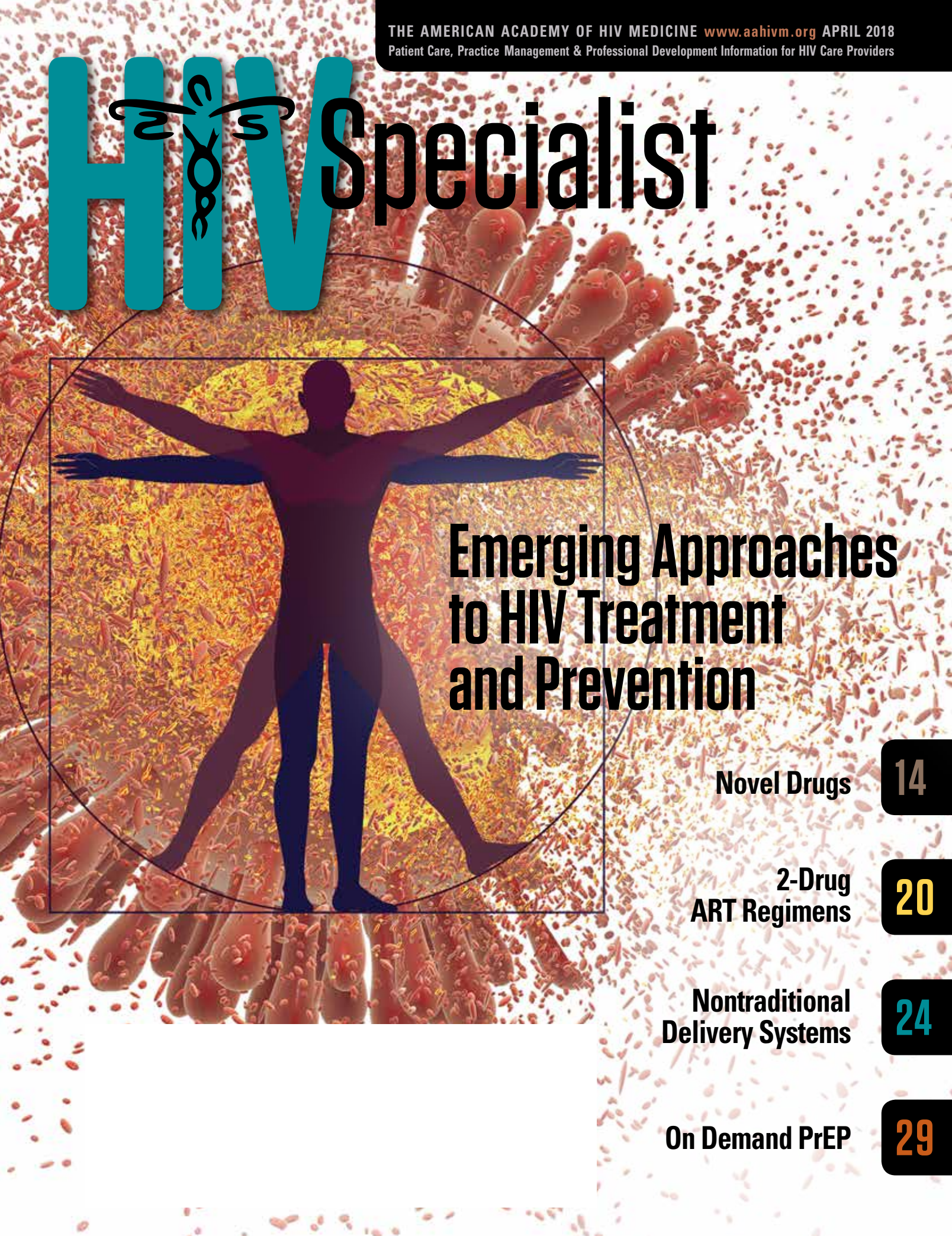


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PUBLICATION DESIGN AND ART DIRECTION

BonoTom Studio, Inc.

703-276-0612, info@bonotom.com

ADVERTISING

Jane Dees Richardson

AAHIVM Advertising Sales

c/o Ad Marketing Group, Inc.

703-243-9046 ext. 102, Fax: 856-219-8957

jrichardson@admarketinggroup.com

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

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Celebrating Progress

IN THE EARLY 1980'S, I was an Acting Deputy Assistant Secretary reporting directly to the Assistant Secretary for Health, Dr. Ed Brandt, in the U.S. Public Health Service (PHS). The most pressing and frightening matter for the Health Service at that time was what would become eventually be named HIV and AIDS. I was fortunate to be an observer in the critical meetings Dr. Brandt chaired with all of the PHS Agency Heads. The sense of urgency was palpable.

Those were the days with many questions and very few answers. Despite scientists at the Centers for Disease Control tracking the disease and researchers at the National Institutes of Health isolating the cause and working on treatments, AIDS was still nearly 100% deadly throughout the decade.

Thankfully, we have seen enormous change. There are few conditions that have evolved from a death sentence to a manageable, chronic condition in modern medical history. We have seen extraordinary treatment advances.

And that leads us to the topic for this issue of the *HIV Specialist: Emerging Approaches to HIV Treatment and Prevention*. This issue includes articles on new pharmaceuticals and new methods of delivery, such as injectables and implants. We also look at new programs and approaches to better facilitate prevention, specifically the use of PrEP.

I want to give a special thank you to our two guest editors, Jason Schafer and Milena McLaughlin.



James M. Friedman

Both PharmD members of AAHIVM, Jason and Milena identified the content and authors for all of the articles in our cover package. They represent what is great about of our much-appreciated pharmacist members, the fastest growing segment of our membership.

Just as the advances in HIV have grown through the years, so too has our organization. This became even more apparent recently during our annual Board

of Directors meeting held in conjunction with CROI in Boston. Each time I leave these meetings, I am always impressed with the dedication of our Board members and our staff. But regardless of whether we are talking about clinical advances or organizational advances, the bottom line is there is a commitment to making the lives of people living with HIV better.

We have still not gotten to the final chapter in the HIV story. There is still no cure and no vaccine. But what a remarkable book it's been so far. So let's keep reading until we can turn off the light and sleep soundly. **HIV**

In the NEWS

New Oncology Guidelines for People Living With HIV and Cancer Seek Appropriate Cancer Treatment

The National Comprehensive Cancer Network (NCCN) has released brand new NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) intended to help make sure people living with HIV who are diagnosed with cancer receive safe, necessary treatment. In 2010, an estimated 7,760 PLWH in the United States were diagnosed with cancer, representing an approximately 50% higher rate than the general population. However, studies have found PLWH are treated for cancer at significantly lower rates than HIV-negative people with cancer, despite most treatment courses being safe and effective in this population.

The new NCCN Guidelines for Cancer in People Living With HIV includes general advice - while highlighting the importance of working in collaboration with an HIV specialist—as well as specific treatment recommendations for non-small cell lung cancer (NSCLC), anal cancer, Hodgkin's lymphoma, and cervical cancer. Additional recommendations can be found in the recently-released NCCN Guidelines for AIDS-Related Kaposi Sarcoma, as well as the AIDS-related B-cell lymphomas section of the NCCN Guidelines for B-cell Lymphomas.

The NCCN Guidelines Panel for Cancer in People Living With HIV included oncologists, radiologists, infectious disease specialists, surgical oncologists, pharmacists, and a patient advocate. The panel stressed the importance of increasing the number of PLWH who participate in clinical trials for cancer treatments. Clinicians working with PLWH who have cancer should use clinicaltrials.gov to help patients find appropriate trials. The NCCN Guidelines for Cancer in People Living With HIV are available free of charge for non-commercial use online at NCCN.org. They can also be viewed via the Virtual Library of NCCN Guidelines mobile app for smartphones and tablets.



