programs and many others to ensure that these programs receive the highest funding levels possible. HIV

ABOUT THE AUTHOR:
Emily McCloskey is the Associate Director of Policy and Legislative Affairs at NASTAD.

AIDS Does Not Discriminate and Neither Should Our Laws

Strengthening Health Care Enforcement to Support People Living with HIV

By Carl Schmid II, Deputy Executive Director, The AIDS Institute and Tyler Andrew Termeer, MS, Executive Director, Cascade AIDS Project

TODAY, INDIVIDUALS LIVING WITH HIV can now live healthy, productive lives—a stark contrast with the early years when a diagnosis often meant near-term death. Patient access to HIV treatment innovations, however, remains a significant issue. People living with HIV are incurring far more than their fair share of the cost of lifesaving medications, and many are not able to access necessary drugs at all. HIV is a disease that does not discriminate, but certain features of the existing and proposed national health care systems are essentially doing just that.

Existing ACA Nondiscrimination Legislation

The Patient Protection and Affordable Care Act (ACA) includes provisions—notably Sections 1311 and 1557—aimed to protect people living with HIV and other chronic conditions from discrimination and to increase their coverage options. HIV advocates, including those with the 200-patient group strong I Am Essential Coalition, firmly agree that the ACA has provided critical coverage, access and patient protections that beneficiaries with chronic conditions such as HIV simply cannot afford to lose.[1]

Actionable regulations are necessary to enforce the ACA for those living with HIV. It took years to establish regulations to implement Sections 1311 and 1557. HIV advocates contend they still lack the specificity necessary to assist in challenging discriminatory plan designs. Nevertheless, the law and its regulations need to be upheld and strongly enforced.

In 2016, the White House Office of National AIDS Policy (ONAP) updated the National HIV/AIDS Strategy, working with federal agencies to refine the domestic plan to combat the HIV/AIDS epidemic.[2] The goals of the Updated Strategy are to:

- Reduce new HIV infections
- Increase access to care and improve health outcomes among people living with HIV
- Reduce HIV-related health disparities and health inequities
- Achieve a more coordinated national response.

It is deeply concerning that under the new administration, the status of the ACA, Medicaid and Medicare, and even ONAP and the National HIV/AIDS Strategy are uncertain.

Discrimination in access to health care is an unfortunate fact of life for many HIV patients. To probe this issue and examine possible solutions, 16 thought leaders in national and state HIV advocacy and policy organizations participated in a roundtable in Washington, D.C. in August 2016. ViiV Healthcare, a global specialist HIV company delivering advanced treatment and care for people living with HIV, organized and sponsored the event. This report reflects the thoughts and opinions of the roundtable participants from the meeting and ongoing discussions based on subsequent political events.

The administration's proposed budget cuts to HIV programming for prevention, research and continued treatment advances send an ominous message. New health care legislation and plans to implement it have the potential to take the country backwards in the fight against HIV/AIDS.

Research-backed solutions and important laws and programs to address the HIV public health crisis are in place, but inequity in access to care persists, and the continued existence and implementation of proven measures to address those inequities are now in jeopardy. Health and Human Services (HHS) and the administration must fortify the evidence-based policies currently in place and improve and enforce regulations to assist in implementation of those policies.

Inequalities in Care

Strides have been made to improve access to care and treatment for people living with HIV. Under the ACA, private health insurance plans can no longer deny insurance because of pre-existing conditions.[3] Plans also cannot drop people from coverage when they get sick, and there are no annual or lifetime limits on coverage.

Within the federal and state marketplaces, plans cannot charge a higher premium based on health status or gender. They must offer Essential Health Benefits (EHBs), including medications and services imperative to the health of people living with HIV, and they are also required to cover services from essential community providers, such as the Ryan White HIV/AIDS Program.[3] Each year, this federal program makes HIV-related health services available to more than half a million people who lack sufficient health care coverage or resources to manage the disease.

However, patients continue to encounter barriers that limit physicians' ability to prescribe medicines to treat HIV and patients' ability to access and afford them. Some insurers impose high levels of cost sharing for necessary care and often refuse to cover key medications, including STRs. For some medications, pricing set by pharmaceutical companies also plays a role.

In 2016, the Center for Health Law and Policy Innovation of Harvard Law School (CHLPI) and the AIDS Research Consortium of Atlanta (ARCA) found that a Georgia-based insurer had placed 16 out of 22 of the most widely used HIV drugs in the highest cost-sharing tier, including every STR.[4] This practice leads to the average plan enrollee in Georgia with HIV spending nearly 20 percent of his/her entire monthly income to fill a single HIV prescription. In comparison, enrollees with rheumatoid arthritis can maintain their similarly priced, four-medication regimen for less than two percent of their monthly income, on average.

In Wisconsin, CHLPI and the AIDS Resource Center of Wisconsin showed an insurer covers only four of the 16 HIV drugs that are a part of the six treatment regimens recommended in the HHS treatment guidelines.[5] This level of coverage leaves five of the six recommended HIV treatment regimens effectively off-limits to enrollees.

The current administration's promise to repeal and replace the ACA has potentially dire implications for people living with, or at risk of, HIV. Looking toward 2018 and beyond, any cost-cutting move to defund state Medicaid expansion programs initiated under the ACA will immediately impair access to care for patients with little or no income. Furthermore, while the replacement plan is being crafted, the administration may choose to relax the ACA's insurance rules in order to "stabilize" marketplaces.

Multiple versions of the bills to repeal the ACA make prognostication difficult, but one potential outcome is that older patients with HIV may suddenly be saddled with premiums or other costs that are more than three times as much as younger enrollees—exceeding the threshold set under the ACA. Some experts also expect to see erosion in the ACA's safeguards preventing health plans from excluding those who have pre-existing conditions and requiring EHB coverage, thereby shifting overall health insurance costs to those who require more comprehensive coverage. Any of these changes could make life significantly tougher for people with chronic illnesses, including HIV.

Even if the White House opts for a less-than-radical overhaul of the ACA, shortcomings in the current ACA regulations and the lack of patient protections for private plans are jeopardizing the well-being of too many Americans living with HIV, as well as those who are at higher risk for HIV. There is an urgent need to more equitably treat the entire, diverse population of people living with HIV and to prevent new infections.

Strengthen Existing Regulations

The ACA was signed into law in March 2010—and regulations implementing Section 1557 were not finalized and effective until July 2016.[3] It's been a long road, and while the new regulations governing nondiscrimination are a starting point, enhancements are needed. A more expansive interpretation of the protections embodied in Sections 1557 and 1311 should not be viewed as merely a means of stabilizing the exchanges as they are constituted today.[6] Rather, enforcement of more robust nondiscrimination protections should be seen as a way to create better functioning marketplaces and the correct balance between personal and governmental responsibility. Whatever shape the current administration's plans for the

future of the ACA may eventually assume, HIV advocates insist that nondiscrimination provisions must be preserved and strengthened in the following ways.

Define health care discrimination. Section 1557 incorporates the nondiscrimination principles found in Section 504 of the Rehabilitation Act, which applies the Americans with Disabilities Act (ADA) definition of disability.[3] Under the ADA standard, HIV is essentially a categorical disability, so all people living with HIV are covered by Section 1557, as the major life activity of "immune function" is substantially impaired for all of them. However, the Rehabilitation Act and ADA were drafted as public accommodation and employment discrimination statutes, not to address discrimination specific to health insurance and health care. Currently, regulations under Sections 1557 and 1311 provide no specific guidance as to what constitutes discrimination in health plan design and coverage. HHS must mandate specific benefits and policies to ensure equal access to care, addressing potential discriminatory practices related to transparency, coverage and cost.

Provide examples of discriminatory plan design and access barriers. Without specific HIV-related examples, health plans do not have clear instruction for how to develop products and procedures that comply with nondiscrimination requirements. Practices that cause concern include, but are not limited to:

- Placing medications on high cost-sharing tiers to dissuade enrollment and/or to push significant costs on to those who do enroll
- Requiring chronically ill patients to pay a disproportionate share of the cost of medication through co-insurance or co-pays
- Failing to cover many/most commonly prescribed HIV regimens, including STRs and PrEP
- Narrowing provider networks, and even excluding entire categories of providers from networks
- Requiring—and sometimes repeatedly requiring—prior authorization or step therapy, which forces members to try one or more "prerequisite therapy" medication(s) first
- Employing excessive utilization management, or evaluation, not tied to efficacy or safety
- Failing to allow providers to easily follow HHS treatment guidelines.

Increase oversight for Pharmacy and Therapeutics (P&T) committees. The experts also recommend that the Centers for Medicare & Medicaid Services (CMS) place requirements on Pharmacy and Therapeutics (P&T) committees at hospitals and insurance plans. P&T committees that manage drug formularies should include providers, follow guidelines and be subject to monitoring.

Establish New Regulations

HIV advocacy and policy leaders also recommend establishing several new provisions through regulations and/or sub-regulations at the federal level to guide insurers. These include:

Require plans to report prior authorization data. While health plans may see prior authorization as an effective tool to cut costs or ensure appropriate treatment, physicians experience prior authorization as a manual, time-consuming process that questions their clinical judgment and takes valuable resources away from patient care.[7] Even more troubling are the treatment delays and negative patient health outcomes prior authorizations often cause. Federal regulations should require insurers to provide information regarding how often prior authorization is required and how often appeals are approved or denied. That way, diverse stakeholders can determine how prior authorizations impact all parties across the continuum of care.

Enact limits to cost sharing. The advocates also called upon CMS to introduce federal monthly out-of-pocket limits for patients, with the same maximum spend, and state limits on co-pays. At present, certain insurers who offer reasonable cost sharing are being forced to leave the marketplaces, unable to compete with insurers utilizing potentially discriminatory plan designs.12 This leaves patients at the mercy of insurers overcharging for lifesaving medications, and it destabilizes the marketplaces by reducing the number of insurers offering plans, thus stifling competition.

Enforce Current Law/Regulations

It is clear that issues with health plan transparency, coverage and cost persist, resulting in barriers to care and potential discrimination for people living with HIV. Thus far, the HHS has demonstrated little capacity to uphold the antidiscrimination provisions of the ACA and may lack some tools and resources necessary to do so. We must extend and enforce Sections 1557 and 1311:

Address complaints to health plans and policies allegedly using discriminatory practices. Participants in the roundtable discussion encouraged wider use of tools, such as complaint letters, to challenge health plan policies that discriminate against individuals living with HIV. They also called on HHS to actively review these complaints — something it has not done in the past. The alternative would be costly and time-consuming litigation to establish legal precedents.

Implement HHS Notice of Benefit and Payment Parameters and CMS Letters to Issuers. The HHS Notice of Benefit and Payment Parameters and CMS Letters still need to be fully executed.[3] These letters address transparency issues and strongly caution insurers to avoid discouraging enrollment of people with chronic conditions. The letters require that:

- All formulary drug lists must be up-to-date and accurately list all covered drugs. P&T committees must meet quarterly and make an effort to review new drugs within 90 days and make a decision within 180 days of a drug being on the market (or provide a justification if they miss this deadline)
- Formulary links must be accessible to the general public through a clearly identified link or tab on the plan website
- Plans are discouraged from mid-year formulary changes, while recognizing that changes related to availability may be necessary.

Engage with state health insurance regulators on nondiscrimination regulation enforcement. Commissioners, legislators, health departments and others at the state level do not necessarily have the experience or resources to review their state health plans through an HIV-treatment lens. In the states where progress has been made, patients and third parties have actively engaged with authorities around issues and complaints. CMS/OCR and advocates must continue working with regulators, providing them with education and tools to competently review and improve their respective state plans.

Enforce and track the Essential Community Providers (ECP) provision. The ECP provision requires plans to:

- Include each type of ECP in their network or justify otherwise
- Highlight the ECPs in their plan on the provider network list
- Show the geographic distribution of the providers in their networks, and account for accessibility by beneficiaries in the coverage area.

CMS has not been able to report what plans have which ECPs, as these data have not been collected. Maintaining and successfully implementing ECPs is essential for ensuring the care and treatment of people living with HIV.

Implement proven monitoring and oversight processes. The success of the health care marketplaces depends on HHS (CMS/OCR) establishing effective approaches for identifying and addressing potentially discriminatory practices.9 Such practices include unreasonably excluding large numbers of treatments and subjecting them to prior authorization or exceedingly high cost sharing. There also must be consequences, such as warning letters for first-time offenders. Continued allegations of discrimination should lead to litigation.

Now Is the Time to Make Antidiscrimination Health Law Meaningful

Today HIV is a manageable chronic disease, but it still remains a serious public health risk, touching every corner of the U.S.3 HIV does not discriminate, and neither should the health care system in the way it treats those living with this disease.

As a nation, our health care system is at a critical crossroads of uncertainty and opportunity. Failure to strengthen and improve public programs could have grave long-term consequences, not just for those living with HIV, but for all of public health in the U.S.

The nondiscrimination and patient protections roundtable took an important step by prioritizing measures that would improve the lives of patients and strengthen the enforcement of rules on which those changes rest. The shared objective at the meeting was to ensure people living with HIV have access to high-quality, affordable care and a strong safety net. The need for cross-stakeholder collaboration to dismantle known barriers to care and prevent new ones from emerging in a political climate demonstrated to be increasingly hostile to regulatory controls can't be overstated. The core aspirations of participants in the roundtable have broad support in government circles and across American civil society: namely, to bring relief to people suffering with chronic health conditions.

The next step is embracing the ideas of key national and state HIV thought leaders to turn these ideals into action. **HIV**

ABOUT THE AUTHORS:

Carl Schmid has been with The AIDS Institute, a national public policy, advocacy and research organization that advocates for people with HIV and viral hepatitis, since February 2004 and currently serves as Deputy Executive Director. He directs the Institute's federal policy priorities before the executive agencies and the Congress.

Tyler Andrew TerMeer, MS, is the Executive Director for Cascade AIDS Project (CAP). Founded in 1983 and incorporated in 1985 as the Cascade AIDS Project, CAP is the oldest and largest community-based provider of HIV services, housing, education and advocacy in Oregon and Southwest Washington.