New Study Shows Women's HIV Risk Triples During Pregnancy, Quadruples Postpartum

A NEW META-ANALYSIS has revealed that women's HIV risk increases substantially during the late stage of pregnancy and in the weeks after giving birth—a finding that re-emphasizes the importance of women-controlled HIV prevention strategies, such as oral pre-exposure prophylaxis (PrEP).

In addition, the analysis hints at yet-unknown physiological changes associated with pregnancy that increase a woman's susceptibility to HIV infection. The research, led by Kerry A. Thomson, Ph.D., M.P.H., University of Washington, was published in the *Journal of Infectious Diseases* on March 5 and presented at the 2018 Conference on Retroviruses and Opportunistic Infections (CROI) in Boston by Renee Heffron, Ph.D., M.P.H., assistant professor, University of Washington at Seattle.

The researchers pooled multiple studies to analyze 2,751 African serodiscordant couples. They compared a woman's risk of contracting HIV when not pregnant, during early pregnancy, during late pregnancy, and during the postpartum period. As a benchmark, they determined the risk of HIV infection per condomless sex act for a non-pregnant, 25-year-old woman not taking PrEP and having sex with an HIV-positive partner

with a viral load over 10,000 copies/mL.

During the studies they reviewed, about a quarter of women became pregnant and 82 women became HIV positive. Ultimately, 78 of those who were positive were included for analysis. The researchers found that, compared with non-pregnant periods, an HIV-negative woman's infection risk jumped nearly threefold during late-stage pregnancy and fourfold during the postpartum period. Specifically, for every 1,000 sex acts, the infectivity rate for non-pregnant and non-postpartum women was 1.05. That rate jumped to 2.19 during early pregnancy and 2.97 during late pregnancy. The rate jumped dramatically during the postpartum period to 4.18. This risk remained even when researchers accounted for other possible confounding factors, such as condom use, age, PrEP use, and the viral load of an HIV-positive partner.

This research has important public health implications. Chiefly, the findings highlight the need for frequent HIV testing throughout pregnancy and the importance of promoting women-controlled HIV prevention strategies during pregnancy and in the months after birth or miscarriage, said Heffron.

In the NEWS

High Uptake and Use of Vaginal Ring for HIV Prevention Observed in Open-Label Study



NEARLY 90% of participants in an open-label study of a vaginal ring infused with a drug to prevent HIV are using the monthly ring at least some of the time, according to an interim analysis of study data. In addition, the rate of HIV infection among participants in the open-label study, which has no placebo

arm for comparison, is half of what might be expected in the absence of the ring, according to mathematical modeling that has significant limitations. These preliminary findings from the HIV Open Label Extension (HOPE) study were presented during a press conference at the 2018 Conference on Retroviruses and Opportunistic Infections (CROI) in Boston.

Participants in the HOPE study are being offered the dapivirine ring to insert into their vagina for a month at a time for up to 12 consecutive months. During the first three months, the women attend monthly study visits where they may obtain a new ring. Thereafter, they attend quarterly visits where they may obtain three rings at a time, a schedule that more closely resembles how the ring might be distributed in a real-world setting. Participants may remain in the HOPE study regardless of whether they accept or use new rings. More than 90% of participants accepted the ring when they entered the study. Adherence to the ring is being assessed by measuring residual levels of dapivirine in returned rings and blood levels of dapivirine. Some 89% of the rings returned as of October 2017 have residual dapivirine levels consistent with some use during the prior month. In contrast, 77% of returned rings in the ASPIRE study had residual dapivirine levels consistent with some use during the prior month, suggesting that adherence in the HOPE study is roughly 16% higher than it was in ASPIRE. Investigators lacked data to precisely quantify the duration of ring use in either study. The ring is designed to be worn continuously throughout the month to provide effective protection. Measurements of blood levels of dapivirine were not included in the interim analysis.

As of October 2017, HOPE study participants have become infected with HIV at a rate of 1.9 new infections per 100 person-years of follow-up. Person-years are the sum of the number of years that each participant has been in the study.

(#143LB and 144LB, 25th CROI, Boston, MA, March 2018)

Varied Characteristics Associated with Missed Clinic Visits Among Youths Living with HIV

FEMALE SEX, BLACK OR MIXED RACE, DRUG USE, and a history of incarceration are associated with poor adherence to regular clinic visits among youth patients living with HIV, according to findings from a cross-sectional study published in *AIDS Care*.

A total of 2,125 individuals living with HIV between the ages of 12 and 24 years were included in this cross-sectional analysis. Investigators sought to identify interventional targets among youths living with HIV (YLH) who attended HIV clinics and who had missed a clinic visit in the last year. Within the last year, approximately 36% of participants reported missing ≥ 2 clinic visits.

Characteristics associated with the greatest chance of missing a clinic visit among YLH included female sex (adjusted odds ratio [aOR], 1.63 compared with males), black or mixed racial heritage (aOR, 1.76 and 1.71, respectively, compared with white YLH), an unknown route of infection (aOR, 1.86 compared with YLH with perinatal infection), and endorsing HIV disclosure (aOR, 1.37 compared with YLH not endorsing disclosure).



HIV Prevention Pill Not Reaching Most Americans Who Could Benefit—Especially People of Color

A NEW CDC ANALYSIS suggests only a small percentage of Americans who could benefit from pre-exposure prophylaxis (PrEP) have had it prescribed. In the first detailed analysis by race and by risk group, CDC researchers also found that while two-thirds of people who could potentially benefit from PrEP are African-American or Latino, they account for the smallest percentage of prescriptions to date.

The findings were presented at the annual Conference on Retroviruses and Opportunistic Infections in Boston by Dawn K. Smith, MD, MPH, MS, epidemiologist and medical officer in the CDC's Division of HIV/AIDS Prevention. Dr. Smith presented the new CDC estimates of PrEP needs and an examination of available data on PrEP prescriptions from a national database of prescriptions filled by commercial pharmacies in the United States.

Results indicate that in 2015, approximately 500,000 African-Americans and nearly 300,000 Latinos across the nation could have potentially benefited from PrEP based on CDC clinical guidelines. However, only 7,000 prescriptions were filled at retail pharmacies or mail order services for African-Americans and only 7,600 for Latinos during a similar time period (September 2015–August 2016). While racial and ethnic data were not available for one-third of the prescription data, the analysis found a substantial unmet prevention need.

The gap between how many people could potentially benefit from PrEP and how many received it was smaller among whites, yet still considerable. Of approximately 300,000 whites who could potentially have benefited from PrEP, only 42,000 prescriptions were filled at retail pharmacies or mail order services. The new national estimate is about 1.1 million Americans overall are at substantial risk for HIV and should be offered PrEP. However, only 90,000 PrEP prescriptions were filled in commercial pharmacies in the year examined.

(#86. 25th CROI, Boston, MA. March 2018.)

Once-Daily Tenofovir Alafenamide Appears Sufficient When Dosed With Rifampicin

Plasma concentrations of tenofovir alafenamide AUC were decreased by 55% and intracellular tenofovir-diphosphate concentrations by 36% when given with rifampicin. But intracellular concentrations were still 76% higher than those with standard dose tenofovir disoproxil fumarate.

These data from RIFT, a pharmacokinetic (PK) study of once-daily tenofovir alafenamide (TAF) with rifampicin (RIF) conducted by Maddalena Cerrone and colleagues from Chelsea and Westminster Hospital, London, UK, The Johns Hopkins University, Baltimore, MD, USA, University of Liverpool, Liverpool, UK, and the University of Cape Town, Cape Town, South Africa, were presented at CROI 2018. The study is the first to measure PK of once-daily TAF with RIF and compare it directly to tenofovir disoproxil fumarate (TDF).