REFERENCES

1. I am Essential Coalition. (2017, February). Maintaining and Enforcing Important Patient Protections & Access to Prescription Drugs. Retrieved from https://www.iamessential.org/wp-content/uploads/2016/11/20.10.17-IAE-Letter-to-Trump-Admin-re-ACA-regs-.pdf
2. WhiteHouse.gov. (2016, December). National HIV/AIDS Strategy for the United States: Updated to 2020: 2016 Progress Report. Retrieved from https://www.whitehouse.gov/sites/whitehouse.gov/files/images/nhas-2016-progress-report.pdf
3. Greenwald, R. (2016, August 30). Health Care Rights Enforcement: Advocacy Efforts and Next Steps. Presentation, Non-discrimination and Patient Protections Roundtable.
4. Center for Health Law and Policy Innovation. (2016, September 6). Discrimination Complaint. Retrieved from http://www.chlpi.org/wp-content/uploads/2013/12/GA-Humana.pdf
5. Center for Health Law and Policy Innovation. (2016, September 6). Discrimination Complaint. Retrieved from http://www.chlpi.org/wp-content/uploads/2013/12/WI-ANTHEM.pdf
6. Antos, J., Capretta, J. (2016, October 11). The Future of the ACA's Exchanges. Health Affairs Blog. Retrieved from http://healthaffairs.org/blog/2016/10/11/the-future-of-the-acas-exchanges/?utm_campaign=KHN%3A+Daily+Health+Policy+Report&utm_source=hs_email&utm_medium=email&utm_content=35721053&_hsenc=p2ANqtz-9LKZx8H7nB-Bhw1YW5b6oHt_5bny0ogHcbLcbLcT1S-PGJG6c89hHHaTiVmiB1JErbMuZmgflltfC44FPwd6P4tpUU9-oogkcxaehJkrYk8NMABDY&_hsmi=35721053
7. American Medical Association. (2016). Prior Authorization Toolkit. Retrieved from http://www.ama-assn.org/ama/pub/advocacy/topics/administrative-simplification-initiatives/electronic-transactions-toolkit/prior-authorization.page

APPLICATIONS NOW BEING ACCEPTED

GILEAD SCIENCES RESEARCH SCHOLARS PROGRAM IN HIV

Supporting innovative scientific research
that will advance knowledge in the field of HIV and provide
support for researchers in Canada and the
United States who are early in their careers

**Each award will be funded up to USD130,000,
to be paid in annual installments of up to USD65,000**

Awards are subject to separate terms and conditions

SCIENTIFIC REVIEW COMMITTEE

Applications will be reviewed by a Committee of
internationally recognized experts in basic and
clinical research in the field of HIV

**Application deadline date is Friday, January 15, 2018,
Midnight Eastern Standard Time**

**For complete program information and to apply for an award,
please visit the website below**

http://researchscholars.gilead.com

Click on the HIV program logo

GILEAD
Advancing Therapeutics.
Improving Lives.

PrEP Update

What the Latest Studies for HIV Prevention Have Found

BY PHILLIP BOLDUC, MD, AAHIVS

HIV PRE-EXPOSURE PROPHYLAXIS (PREP) with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) was first approved by the Federal Drug Administration (FDA) in 2012 for "at risk" sexually active adults. Soon after, additional guidelines for heterosexual men and women and injection drug users were issued. In 2014, the Centers for Disease Control (CDC) issued the first practice guideline on PrEP.[1] This intervention has become a critical component of HIV prevention over the past three years. This article covers some recent highlights from the recent PrEP literature and studies presented at the 9th IAS Conference on HIV Science held this past summer in Paris.

Potent Prevention: PrEP and HIV Treatment

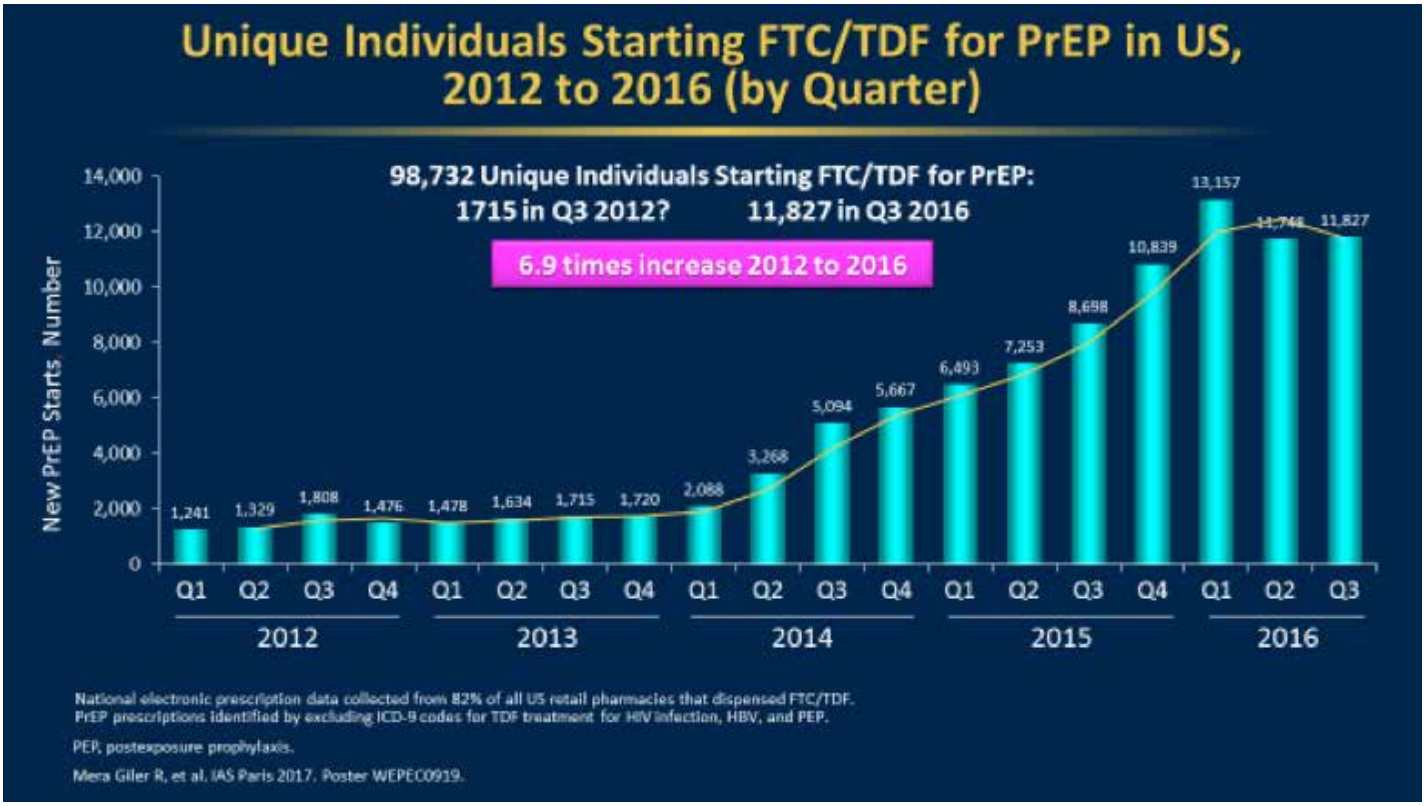
Tenofovir disoproxil fumarate / emtricitabine (TDF/FTC) used for PrEP has consistently been shown to be a safe and highly effective prevention tool. Early PrEP trials that had poor results, especially with women, were marked by poor adherence. With consistent medication adherence, protection from HIV ranged from 74-92% in the Bangkok, Partners, and IPrEx PrEP trials. Two recent studies, including an observational cohort from Kaiser Permanente California, showed no PrEP failures and the PROUD study among high-risk MSM in London found an 86% HIV infection risk reduction that actually lead to early study termination.[2,3] Treatment of HIV with ART has also been shown to be a powerful tool to prevent viral transmission as seen with the HPTN 052 study. This international study found no linked HIV transmissions after six months of viral suppression.[4] More recently the "Opposites Attract" cohort study presented at the IAS meeting, found no HIV transmissions among 16,889 acts of condomless anal intercourse when the HIV+ partner was virally suppressed.[5]

The 2014 PrEP guidelines currently recommend PrEP for the uninfected member of an HIV serodiscordant couple without mention if the HIV+ person is fully suppressed on ART.[1] In light of new data, PrEP for the uninfected partner should be an individualized decision based on the reliability of both the viral suppression in the HIV-infected person and the degree of monogamy of the couple.

PrEP Uptake and Cost-Effectiveness

The cost-effectiveness of PrEP has been questioned since its FDA approval. This remains a complex issue and is dependent on many factors including variable drug pricing, HIV testing and linkage to care rates, and, most importantly, local HIV prevalence and individual risk behavior. The CDC has recommended PrEP for at-risk individuals since its approval without regard to cost. A study from the CDC (see Table 1) found that approximately 1.2 million adults in the U.S.

FIGURE 1



should be considered for PrEP based on risk.[6] However, as of the 3rd quarter of 2016, only 96,782 individuals in the U.S. had been started on PrEP in nearly four years, or roughly 7.9% of eligible persons (See Figure 1).[7]

While PrEP uptake in 2012 and 2013 was quite slow, steady increases in 2014-2015 were followed by a concerning and unexplained downturn in the 2nd and 3rd quarters of 2016. To whatever extent the cost of PrEP has been a concern for some clinicians, the June 2017 FDA approval of generic TDF/FTC should reduce the cost of PrEP, although no generic product is currently available. The number needed to treat (NNT) with PrEP to avoid one HIV infection, estimated at 10-70 depending on risk level per Elion.[8] This is quite favorable compared to other common medical interventions, such as an NNT of 104 for statins for primary prevention of heart disease. Therefore, even at current pricing, with a low NNT and the additional $229,800 lifetime cost of an HIV diagnosis, PrEP is likely to be cost-effective when prescribed for at-risk individuals.[9]

Finding Patients at Risk for HIV

To identify at-risk patients, clinicians must obtain a comprehensive, non-judgmental sexual history. "Don't ask, won't know" is a cautionary reminder that we need to ask, and keep asking, our patients about their sexual and substance use behaviors in order to identify those patients who would benefit from PrEP (see Table 1).

While all patients should be asked at every visit, clinicians also need to be aware of who is at the highest risk of HIV infection. White and minority MSM together account for 66% of new HIV diagnoses despite being only 2% of the population. U.S. Latinos (24%) and especially Blacks (44%) are markedly disproportionately represented among new HIV diagnoses compared to their percentage of the US population (17% and 14%, respectively).[10] Finally, HIV incidence in the U.S. has risen dramatically and is highest in the Southeastern US. Taken together, the highest-risk individuals are southern black MSM. The CDC estimates that at current rates, 50% of all black gay and bisexual men living today will become HIV-infected in their lifetime. For a moving look at the particularly vulnerable population emblematic of these epidemiologic trends in the U.S, see the June 6, 2017 *NY Times Sunday Magazine* article by Linda Villarosa, America's Hidden H.I.V. Epidemic, at https://www.nytimes.com/2017/06/06/magazine/americas-hidden-hiv-epidemic.html?mcubz=0 .

TABLE 1

	MSM	Heterosexual Women and Men	IDU
Consider for HIV-negative people at substantial risk for acquiring HIV infection	■ HIV-positive sexual partner ■ Recent bacterial STI ■ High number of sex partners ■ Inconsistent or no condom use ■ Commercial sex work ■ High-prevalence area or network		■ HIV-positive sexual partner ■ Sharing infection equipment ■ Recent drug treatment (but currently injecting)
Clinically eligible	■ Documented negative HIV test result before prescribing PrEP ■ No signs/symptoms of acute HIV infection ■ Creatnine clearance >60 mL/min; no contraindicated medications ■ HBV status known and, if appropriate, vaccination given		
Regimens preferred	■ Emtricitabine/tenofovir DF (200/300 mg) qd ■ Daily, continuing, oral dose ≤90-day supply		
Alternative	None	■ Tenofovir DF (300 mg) qd ■ Daily, continuing, oral dose ≤90-day supply	

TABLE 2

	MSM	Heterosexual Women and Men	IDU
Specific tests	Oral/rectal gonorrhea and chlamydia NAAT, and syphilis serology	■ Assess pregnancy intent ■ Pregnancy test every 3 months	Access to clean needles/ syringes and drug treatment services
Other services every 3 months	HIV antibody text[a], medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment		
At 3 months and every 6 months thereafter		Assess renal function	
Every 6 months		Test for bacterial STIs	

This leads us to reflect on whether the benefits of PrEP have reached the highest-risk patients. Whites comprised 73% of PrEP usage in 2016 but only 26% of new HIV infections in 2015. Latinos and Blacks lagged far behind with PrEP usage (13% and 10% of PrEP prescriptions, respectively) compared to their share of new HIV infections.[7] The flipped ratio of risk to PrEP uptake must be addressed by identifying and promoting PrEP more effectively in persons at the highest risk of becoming infected with HIV.

In considering hard-to-reach patients, it is also worth noting the reasons for not using PrEP. In a national on-line survey of 2,926 MSM in the U.S., 75% reported condomless anal sex twice or more in the last 3 months, but 85% had never used PrEP and 22% were unaware of PrEP altogether.[11] Black, less-educated, and foreign-born MSM were more likely to lack access to PrEP, whereas older MSM were more concerned about drug side effects.