TAF achieves lower plasma and higher

intracellular tenofovir (TFV) concentrations than TDF, but it is a substrate of drug transporters so has potential for drug interactions, especially with inducers like RIF.

A recent parallel design PK study showed when twice-daily TAF was given with RIF intracellular TFV-diphosphate (DP) decreased by 24% and plasma TAF by 15% compared with once-daily TAF alone.

RIFT is a Phase 1, open label, single arm, single centre evaluation in 23 HIV negative participants (21 completed). Participants received TAF FTC 25/200 mg once daily (28 days) with food, followed by TAF/FTC + RIF 600 mg once daily (28 days, RIF on empty stomach followed by TAF FTC with meal after 30 mins), followed by TDF 300 mg once daily (28 days) with food.

The investigators performed intensive PK sampling on days 28 (TAF/FTC), 56 (TAF/FTC+RIF) and 84 (TDF). Plasma TAF, TFV, FTC

and intracellular TFV-DP and FTC-triphosphate (FTC-TP) concentrations were measured by validated LC-MS methods. Participants were genotyped for polymorphisms.

Twenty-one participants completed all PK phases. FTC-TP PK parameters were not affected by RIF. There were no significant associations with any polymorphisms. There were two Grade 3 adverse events and 2/23 participants discontinued: one due to a case of transient hypertransaminitis during administration of TAF/FTC only (the investigators judged this to be unlikely drug related); one due to gastrointestinal symptoms (judged likely RIF-related).

The investigators concluded that although RIF co-administration decreased the plasma TAF by 55% and intracellular TFV-DP AUC by 36%, intracellular TFV-DP AUC was 76% higher with TAF + RIF than with TDF (300 mg once daily) alone.

In the NEWS

Nominations to the CDC/HRSA Advisory Committee on HIV, Viral Hepatitis and STD Prevention and Treatment

HRSA published a notice in the Federal Register to request nominations to the CDC/HRSA Advisory Committee on HIV, Viral Hepatitis and STD Prevention and Treatment (CHAC). HRSA is seeking four candidates who have expertise in public health; epidemiology; laboratory practice; immunology; infectious diseases; behavioral health and science including, but not limited to opioid use and related expertise; health education; healthcare delivery; state health

programs; clinical care; preventive health; medical education; health services and clinical research; and healthcare financing to serve up to 4-year terms on the CHAC. In addition, people living with HIV and affected populations as well as individuals employed by state and local health and education agencies, HIV/viral hepatitis/STD community-based organizations, and the ethics or religious community are encouraged to submit nomination packages for consideration.

Nomination packages may be submitted directly by the individual being nominated or by the person/organization recommending the candidate. Materials need to be sent by electronic mail to CHACAdvisorycomm@hrsa.gov on or before May 30, 2018, for consideration in the current membership cycle. For more information please contact CDR Holly Berilla, HRSA, HIV/AIDS Bureau, at CHACAdvisoryComm@hrsa.gov or by telephone at 301-443-9965.

CDC Campaigns Provide New Free CME Opportunities

THE CENTERS FOR DISEASE CONTROL (CDC) has recently launched new free CME programs from their "Prevention IS Care" and the upcoming "Prescribe HIV Prevention (PrEP)" campaigns.

HIV Treatment and Care: A Focus on Mental Health and Substance Use is a new web-based CME program from the Centers for Disease Control (CDC) and Medscape Education that discusses the impact that mental health and substance use disorders can have on HIV treatment and care. This CME activity demonstrates how HIV care providers can screen patients for mental health and substance use disorders, address factors related to mental health and substance use, and help patients adhere to HIV treatment and remain in care.

Advancing PrEP in Practice: Practical Strategies for Everyday Challenges is a newly launched interactive CME/CNE program from the Centers for Disease Control (CDC) and Medscape Education with the goal of improving recognition among primary care providers of patients who could benefit from human immunodeficiency virus (HIV) preexposure prophylaxis (PrEP) medications.

Both programs can be found on the Prevention IS Care website at <https://www.cdc.gov/actagainstaids/campaigns/pic/index.html>.

New Analyses from Investigational Darunavir-Based STR Pivotal Phase 3 Trials at CROI

THE JANSSEN PHARMACEUTICAL COMPANIES

of Johnson & Johnson announced post-hoc analyses of the pivotal EMERALD and AMBER Phase 3 trials of its investigational, complete, once-daily, single-tablet regimen (STR) of darunavir 800mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg (D/C/F/TAF) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults.

The analyses were presented at the annual Conference on Retroviruses and Opportunistic Infections (CROI) in Boston. Results from 48-week sub-analyses were consistent with the primary data presentation of the pivotal Phase 3 data from the EMERALD and AMBER clinical trials. Subgroups of patients were analyzed and included patients who had varying levels of treatment experience, virologic failure (VF) to non-darunavir based regimens, experience with multiple antiretrovirals (ARVs), and in some cases, unknown baseline resistance-associated mutations (RAMS) to agents other than study drugs.

HCV, A Shift From Clinical Trials to Community Implementation

A Report From CROI

ALTHOUGH IN PAST YEARS the Conference on Retroviruses and Opportunistic Infections (CROI) featured presentations on the large Direct-Acting Antiviral (DAA) clinical trials, this year's conference exhibited a notable shift. Registrational trials of what is now a fully stocked armamentarium of HCV antivirals have given way to implementation science, addressing new challenges in operationalizing HCV treatment. From scaling up community-based treatment programs and those targeting People who Inject Drugs (PWIDs), to uncovering the hidden epidemic of sexually transmitted HCV and the overlap of HCV and PrEP, to the prospect of micro-elimination of HCV in HIV/HCV co-infected populations, the conference illustrated that a host of challenges and research gaps remain. Below are just a few of the highlights of the HCV-related posters and presentations at the 25th Annual CROI conference.

Sexually Transmitted HCV and the HCV/PrEP Interface

There was a recurring theme amongst the abstracts that sexually acquired HCV infection rates are increasing, particularly in men who have sex with men (MSM) and in patients living with HIV, with new insights offered as to why this might be. Yet, there were mixed results on whether HIV status affected treatment cure rates.

PROBE-C, a European cohort, suggested that acute HCV clearance is less common in MSM living with HIV, approximately 10% (#129, Boesecke et al), while Gras et al (#585), found that using an antigen or PCR-based test could diagnose HCV infection a median of 2 months prior to routine ALT and HCV antibody screening. Both studies recognized that early identification and treatment of this high incidence, MSM living with HIV population may curb new HCV infections.

New mechanisms might explain how HIV increases HCV transmission: HIV-1 exposure *ex vivo* changed Langerhans' cellular function to increase HCV uptake in mucosal tissue and transmission to hepatocytes (#588, Nijmeijer et al). And on an epidemiologic level, a Swiss phylogenetic study demonstrated that a quarter of new HCV infections, in MSM living with HIV, were from international origins, suggesting that HCV treatment scale up needs to be an international collaborative effort (#130, Salaza-Vizcaya et al), perhaps especially in HIV/HCV micro-elimination goals.

From scaling up community-based treatment programs and those targeting People who Inject Drugs (PWIDs), to uncovering the hidden epidemic of sexually transmitted HCV and the overlap of HCV and PrEP, to the prospect of micro-elimination of HCV in HIV/HCV co-infected populations, the conference illustrated that a host of challenges and research gaps remain.