Another population with increasing rates of HIV infection in the U.S. is adolescents and young adults, yet the majority of PrEP trials to date have excluded persons less

"Don't ask, won't know" is a cautionary reminder that we need to ask, and keep asking, our patients about their sexual and substance use behaviors in order to identify those patients who would benefit from PrEP.

than 18 years old. In the Adolescent Trials Network Study 113, 78 youth aged 15-17 were enrolled in an open-label PrEP study. They found PrEP to be safe, well-tolerated, and effective when taken, although adherence waned from 54% at 4 weeks to 22% at 48 weeks, highlighting adherence challenges in this age group.[12]

PrEP Concerns

An early predicted consequence of PrEP was the phenomena of risk compensation, i.e. that individuals taking PrEP would increase their sexual risk-taking behavior. This was not seen in the iPrEx PrEP study, nor in Partners PrEP.[13,14] In both trials, PrEP and placebo participants demonstrated decreasing risk behavior through the study (which included risk-reduction counseling). Other PrEP studies have seen increased sexually transmitted infection (STI) rates, but no greater than increases in the baseline population, e.g. not attributable to being on PrEP. In actuality, being engaged in proper PrEP care, which includes every six month STI screening and treatment, was shown in a modeling study to have the potential to reduce overall STI rates by 40-42% by finding and reducing the community burden of STIs.[15]

Another concern when PrEP first arrived was that it would foster resistance to tenofovir. Fortunately, this has not been seen. There have been only three reported cases of PrEP failure in the setting of good adherence. Two cases involved transmission of a rare HIV strain that was already resistant to tenofovir. A third case involved a patient infected with wild-type virus that is as yet unexplained.[16] Regardless of adherence level, there have been no case reports of PrEP both failing and leading to de novo tenofovir resistance in the newly infected individual.

New Directions: On-Demand PrEP

In a study of on-demand PrEP by Molina (ANRS IPERGAY), 361 men and transgender women who have sex with men participated in this randomized trial from France and Canada.[17] This is an open-label extension study of TDF/FTC, with two tablets taken 2 to 24 hours before sexual intercourse and one tablet each at 24 and 48 hours after the initial dose. Compared to the placebo group of the randomized IPERGAY phase, this method of on-demand PrEP reduced HIV infections from 6.60 to 0.19 per 100 person-years, a relative reduction of 97%. Fourteen percent of participants reported self-limited gastrointestinal side effects and only four (1%) discontinued PrEP. Although condomless sex increased from 77% to 86% of participants in the extension study, an observed bacterial STI increase (from 49 to 59 per 100 person-years) did not reach statistical significance.[17]

The IPERGAY study would seem to prove that on-demand PrEP is highly effective. However, study participants took a median of 18 pills per month, which is an average of one 4-pill course of Truvada per week. However, we know from an open-label extension of the iPrEx study, that subjects who took four or more doses of Truvada per week achieved a 100% HIV risk reduction.[18] This raises the question as to whether the patients in IPERGAY were simply taking enough on-demand TDF/FTC each week to achieve the same drug levels found to be protective when taken in a non-event-driven fashion in the iPrEx study, whose participants took the medication daily.

This question was addressed in an abstract presented by Antoni at IAS.[19] In a subgroup analysis of the IPERGAY open-label extension study, in people taking fewer than 15 pills per month (9.5 on average), on-demand PrEP still provided 100% protection against HIV infection, although

In light of new data, PrEP for the uninfected partner should be an individualized decision based on the reliability of both the viral suppression in the HIV-infected person and the degree of monogamy of the couple.

the study size was small (134 patient-years). This data implies that on-demand PrEP is effective even when used less often than once weekly. This will hopefully be borne out as more patient-year data accrue in this study. Although many clinicians feel this data is compelling enough to support off-label on-demand PrEP by their patients, FDA labeling and CDC recommendations remain to prescribe PrEP as one tablet daily.

Other Future PrEP Directions

Areas of active PrEP research include long-acting injectable agents, dapivirine vaginal ring, and use of tenofovir alafenamide fumarate (TAF) in TDF. Although no clinically significant nor durable renal toxicity has been seen from TDF in multiple PrEP trials, longstanding experience in HIV treatment recognizes renal toxicity with TDF, primarily in patients with concomitant renal disease. TAF is more effectively concentrated in target CD4 cells than TDF, allowing for 1/12th of the administered dose, lower serum and renal tubular concentrations, and thus less renal toxicity. Co-formulated TAF/emtricitabine (Descovy™) is already available for HIV treatment, but its use for PrEP is not yet FDA-approved pending completion of an efficacy trial ("Discover" Study, which fully enrolled in June 2017).

Under study in HPTN-077 is the safety and tolerability of the experimental long-acting integrase inhibitor cabotegravir. It can be given as an injection of either 600 or 800mg every 8 or 12 weeks, respectively. Mild to moderate injection site reactions were common but diminished over time. Only one of 199 study subjects discontinued the drug due to side effects.[19] An efficacy study (HPTN-083) is now underway. Even if cabotegravir proves to be a potent PrEP agent, there are concerns about the drug's several months' long "tail" of diminishing drug levels and the possibility that INSTI resistance might occur if someone becomes infected with HIV during this period. This will be monitored during an open-label follow-up phase. Finally, the Hope and Dream studies are both enrolling women for study of the dapivirine vaginal ring. HIV

ABOUT THE AUTHOR:
Philip J. Bolduc, MD, AAHIVS, is the HIV Program and Fellowship Director and Assistant Professor of Family Medicine and Community Health at the University of Massachusetts Medical School and Family Health Center of Worcester.

REFERENCES

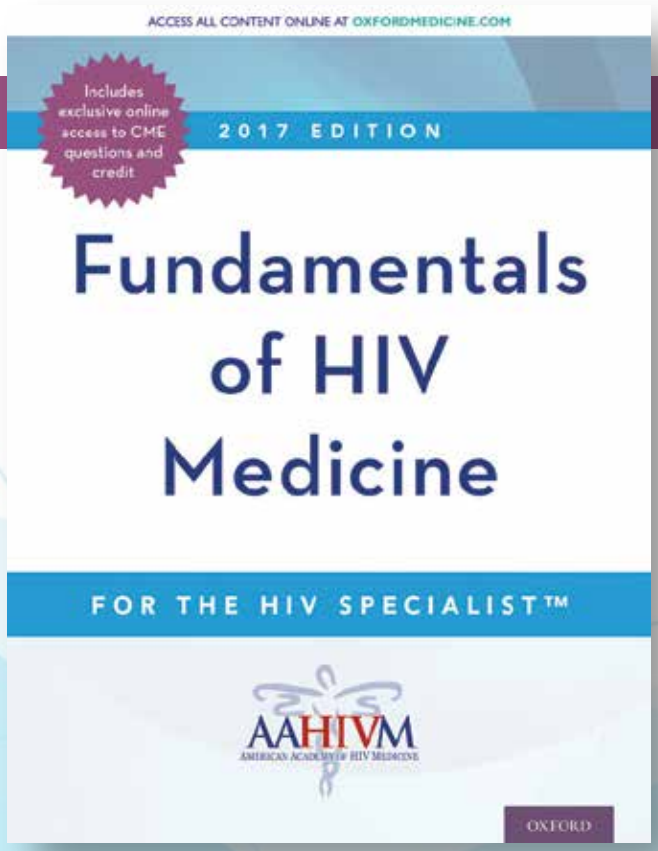
1. 2014 CDC/USPHS PrEP guidelines. @ cdc.gov/hiv/pdf/PrEPguidelines2014.pdf
2. Volk JE, et al. Clin Infect Dis. 2015; 61:1601-1603
3. White E, et al. IAS 2017 Abstract TUAC0101
4. Cohen MS, et al. N Engl J Med. 2016; 375(9):830-839
5. Bavinton B, et al. IAS July 2017, Abstract TUAC0506LB
6. Smith DK, et al. MMWR Morb Mortal Wkly Rep. 2015; 64:1291-1295
7. Mera Giler R, et al. IAS Paris 2017. Abstract WEPEC0919.
8. Elion R et al. IAS Paris 2017. Abstract WEPEC0917
9. Schackman BR et al. Med Care. April 2015; 53(4): 293–301
10. CDC. https://www.cdc.gov/hiv/pdf/library/slidesets/cdc-hiv-surveillance-race-ethnicity.pdf.
11. Mayer, KH et al. at IAS July 2017. Abstract MOPEC0648
12. Hosek S et al. JAMA Pediatr. Published online September 5, 2017]
13. Grant RM, et al. N Engl J Med. 2010;363:2587-2599
14. Baeten JM, et al. N Engl J Med. 2012;367:399-410
15. Jenness SM et al. Clin Infect Dis Sept 1, 2017;65(5):712-18)
16. Knox DC et al N Engl J Med 2017; 376(5):501-502.
17. Molina JM et al. Lancet HIV. 2017; 4(9): E402-410.
18. Grant RW; Lancet Infect Dis. 2014; 14:820-829)
19. Antoni G, et al. J Int AIDS Soc. 2017; 20(suppl 5):30-31. Abstract TUAC0102)
20. Landovitz R et al. IAS July 2017. Abstract TUAC0106LB