Furthermore, PREP-using MSM were found to have similar incident rates as their counterparts living with HIV, 1.03 and 1.24 per 100 person-years, respectively (#590, Cotte et al), and at least in France, this HCV incidence and reinfections in MSM living with HIV has increased steadily over the past 4 years (#591, Cotte et al). In contrast, New York City's Sexual Health Clinic found 0.24% HCV prevalence in their MSM initiating PREP and PEP in 2016-2017, lower than the general population (#592, Mikati et al). Though this lower than expected prevalence might be confounded by the individuals seeking PREP and/or PEP, they boasted a racially diverse population of MSM with a high STI incidence of 25%. In Philadelphia, investigators noted that their co-infected population is now younger than 50 years old, and more likely to have acquired their HCV sexually, whether MSM or heterosexual, as compared

to years prior to 2012 (#593, Higgins et al). These studies serve as reminders to constantly reassess local population risks for timely screening and diagnoses.

Care Continuum in HIV/HCV Population

In Austria, HIV clinics that provide DAA treatment were compared to hepatologist offices. They found that HIV clinics that prescribed HCV treatment did so more frequently, and thus achieved higher percentages of cure in a co-infected population, (#596 Zangerle et al): overall, 96% of cohorts living with HIV screened; 99% of those had RNA results; nearly 70% had chronic infection; ~65% had started treatment and ~50% of their HIV cohort achieved SVR. They concluded that while en route to achieving HCV elimination, they would need to “hasten and improve ‘a no matter who provides HCV therapy’ strategy.” In contrast, a U.S. multisite HIV Research Network study showed glaring ‘drop-off’s’ in the HCV care cascade: 79% of PLWH were screened for HCV, and of those with chronic infection, only 16% had started DAA (#597 Radwan et al).

It seems as if achieving sustained virologic response (SVR) in treated patients is rule. In a multicenter CNICS study, 97% of HIV/HCV co-infected patients had sustained virologic response, even among those with FIB-4 scores greater than 3.25, with HCV RNA greater than 6 million, those who were treatment-experienced, identified as black, and independent of genotype (#610 Kim et al). However, in the Madrid Registry, HIV was an independent factor for failure of Ledipasvir/Sofosbuvir in genotype 1, non-cirrhotics (#607 Berenguer). These results might be contextualized by another Spanish

A federally qualified health center, using a hub and spoke model of an Infectious Disease-centered team with several primary care providers, increased treatment capacity more than two-fold, while maintaining cure rates across genotypes and disease stages.

study, showing CD4 count <200 mm³ units was associated with decreased likelihood of HCV virologic response, as was <95% DAA adherence (#608 Dominguez-Dominguez). And an insightful multinational Spanish-American study found that psychiatric illness and drug use were the only two predictors of DAA failure in co-infected individuals (#609 Cachay).

The German cohort, GECCO, found that MSM reinfection rates were higher than IDU, and even more prevalent in patients living with HIV (#612 Boesecke), again pointing to the need of enhanced screening.

Feasibility of HCV Treatment in a Variety of Settings

At a federally qualified health center, Rojas et al (#599) found that using a hub and spoke model of an Infectious Disease-centered team with several primary care providers, increased treatment capacity more than two-fold, while maintaining cure rates across genotypes and disease stages. Similarly, ACTIVE-C, an Alabama collaborative, compared community clinics to their academic liver center partner and demonstrated similar cure rates, but treated more uninsured, more African-Americans, and more people living in urban counties and in low-income zip codes (#594 Franco et al). Using longitudinal data collection from the Massachusetts Department of Public Health—the state with the highest reported HCV prevalence at 3.5%—Vo et al reported that 49% of positive HCV EIA had a confirmatory HCV RNA. Of those, 78% were retained in care, 39% had a genotype reported and only 2% had SVR (#595).

Nijhawan et al evaluated the hard to reach jail population, where HCV rates are estimated to be 10% higher than the general population. In a Dallas County jail, 79% of those with a positive HCV antibody, received an RNA test. Of the 78% with chronic infection, 85% received the intervention: disease education, prevention counseling and information about linkage to care after release (including a nurse navigator outreach phone call and a hotline number). Of those released to the community, over half had received a first phone call, with 7% scheduling a liver clinic appointment. The study reports that reaching this vulnerable population was facilitated by identifying which individuals are released to the community, having accurate contact info, repeated phone call attempts, having a hotline for patients to call and establishing financial eligibility at community clinics after release (#598).



There was a recurring theme amongst the abstracts that sexually acquired HCV infection rates are increasing, particularly noted in men who have sex with men (MSM) and in HIV+ patients, with new insights offered as to why this might be. Yet, there were mixed results on whether HIV status affected treatment cure rates.

Lam et al (#601) found that 52% of Kaiser-insured HIV/HCV co-infected patients started DAA therapy in the first two years of their availability. Being male, having advanced fibrosis and having HCV genotype 1, were all associated with higher likelihood of DAA initiation. Reduced DAA initiation was associated with Medicare or Medicaid enrollment, prior drug abuse and lower baseline CD4; while age, race, alcohol, smoking, HIV RNA, prior treatment and neighborhood deprivation index were not associated with DAA initiation. Kostman et al (#600) examined Diplomat Pharmacy records across the U.S., and reported 36% of HCV treatment prescriptions between January 2016-April 2017 resulted in complete denials, and was highest amongst commercial insurances (52%) and Medicaid (35%) versus Medicare (15%).

Among Canadian co-infected individuals, Saeed et al (#611) noted reductions in both outpatient and inpatient healthcare utilization after DAA therapy (adjusted IRR of 0.8 and 0.72, respectively), underscoring the cost savings of earlier treatment.

Reaching this vulnerable [jail] population was facilitated by identifying which individuals are released to the community, having accurate contact info, repeated phone call attempts, having a hotline for patients to call and establishing financial eligibility at community clinics after release.

The Big Picture

In one of the final symposia of the conference, a series of oral presentations framed the challenges ahead in the field of HCV treatment. In a chilling review of the interplay between the opioid crisis and HIV/HCV transmission, Sally Hodder (#163) described how the powerful forces of poverty, hopelessness, and intergenerational addiction and drug use are fueling new infections, which are up 250% since 2009. Increased testing efforts in Appalachia have identified pregnant women as one of the most difficult populations to treat. She issued an urgent call for more research in this area, as well as a coordinated, comprehensive response to include harm reduction, availability of substance abuse treatment, an even social enterprise, reintegration and economic development to help stave off the syndemics of opioid addiction and HIV/HCV transmission.

Turning to the global prospect of HCV elimination, Jordan Feld (#164) outlined the steps needed to achieve the WHO goals of reducing new infections by 90% and HCV related deaths by 65%. Using the care continuum as a model, he reviewed how treatment without screening and linkage



Increased testing efforts in Appalachia have identified pregnant women as one of the most difficult populations to treat.

would quickly collapse programs, while either without prevention will prove futile in reaching elimination targets.

Massimo Colombo reviewed the rising challenge of liver cancer (#165), which is the fastest growing cancer in the world, and perhaps operationally overlooked in elimination discussions. Finally, Christine Durand described a new reality after the HOPE Act, in which HIV+ and HCV+ organs can be used in certain situations to broaden the pool of organ donors (#166). This new strategy is truly a testament to how far the field has come with post-transplant HCV therapeutics, as well as a haunting reminder of the scale of the opioid crisis, which through unintentional overdose has converted many of our potential HCV patients into organ donors.

In summary, now that the HCV cure has become achievable and more widely available, the field of HCV research—having rocketed from basic to translational to clinical science in just a decade—heads towards implementation and implementation science with the promise of global elimination, and millions of years of life saved. **HIV**



ABOUT THE AUTHORS

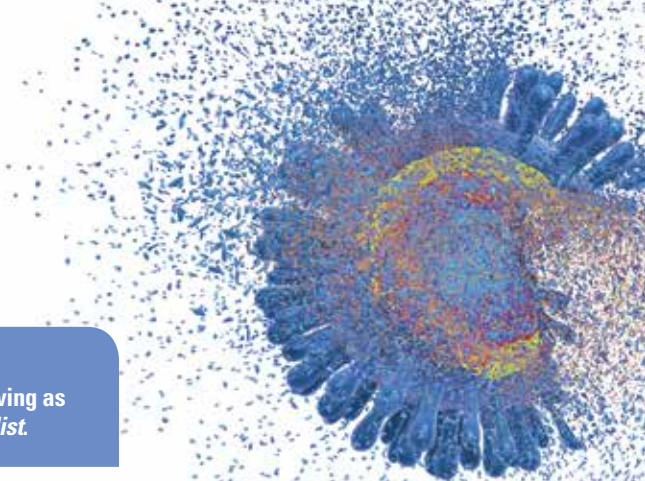
Christian Ramers, MD, MPH, AAHIVS, is an Infectious Disease and HIV specialist and serves as an Assistant Medical Director at FHCSD. He has led grant-funded research and educational projects in HIV and HCV and maintains a large bilingual practice serving underserved, homeless, and immigrant populations in urban San Diego.



Sarah A. Rojas, MD, AAHIVS, enjoys her full spectrum family medicine practice, and has been an HIV researcher and advocate for over a decade. Currently, as a research consultant at FHCSD, she works on community-based projects related to PREP, HCV and HIV and addressing health disparities



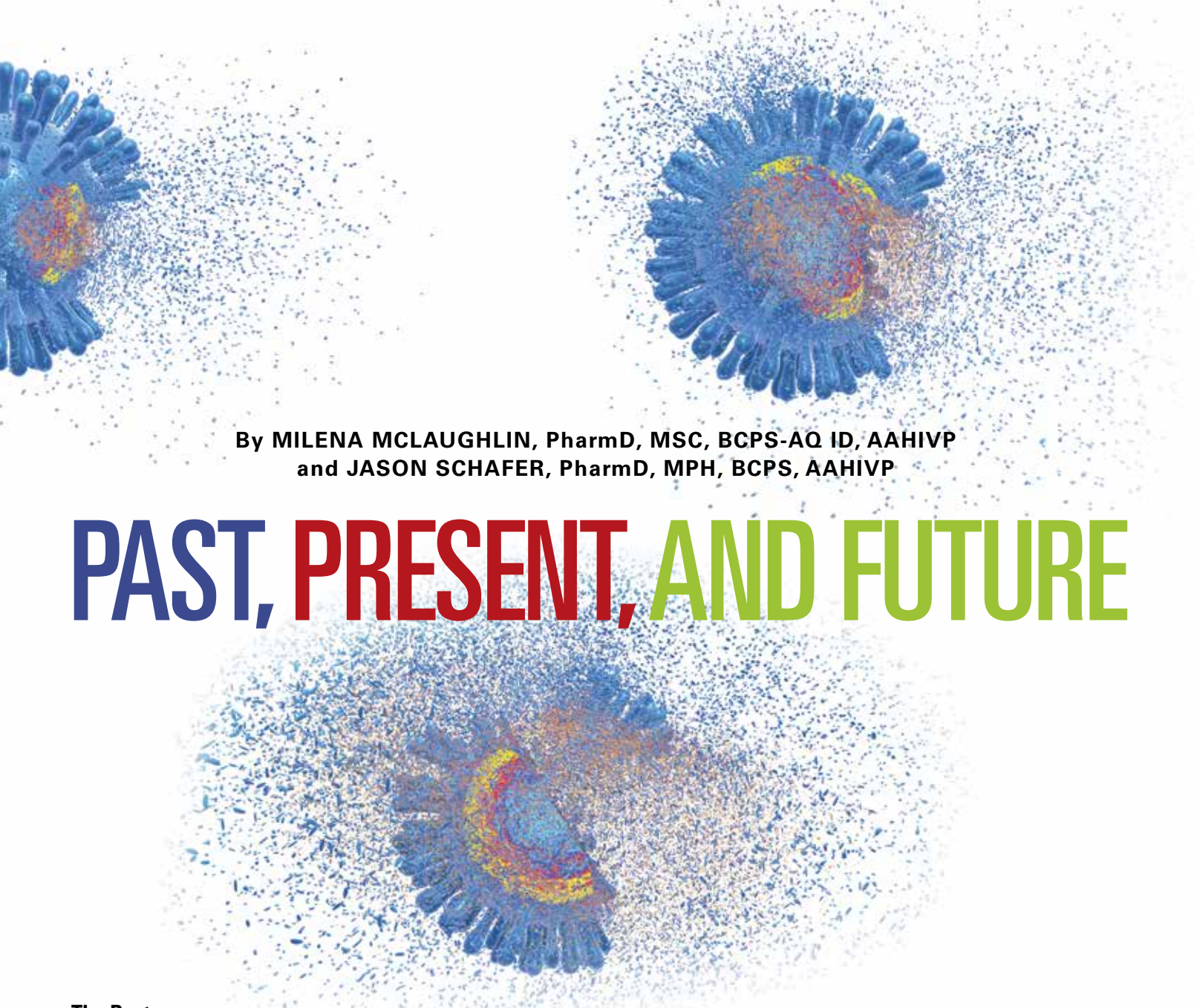
The evolution of antiretroviral therapy...



AAHIVM would like to thank Milena McLaughlin and Jason Schafer for serving as co-editors for this issue of *HIV Specialist*.

ON JUNE 5TH, 1981, the United States Centers for Disease Control and Prevention (CDC) published a Morbidity and Mortality Weekly Report (MMWR), describing five cases of a rare lung infection, *Pneumocystis carinii pneumonia* (PCP), in young, otherwise healthy, gay men.¹ This would become the first report of what would later be called the Acquired Immune Deficiency Syndrome (AIDS) epidemic. Clusters of other cases of rare diseases such as Kaposi's Sarcoma continued to be reported.² In the decades that followed these reports, the detection, diagnosis, and treatment of Human Immunodeficiency Virus (HIV) would evolve in rapid fashion. Clinicians, researchers, and patients constantly look to the future. Vaccine studies and cure research are met with cautious optimism.

The articles in this issue of *HIV Specialist* will review novel and non-traditional delivery systems for the treatment and prevention of HIV, novel pre-exposure prophylaxis (PrEP) data and programs, "test and treat" programs, and two-drug therapy regimens. This review will summarize the past, present, and future of antiretrovirals (ARVs) for the treatment and prevention of HIV.



By MILENA MCLAUGHLIN, PharmD, MSC, BCPS-AQ ID, AAHIVP
and JASON SCHAFER, PharmD, MPH, BCPS, AAHIVP

PAST, PRESENT, AND FUTURE

The Past

Treatment of HIV has a long and rich history. The first decade after the initial report of HIV saw the first immunoassay test and the approval of zidovudine (1987).³ This was followed in the 1990s by many more therapies and the advent of triple drug therapy. Combination tablets and single tablet regimens then followed.

New formulations of existing products also simplified treatment (e.g. ritonavir tablets vs capsules) and improved bioavailability.³ The US President's Emergency Plan for AIDS Relief (PEPFAR) changed the discussion regarding the approach to universal access to treatment and care to accelerate control of the epidemic.⁴ The US Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV have been updated over 30 times.⁵

Early innovations, such as giving medication sequentially and alternating therapies, gave way to triple drug therapy with data provided by a small study with indinavir, zidovudine, and lamivudine.^{6,7} Initial use of the nucleoside reverse transcriptase inhibitors (NRTIs) also led to the discovery that treatment of HIV led to decreased rates of vertical

transmission.⁸ The use of low-dose ritonavir as a “boosting” agent for saquinavir set the stage for the recommendations currently in use and the need for decreased doses of other protease inhibitors.^{7,9} Monitoring HIV RNA, or “viral load” was recommended after HIV in the plasma was shown to be predictive of disease progression and death.¹⁰ Despite a low quality of life with the older agents, HIV was now a manageable, chronic disease.