AAHIVM
AMERICAN ACADEMY OF HIV MEDICINE

OXFORD
UNIVERSITY PRESS

Fundamentals of HIV Medicine

Editor in Chief **W. David Hardy,** MD, AAHIVS



Compiled by *American Academy of HIV Medicine*

Published by the American Academy of HIV Medicine, this comprehensive clinical care publication for the treatment of HIV/AIDS offers the most up-to-date overview of the latest HIV treatments and guidelines.

Fundamentals of HIV Medicine is authored by more than 50 expert clinicians in immunology, HIV epidemiology, gerontology, substance abuse treatment, infectious disease medicine, and other fields central to its medical management, and includes online access to CME.

ISBN: 9780190493097 | Paperback
April 2017 | 616 pages | ~~RRP $150.00~~ **$127.50**

15% Discount

Visit our website to claim your 15% discount code by entering AAHIVM15 at checkout. AAHIVM members receive a 30% discount. Email **communications@aahivm.org** to request your members-only discount code. Valid until December 2017.

Order your copy today at

www.oup.com/academic/medicine

Increasing the Number of HIV Care Providers—One Fellow at a Time

Los Angeles HIV Public Health Fellowship Program Adds Talent to a Shrinking Workforce

BY SHANNA LIVERMORE, MPH, MCHES®

OVER THE PAST DECADE, WE HAVE SEEN EVIDENCE that suggests the supply of HIV clinicians might not be keeping pace with the growth in the demand for HIV health care services. In September of 2010, amid growing concern about the potential shortage of HIV clinicians, the Health Resources and Services Administration within the U.S. Department of Health and Human Services (HHS) sponsored the first national study to quantify the number of clinicians providing HIV medical care in the United States and to forecast the magnitude of the HIV clinician shortage or surplus.[1] HHS initiated the study to assess whether there were sufficient providers available to address the goals of the National HIV/AIDS Strategy, launched by the White House Office of National AIDS Policy in 2010 to reduce new HIV infections, increase access to care and improve health outcomes for people with HIV, and reduce disparities in access to care among individuals living with HIV.[2] The results from that national HIV clinician workforce study were release in this magazine in August of 2016.

Overall, the study showed a small but rapidly expanding shortage of HIV providers. The forecasting model predicted that by 2015 the supply of HIV clinicians will be sufficient to meet only three quarters of total demand for HIV-related medical services under current market-based assumptions. Expanded HIV testing and diagnosis and improvements in linkages, engagement, and adherence to care—without an increase in the number of health care providers willing to treat people with HIV or improvements in the productivity of the HIV workforce—will only make the forecasted deficit of HIV providers worse.

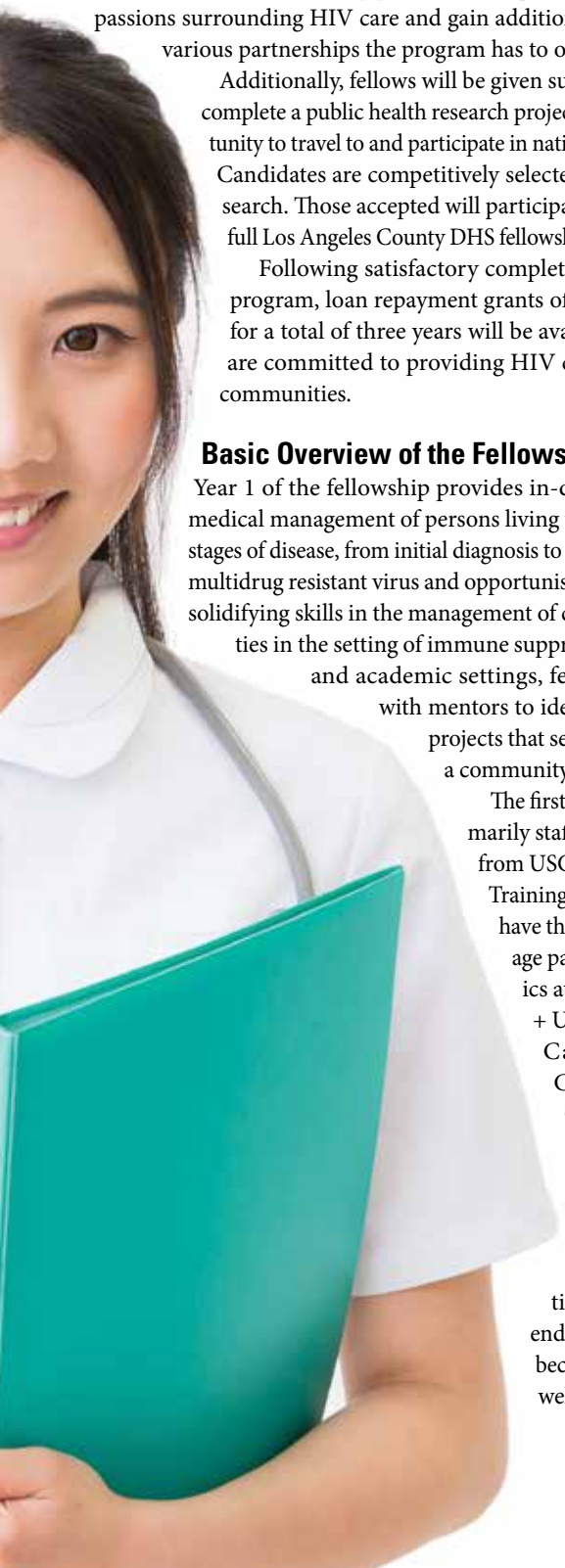
These statistics illustrate why the availability of HIV fellowship programs is so essential to the growth of the clinical community. One such program is the Los Angeles HIV Public Health Fellowship program. This is a unique clinical and research fellowship for physicians committed to improving primary care for people living with HIV in under-served communities. This program brings together the unique strengths of Los Angeles County Department of Health Services (DHS), the AIDS Education Training Center at Keck School of Medicine of USC, ViiV Healthcare, and the UCLA David Geffen School of Medicine Clinical

Leaders Program.