The Present

Currently there are 40 individual and combination medications approved for the treatment of HIV and one approved for the prevention of HIV infection.¹¹ The life expectancy of a person living with HIV nears that of a person not living with HIV.¹² There are enough options that patients may “switch” their therapy to one that requires fewer tablets or frequency of dosing, lesser food requirements, or has lesser side effects. Patients on “salvage” therapy also have options for effective treatment.^{13,14} “Treatment as prevention” and PrEP have led to a decrease in new infections.^{15,16} The newly endorsed “undetectable=untransmittable” data provides patients and

those at risk of infection with important information about the virus.¹⁷ Test and treat is a new strategy to approaching the epidemic.¹⁸

However, there are many challenges that remain. While many of the newer agents are tolerable, long term side effects (e.g. metabolic and cardiovascular) and drug-drug interactions remain a concern.¹⁹ Patients faced with the need to take “lifelong” therapy for upwards of fifty years require agents with safer long term side effects. The approval of tenofovir alafenamide will likely reduce the incidence of bone and renal toxicity; however, long term data over a lifetime is needed to guide therapy.²⁰ While there are many treatment options available to decrease HIV RNA, an agent to increase CD4 T-lymphocyte count remains elusive.

Safer alternatives may be available to some patients, however, global access to care continues to evolve. Even within the US, access to HIV therapy remains an issue for many patients faced with high deductibles and copayments.^{21, 22} Disparities in treatment continue to exist for specific patient populations.²³ Many programs are in place to close the gap between access in developed and non-developed countries.⁴ The current WHO guidelines recommend that all patients are started on ARV therapy regardless of CD4 T-lymphocyte count.²⁴ The scale up of these programs requires the funding and infrastructure to treat a larger number of patients.

Special patient populations are also in the spotlight. Overall, the available data on treatment of pediatric and adolescent patients falls behind the availability of data for adults. If a drug is approved for use

in children, dosage formulations may not be available for all stages of care. Women continue to face many issues surrounding contraception and ARV therapy.²⁵ Disparities in PrEP efficacy for women versus men require more data and evidence for clinicians to be able to provide appropriate patient counseling.²⁶ Management of comorbidities, drug-drug interactions, and polypharmacy in an aging population must be addressed by clinicians.^{19, 27}

As tolerability of medications is no longer a main concern, the conversation has shifted to medication adherence and engagement in care.²⁸ The “HIV Cascade” has many steps for which intervention and research are required.^{29, 30} Engagement and continuation of ARV therapy after transitions in care remains an issue. The transitions from adolescent to adult and prison to society each have their own unique challenges.^{31, 32}

The Future

Given the high efficacy, safety, tolerability, and convenience of contemporary ARV therapy, it can be challenging to identify where and to what extent improvements can be made. However, considering the vast advancements in treatment that have already occurred, it may be naïve to think that the current approach to HIV treatment is the best and only way.

New agents under investigation are challenging the current treatment paradigm of three active antiretroviral medications by mouth every day to maintain viral suppression. Several two drug therapy options are emerging that may simplify treatment and reduce cost.³³ Long-acting

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medications dosed every week or every month may be easier for some patients, improve medication adherence, and increase cost effectiveness.³⁴

A few longer acting antiretrovirals in development will provide additional oral therapy options, but the majority will likely be delivered via alternative drug delivery systems.^{34,35} This includes the potential delivery of agents such as cabotegravir and rilpivirine as long acting injectables, dapivirine within a vaginal ring, and tenofovir alafenamide as a subdermal implant.³⁵⁻³⁷ These methods of drug delivery may seem foreign to some providers of HIV medicine, but they are common methods for delivering medications in other areas of healthcare and may represent a novel and effective method to ensure medication adherence and effective treatment.³⁸

In addition to challenging the number of medications necessary for HIV treatment and their modes of delivery, new agents with novel drug therapy targets may also challenge the status quo. Capsid assembly, glycoprotein 120 attachment, and Rev-dependent mRNA expression are among the novel drug therapy targets under current investigation.³⁹⁻⁴¹ Agents in these classes along with the recent approval of a novel anti-CD4 monoclonal antibody may provide future therapy options, particularly for those with heavy treatment experience.⁴²

The last component of the treatment paradigm, the consistent need for antiretroviral medications, may be the most challenging of all to

change. Will broadly neutralizing antibodies, therapeutic vaccines, latency reversing agents, or CRISPR technology ever become routine methods for inhibiting, suppressing, or eliminating HIV? Evidence for these approaches and others continue to emerge and provide optimism that the future may hold a potential cure.^{43,44}

The remaining articles in this magazine take a deeper dive into the future of HIV medicine, providing more in-depth discussion of emerging treatment and prevention options. From new agents and drug therapy targets, approaches to drug delivery, and novel practice models, these articles demonstrate that the future of HIV treatment and prevention is evolving and the status quo is likely to change again. **HIV**

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ABOUT THE AUTHORS:

Milena McLaughlin, PharmD, MSc, BCPS-AQ ID, AAHIVP, is an Assistant Professor in the Department of Pharmacy Practice at Midwestern University's Chicago College of Pharmacy in Downers Grove, IL. She is also an HIV/ID Clinical Pharmacist in the Department of Pharmacy at Northwestern Memorial Hospital in Chicago, IL.



Jason Schafer, PharmD, MPH, BCPS, AAHIVP, is an Associate Professor in the Department of Pharmacy Practice at Jefferson College of Pharmacy at Thomas Jefferson University in Philadelphia, PA.



A **2018** UPDATE

Novel Drugs

in the Pipeline for
HIV Treatment

BY NEHA SHETH PANDIT, PharmD, AAHIVP, BCPS
JOMY GEORGE, PharmD, BCPS AQ-ID

CURRENT US HIV TREATMENT GUIDELINES state that people living with HIV (PLWH) should be offered treatment; however, it is estimated that ~50% are not engaged in care and virologically suppressed.¹² Some barriers to virologic suppression include daily oral dosing, comorbidities, adverse effects, and drug-drug interactions. Novel antiretroviral therapy (ART) options are necessary to minimize these barriers and adequately maintain or achieve virologic suppression. The ART pipeline includes new medications in existing drug classes as well as medications with novel mechanisms of action.

Nucleoside reverse transcriptase inhibitor (NRTI)

MK-8591

MK-8591 (EFdA), has a novel 3'-hydroxyl moiety that allows for a higher affinity to reverse transcriptase. EFdA-monophosphate prevents DNA synthesis by inhibition of reverse transcriptase translocation.³ The active anabolite of MK-8591 was found to have a longer half-life in human peripheral blood mononuclear cells compared to other NRTIs, allowing for extended interval dosing. In an open-label study, ART-naïve patients (n=6) were given one dose of MK-8591 10 mg. The half-life of the anabolite was 128 hours which resulted in a 1.78 log₁₀ drop in HIV-1 RNA.⁴ MK-8591 appears to maintain its efficacy in the presence of the E138K and M184V mutations.⁵ A recent dosing study evaluated 0.25 mg, 0.75 mg and 5 mg in 12 healthy adults and found that MK-8591 levels were above the target concentration for efficacy among all dosing strategies and remained elevated up to 30 days after treatment cessation.⁶ MK-8591 is being evaluated in a Phase 2 trial with doravirine (DOR) and lamivudine (3TC) in ART-naïve PLWH to determine appropriate dosing.⁷

Non-nucleoside reverse transcriptase inhibitors (NNRTI)

Doravirine

Doravirine (DOR) is being studied in a non-inferiority study for ART-naïve patients. Patients were randomized to oral DOR 100 mg daily or darunavir 800 mg with ritonavir 100 mg daily (DRV/r) for 48 weeks plus either tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) or abacavir (ABC)/3TC. DOR (n=383) was found to be noninferior to DRV/r (n=383) with 83.8% and 79.9%, achieving virologic suppression, respectively.⁸ In patients with a baseline HIV-1 RNA of >100,000 copies/ml, 81% and 76.4% achieved virologic suppression, in the DOR and DRV/r group, respectively. In patients with a baseline HIV-1 RNA ≤100,000 copies/ml, 90% of the DOR group achieved virologic suppression. In a study comparing DOR (n=66) to efavirenz (EFV) (n=66) with TDF/FTC at 48 weeks, 77.8% and 78.7% achieved

virologic suppression, respectively.⁹ Both studies found DOR to have a favorable lipid profile and was overall well-tolerated compared to DRV/r and EFV; however, neuropsychiatric symptoms and nausea did occur.^{8,9} A New Drug Application was submitted for DOR with other agents in addition to a fixed-dose combination tablet of DOR/TDF/FTC. A response is anticipated in October 2018.¹⁰

Elsufavirine

Elsufavirine is an oral NNRTI, which was recently approved in Russia for the treatment of HIV in combination with other antiretrovirals.¹¹ Like other available NNRTIs, elsufavirine has a long plasma half-life of about 8 days, allowing for once daily dosing. Safety and efficacy of elsufavirine 20 mg was compared to EFV 600 mg plus a TDF/FTC backbone in 120 ART-naïve patients.¹² Median baseline viral load and CD4 T-lymphocyte count in the elsufavirine and EFV groups were 50,000 copies/ml and 63,000 copies/ml; and 349 cells/mm³ and 379 cells/mm³, respectively. After 48 weeks, 81% and 73.7% of participants achieved a HIV-1 RNA < 400 copies/ml in the elsufavirine and EFV groups, respectively. Although efficacy rates were similar, there were significantly more patients who experienced adverse effects in the EFV versus elsufavirine arm, 77.6% vs. 36.7%. Common drug associated adverse effects in the elsufavirine versus EFV arm were headache (15% versus 24%), dizziness (6.7% versus 26.7%), and sleep disorders (5% versus 20.7%). Different formulations including sustained release oral, once weekly oral, and long acting parenteral forms are in development and being studied outside the US for the treatment and prevention of HIV.¹¹

Fusion Inhibitor

Albuvirtide

Albuvirtide has a similar mechanism of action to enfuvirtide. It is being developed as a long-acting agent in ART-experienced patients who have failed first and second line therapies.^{13,14} Albuvirtide has a longer half-life (11 days) compared to enfuvirtide due to its ability to conjugate to serum albumin. This allows for weekly intravenous

administration.¹⁴ It demonstrated potent antiviral activity with twice-daily oral lopinavir/ritonavir (LPV/r) in ART-naïve (n=20) and experienced (n=92) Chinese adults with HIV.^{15,16} Interim results in ART-experienced patients reported albuvirtide plus LPV/r was non-inferior to LPV/r + TDF + 3TC. The most common adverse effects reported in the albuvirtide arm were diarrhea, headache, and dizziness. High cholesterol and triglycerides were also reported more often in the albuvirtide arm. Albuvirtide may offer another option for patients who cannot tolerate twice-daily subcutaneous enfuvirtide. Albuvirtide is currently in Phase 3 studies and will also begin studies with a broad spectrum HIV neutralizing antibody.¹⁷

CCR5 antagonist **Cenicriviroc (CVC)**

Cenicriviroc is an oral CCR5/CCR2 antagonist which inhibits viral entry into host cells.¹⁸ Its activity against CCR2 suggests that it could have anti-inflammatory effects in patients with chronic immune activation and in fact has been studied for non-alcoholic steatohepatitis (NASH) in both PLWH and patients without HIV.^{19,20} CVC with TDF/FTC was compared to EFV/FTC/TDF in a 48-week trial of ART-naïve patients with R5 tropic HIV-1.²¹ Participants (n=143) were mostly Black or White men. Median baseline HIV-1 RNA and CD4 T-lymphocyte count were 4.5 log₁₀ copies/ml and 385 cells/mm³, respectively. The 48-week results reported 68% and 50% achieved virologic suppression in the CVC 100 mg and EFV groups, respectively (p>0.05). No significant differences in virologic suppression rates were observed when analyzed by baseline viral load stratification (< or > 100,000 copies/ml). The most frequent treatment related adverse effects reported were nausea, headache, diarrhea, and abnormal dreams. CVC was well tolerated as approximately 20% of EFV patients discontinued therapy. CVC represents a potential treatment option in patients with R5 tropic HIV-1 in addition to inflammatory conditions such as NASH. Furthermore, CVC is currently in Phase 3 studies for the treatment of NASH in patients without HIV.²²

Rev Inhibitor **ABX-464**

ABX-464 halts HIV replication by inhibiting Rev activity, an HIV protein needed to make complete HIV RNA strands.^{23,24} It was evaluated in ART-naïve adults (n=63) at varying doses for 2-3 weeks.²⁴ A >0.5 log₁₀ copies/ml drop from baseline was reported with ABX-464 150 mg by mouth daily. ABX-464 was evaluated for safety and efficacy in virally suppressed patients receiving ART (n=30).²⁵ Participants were randomized to add oral ABX-464 or placebo to their current ART for 28 days after which treatment was interrupted. An overall reduction in viral DNA was reported in 53% (8/15) of ABX-464 treated patients. The average time to viral rebound was 14 and 13 days

in the placebo and treatment groups, respectively. The most common adverse effects in both studies were headache and abdominal pain. A follow-up Phase 1/2 study will evaluate ABX-464 treatment for 84 days and assess the time to maximal reduction of HIV reservoirs in recently and chronically infected people with suppressed HIV-1 RNA.²⁶

gp120 attachment inhibitor **Fostemsavir**

Fostemsavir is being developed for ART-experienced patients who have ≤2 active therapy options.¹³ Fostemsavir is a prodrug of temsavir (BMS-626529) and binds to the HIV gp120 protein, preventing HIV and CD4 T-lymphocyte attachment. Potent antiviral activity has been reported in an 8 day monotherapy and 48 week Phase 2b trial.^{27,28} Varying dosages of oral fostemsavir given with raltegravir (RAL) and TDF were compared to atazanavir/ritonavir (ATV/r) plus RAL and TDF in ART-experienced patients (n=200).²⁸ Participants were mostly white males with a median age of 40 years. Median baseline HIV-1 RNA and CD4 T-lymphocyte counts ranged from 4.88-5.01 log₁₀ copies/ml and 214-249 cells/mm³, respectively across all treatment groups. A higher success rate was reported in the baseline HIV-1 RNA <100,000 copies/ml group in both treatment arms. Drug resistance was detected in 8 patients receiving fostemsavir. Four of these 8 also exhibited emergent RAL associated mutations. The most common adverse effect reported with fostemsavir was headache (14%). The clinical relevance and the need to assess pre-existing mutations that confer resistance to fostemsavir require further investigation. Fostemsavir is currently being evaluated in Phase 3 clinical trials which include heavily treatment experienced patients failing current optimized background therapy.²⁹

Monoclonal Antibodies (mAb) **Ibalizumab**

Ibalizumab (Trogarzo) was approved by the FDA in March 2018 and is the first biologic agent available for the treatment of HIV.³⁰ It is an anti-CD4 mAb and binds to domain 2 of the CD4 receptor, blocking a conformational change necessary for viral entry.³¹ Safety and efficacy were studied in a 24 week Phase 3 trial of ART-experienced patients (n=40).^{31,32} These participants were infected on average for 21 years and about 30% of them had been treated with ≥10 antiretrovirals. Mean baseline HIV-1 RNA and CD4 T-lymphocyte count were 5 log₁₀ copies/ml and 161 cells/mm³ (50% <100 cells/mm³), respectively. An intravenous loading dose (2000 mg) of ibalizumab was given in the first week, then biweekly (800 mg) for 24 weeks. An optimized background regimen (OBR) with at least one active agent was initiated on study day 14. About 40% of patients required an investigational agent (fostemsavir) as part of their OBR and close to 50%

of the population was resistant to ≥ 3 antiretroviral classes. At 24 weeks, the mean reduction in viral load was 1.6 log₁₀ copies/ml and 43% of participants achieved virologic suppression. After 24 weeks, participants were allowed to continue ibalizumab with an OBR for up to 48 weeks (n=27). All 15 participants with suppressed plasma HIV RNA at 24 weeks maintained through week 48.³³ Commonly reported adverse effects were diarrhea, dizziness, nausea, and rash. Infusion related adverse effects were not reported. Ibalizumab offers a viable option in patients with multi-drug resistant HIV who have little to no other options.