The purpose of this fellowship is to train physicians in the knowledge and skills necessary to provide expert HIV care. Each fellow will develop and initiate patient-centered primary care and community-specific HIV interventions. The fellowship provides a unique opportunity to explore passions surrounding HIV care and gain additional skills through the various partnerships the program has to offer.

Additionally, fellows will be given support to develop and complete a public health research project, as well as an opportunity to travel to and participate in national HIV conferences. Candidates are competitively selected through a national search. Those accepted will participate for two years, with full Los Angeles County DHS fellowship salary and benefits.

Following satisfactory completion of the fellowship program, loan repayment grants of up to $50,000 a year for a total of three years will be available to fellows who are committed to providing HIV care in under-served communities.



Basic Overview of the Fellowship

Year 1 of the fellowship provides in-depth training in the medical management of persons living with HIV/AIDS at all stages of disease, from initial diagnosis to advanced treatment of multidrug resistant virus and opportunistic infections. Besides solidifying skills in the management of common co-morbidities in the setting of immune suppression in community and academic settings, fellows will also work with mentors to identify and implement projects that seek to improve care on a community or system wide level.

The first year of training is primarily staffed by clinical faculty from USC AIDS Education and Training Center, where fellows have the opportunity to manage patients at the HIV clinics at Los Angeles County + University of Southern California Medical Center (LAC+USC), Children's Hospital of Los Angeles, Los Angeles County Jail System, and selected community clinical sites. Fellows participate in educational endeavors and projects to become HIV educators as well as clinicians.

Sample Clinical Rotations

- Communicable Disease/Infectious Disease Clinic
- Inpatient ID Service
- Colorectal Clinic
- Community HIV Clinics
- Correctional HIV Clinics
- Dermatology
- Emergency Department
- Hematology/Oncology
- HIV Resistance Test Interpretation
- HIV Test Counseling
- Neuropsychology
- Neurology
- Palliative Care
- Pediatric & Adolescent
- Pulmonary Medicine
- OB/GYN
- STD Clinics
- Women's Health

Year 2 of the fellowship provides the opportunity to take masters level coursework at the UCLA Fielding School of Public Health. Course topics include research methods, biostatistics, health policy, community-based partnerships, understanding health disparities, and more. Coursework will be balanced with other fellowship requirements (clinical responsibilities and scholarly project). Fellows will join physicians in other post-graduate programs, providing excellent opportunities for cross-disciplinary learning that is specifically geared towards practicing providers. In addition, fellows will work to complete a public health research project with their faculty mentor.

Applications are currently being accepted! If you have any general questions about the fellowship or would like to request additional information, please contact Shanna Livermore in Los Angeles County Department of Health Services by emailing Shanna.Livermore@med.usc.edu. For specific inquiries, please contact Raymond Perry, M.D., Director of the DHS HIV Public Health Fellowship at rperry@dhs.lacounty.gov or Jerry D. Gates Ph.D., Director USC AETC at jdgates@med.usc.edu for clinical related questions. HIV

ABOUT THE AUTHOR:
Shanna Livermore, MPH, MCHES, is the Program Manager and Clinical Training Program Coordinator for the Department of Family Medicine at the Keck School of Medicine at the University of Southern California.

REFERENCES

1. Gilman B, Bouchery E, Barrett K, et al. HIV clinician workforce study final report. Report submitted to U.S. Department of Health and Human Services, Health Resources and Services Administration, HIV AIDS Bureau. Cambridge, MA: Mathematica Policy Research; May 2013.

2. White House Office of National AIDS Policy. National HIV/AIDS Strategy for the United States. Washington, DC: White House Office of National AIDS Policy; July 2010. http://www.whitehouse.gov/administration/eop/onap/nhas. Accessed November 18, 2012.

Choosing the HIV Career Path

The following is an interview with Dr. Gilmer Youn, a Los Angeles HIV Public Health Fellowship alumnus from 2012–2013. Dr. Youn is now providing HIV Primary Care at Alta med in Los Angeles.

Why did you choose to pursue a career in HIV Primary Care?

"As I was finishing my fellowship in Infectious Disease, I thought back to my most memorable experiences in medical school and remembered that most of them occurred while volunteering at the UCSD Student-Run Free Clinic. I realized that providing long-term continuity of care for patients was the most fulfilling part of medicine for me. That's why I chose to work at AltaMed in East Los Angeles, where I am the primary care physician for a large panel of HIV positive patients. I also provide Hepatitis C care for mono-infected patients and PrEP for HIV prevention. I really enjoy taking care of the mix of patients that receive our specialty services."

What brought you to the HIV Fellowship in particular?

"There are few programs in the country like the Los Angeles HIV Public Health Fellowship. During my time there, Hepatitis C training was added to the curriculum. I am grateful to Dr. Martin Sattah for teaching me about Hepatitis C; we really learned a lot together along with physician assistant Mussolini Africano. Thanks to the fellowship, I received in-depth training on HIV resistance, learned how to teach others about HIV through the mini-camp series we offered to community residents, and learned the importance of teamwork. Without clerks, social workers, therapists, medical records, and providers working together, good HIV care would not be possible."

What did you particularly enjoy about this fellowship program?

"The one on one conversations I had with patients in the emergency department after they were newly diagnosed with HIV. Even though I felt more prepared for these conversations as the years went on, they were never easy and each patient presented with unique life situations and questions. The same types of conversations I had in training are the conversations I have every week with patients at AltaMed. The range of reactions vary from depression to denial/shock to nonchalance, but the most important lesson I learned from my mentor Dr. Kathleen Jacobson is to instill hope. They may not remember the details but they will remember that we offered them hope and showed that we care."

What was your favorite clinical experience and why?

"Taking care of a newly diagnosed patient with HIV/AIDS with a difficult path to recovery. Every time we made some progress, a new complication would arise. This happened several times. He would get discouraged because he saw others around him getting better without any hiccups. He tried his best to maintain hope and a positive outlook. I continued to take care of him and he made a remarkable recovery to the point where he started working again."

What was the best part of your training in the fellowship?

"Mentorship. I am forever indebted to the HIV faculty for educating me and preparing me for this (hopefully) long journey." HIV

Mytesi®
(crofelemer) 125 mg delayed-release tablets

The following is a brief summary only; see full prescribing information for complete product information at www.mytesi.com.

INDICATIONS AND USAGE

MYTESI is an antidiarrheal indicated for the symptomatic relief of non-infectious diarrhea in adult patients with HIV/AIDS on antiretroviral therapy.

DOSAGE AND ADMINISTRATION

The recommended dose of MYTESI is one 125 mg delayed-release tablet taken orally two times a day, with or without food. MYTESI tablets **should not be crushed or chewed**. Tablets should be swallowed whole.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Risks of Treatment in Patients with Infectious Diarrhea

If infectious etiologies are not considered, and MYTESI is initiated based on a presumptive diagnosis of non-infectious diarrhea, then there is a risk that patients with infectious etiologies will not receive the appropriate treatments, and their disease may worsen.

Before starting MYTESI, rule out infectious etiologies of diarrhea. MYTESI is not indicated for the treatment of infectious diarrhea.

ADVERSE REACTIONS

Clinical Trials Experience

A total of 696 HIV-positive patients in three placebo-controlled trials received MYTESI for a mean duration of 78 days.

Adverse reactions for MYTESI that occurred in at least 2% of patients and at a higher incidence than placebo are provided in Table 1.

Table 1: Adverse Reactions Occurring in at Least 2% of Patients in the 125 mg Twice Daily Group

Adverse Reaction	Crofelemer 125 mg BID* N = 229; n (%)	Placebo N = 274 n (%)
Upper respiratory tract infection	13 (5.7)	4 (1.5)
Bronchitis	9 (3.9)	0
Cough	8 (3.5)	3 (1.1)
Flatulence	7 (3.1)	3 (1.1)
Increased bilirubin	7 (3.1)	3 (1.1)
Nausea	6 (2.6)	4 (1.5)
Back pain	6 (2.6)	4 (1.5)
Arthralgia	6 (2.6)	0
Urinary tract infection	5 (2.2)	2 (0.7)
Nasopharyngitis	5 (2.2)	2 (0.7)
Musculoskeletal pain	5 (2.2)	1 (0.4)
Hemorrhoids	5 (2.2)	0
Giardiasis	5 (2.2)	0
Anxiety	5 (2.2)	1 (0.4)
Increased alanine aminotransferase	5 (2.2)	3 (1.1)
Abdominal distension	5 (2.2)	1 (0.4)
* Twice daily		

Adverse reactions that occurred in between 1% and 2% of patients taking a 250 mg daily dose of MYTESI were abdominal pain, acne, increased aspartate aminotransferase, increased conjugated bilirubin, increased unconjugated blood bilirubin, constipation, depression, dermatitis, dizziness, dry mouth, dyspepsia, gastroenteritis, herpes zoster, nephrolithiasis, pain in extremity, pollakiuria, procedural pain, seasonal allergy, sinusitis and decreased white blood cell count.

DRUG INTERACTIONS

Drug Interaction Potential

In vitro studies have shown that crofelemer has the potential to inhibit cytochrome P450 isoenzyme 3A and transporters MRP2 and OATP1A2 at concentrations expected in the gut. Due to the minimal absorption of crofelemer, it is unlikely to inhibit cytochrome P450 isoenzymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and CYP3A4 systemically.

Nelfinavir, Zidovudine, and Lamivudine

MYTESI administration did not have a clinically relevant interaction with nelfinavir, zidovudine, or lamivudine in a drug-drug interaction trial.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

Reproduction studies performed with crofelemer in rats at oral doses up to 177 times the recommended daily human dose of 4.2 mg/kg revealed no evidence of impaired fertility or harm to the fetus. In pregnant rabbits, crofelemer at an oral dose of about 96 times the recommended daily human dose of 4.2 mg/kg, caused abortions and resorptions of fetuses. However, it is not clear whether these effects are related to the maternal toxicity observed. A pre- and postnatal development study performed with crofelemer in rats at oral doses of up to 177 times the recommended daily human dose of 4.2 mg/kg revealed no evidence of adverse pre- and postnatal effects in offspring. There are, however, no adequate, well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether crofelemer is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from MYTESI, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of MYTESI have not been established in pediatric patients less than 18 years of age.

Geriatric Use

Clinical studies with crofelemer did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients.

Use in Patients with Low CD4 Counts and High Viral Loads

No dose modifications are recommended with respect to CD4 cell count and HIV viral load, based on the findings in subgroups of patients defined by CD4 cell count and HIV viral load.

The safety profile of crofelemer was similar in patients with baseline CD4 cell count less than 404 cells/μL (lower limit of normal range) (N=388) and patients with baseline CD4 cell counts greater than or equal to 404 cells/μL (N=289).

The safety profile of crofelemer was similar in patients with baseline HIV viral loads less than 400 copies/mL (N = 412) and patients with baseline HIV viral loads greater than or equal to 400 copies/mL (N = 278).

PATIENT COUNSELING INFORMATION

- Instruct patients that MYTESI tablets may be taken with or without food.
- Instruct patients that MYTESI tablets should not be crushed or chewed. Tablets should be swallowed whole.

Rx Only

Manufactured by Patheon, Inc. for

napo pharmaceuticals
a subsidiary of jaguar health®

Napo Pharmaceuticals, Inc., San Francisco, CA 94105

US Patent Nos. 7,341,744 and 7,323,195.
NP-365-1 07/17

The botanical drug substance of MYTESI is extracted from *Croton lechleri* (the botanical raw material) that is harvested from the wild in South America.

In adult HIV patients on ART who have noninfectious diarrhea

When Enough is Enough,

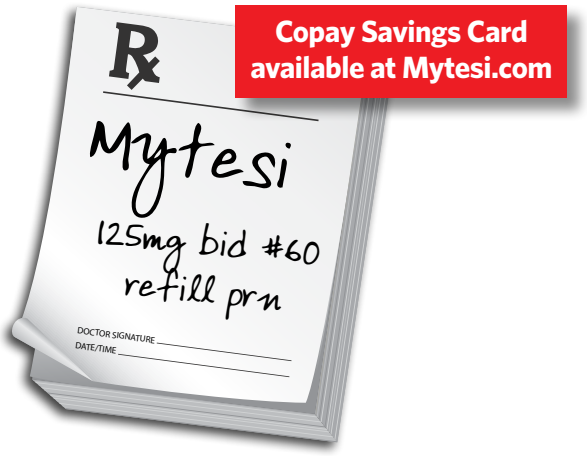
Mytesi—A different way to treat diarrhea

An antisecretory antidiarrheal that:

- Works by normalizing water flow in the GI tract to provide symptomatic relief of diarrhea
- Is not an opioid and does not affect GI motility

Mytesi has been proven to have:

- No clinically relevant drug-drug interactions
- Adverse events comparable to those with placebo



Copay Savings Card available at Mytesi.com

Important Safety Information About Mytesi

Mytesi (crofelemer) is an antidiarrheal indicated for symptomatic relief of noninfectious diarrhea in adult patients with HIV/AIDS who are on antiretroviral therapy (ART). Mytesi is not indicated for the treatment of infectious diarrhea. Rule out infectious etiologies of diarrhea before starting Mytesi. If infectious etiologies are not considered, there is a risk that patients with infectious etiologies will not receive the appropriate therapy and their disease may worsen. In clinical studies, the most common adverse reactions occurring at a rate greater than placebo were upper respiratory tract infection (5.7%), bronchitis (3.9%), cough (3.5%), flatulence (3.1%), and increased bilirubin (3.1%).

napo pharmaceuticals
a subsidiary of jaguar health

Please see brief summary of Full Prescribing Information on adjacent page.

Mytesi®
(crofelemer) 125 mg
delayed-release tablets