PRO-140

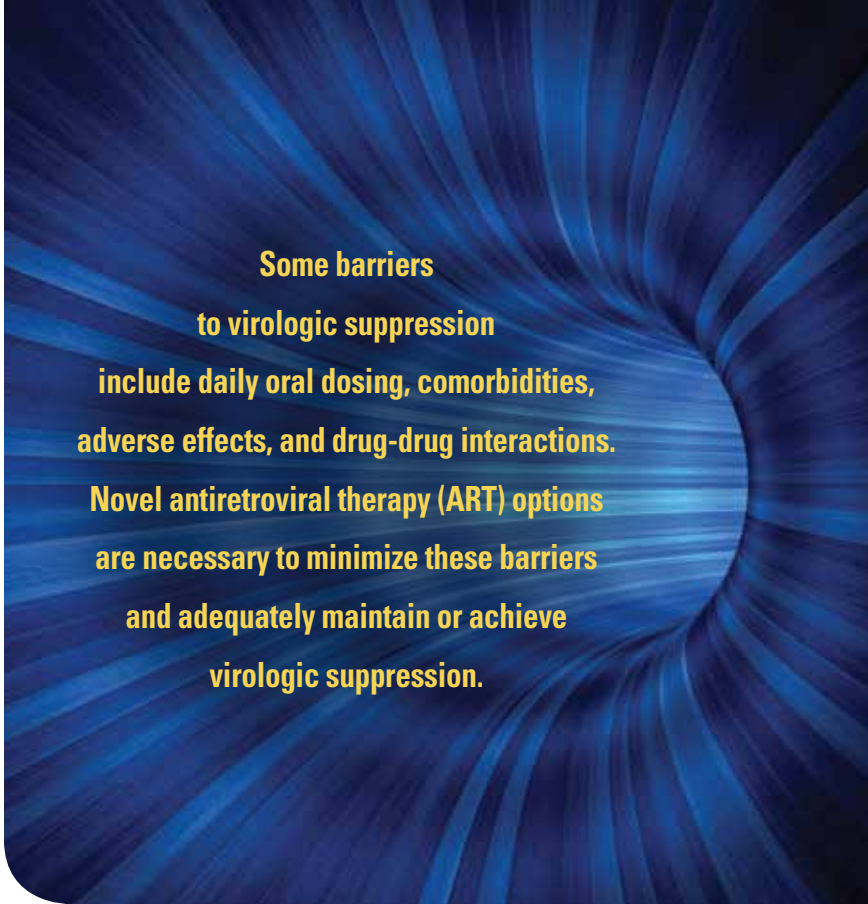
PRO-140 targets CCR5 and is being investigated as a stand-alone long-acting maintenance drug in virologically suppressed patients.^{34,25} Patients (n=42) with R5 tropic HIV-1 on a stable regimen with HIV-1 RNA <40 copies/ml received weekly subcutaneous (SC) injections for 1 week while on ART after which ART was discontinued and PRO-140 monotherapy was maintained.³⁶ An update of 16 patients found that 13/16 (81%) and 10/16 (62.5%) maintained a HIV-1 RNA <40 copies/ml for up to 40 weeks and 2 years, respectively. Five people experienced viral rebound after a mean of 330 days.³⁷ Serious adverse effects were not reported. Injection site reactions were mild. PRO-140 is also being studied in heavily ART-experienced patients on an OBR in which participants are being administered a single SC dose of PRO-140 or placebo in addition to their existing failing regimen for 1 week then continued on weekly PRO-140 with an OBR for 24 weeks.³⁸

UB-421

UB-421 binds to domain 1 of the CD4 receptor and is being developed in Taiwan.³⁹ UB-421 monotherapy was evaluated in 29 virologically suppressed adults who received 8 total UB-421 infusions weekly (8 weeks) or biweekly (16 weeks) after ART interruption.³⁹ Twenty seven of the 29 participants who completed the study did not experience viral rebound during the monotherapy period. The most common treatment related adverse effect was skin rash. This agent is projected to be investigated in Phase 3 trials.¹³

Latency Reversing Agents (LRAs)

A functional cure for HIV is limited by the ability of HIV to survive in latent reservoirs. Many LRAs are currently being studied as adjuvant therapy with a therapeutic vaccine in Phase 1/2 studies as part of a 'kick and kill' strategy. This strategy 'kicks' latent cells into an active state and 'kills' the cell using immune response. Studies have described the utility of LRAs to minimize HIV reservoirs by promotion of latent cell activation; however, these data have not shown a significant decline in HIV reservoir cells.⁴⁰ Histone deacetylation inhibitors and toll-like receptor agonists are two types of LRAs that are being evaluated.



**Some barriers
to virologic suppression
include daily oral dosing, comorbidities,
adverse effects, and drug-drug interactions.
Novel antiretroviral therapy (ART) options
are necessary to minimize these barriers
and adequately maintain or achieve
virologic suppression.**

Toll-like receptor (TLR) agonists

Toll-like receptors are used to activate an immune response during an infection. Many TLR agonists have been found to activate latent HIV cells. Currently poly-ICLC (TLR3), vesatolimod (GS-9620/TRL7), and lefitolimod (TLR9) have all been studied in Phase 1/2 trials and have shown positive results in activating latent HIV cells.⁴¹⁻⁴³

Histone deacetylation inhibitors (HDACi)

Romidepsin was most recently studied with a therapeutic vaccine that resulted in 5 out of 13 participants being able to remain off ART and maintain an HIV RNA of <2000 copies/ml.⁴⁴ Vorinostat is similarly being studied in combination with 2 different therapeutic vaccines.^{45,46} Panobinostat was determined to activate latent cells in a study with 15 participants but did not show an overall decrease in the number latently infected cells.⁴⁷ Due to these results, it is now being studied with peginterferon alfa-2a to activate the immune response in patients who are virologically suppressed.⁴⁸

Capsid Inhibitors GS-CA1

The HIV capsid core is made up of p24 protein which undergoes assembly during maturation to form the core. GS-CA1 alters the assembly and disassembly of the capsid core leading to non-infectious, defective virions. In preclinical studies, GS-CA1 has been found to have high *in vitro* potency compared to EFV, ATV, and dolutegravir (DTG) in addition to effective concentrations for up to 10 weeks post a single injection. GS-CA1 will likely enter Phase 1 trials in 2018.⁴⁹



Long-acting (LA) ART

LA rilpivirine and LA cabotegravir

Novel formulations of ART stand to provide patients with an alternative to taking oral ART daily. Rilpivirine (RPV) is a FDA approved NNRTI that is currently available as a 25 mg tablet. Cabotegravir (CAB) is an investigational integrase strand inhibitor (INSTI). Both medications are being explored as long-acting agents given concomitantly for HIV treatment and prevention. Cabotegravir is also being studied as a long-acting oral tablet for HIV treatment.

In the LATTE-2 study ART-naïve participants underwent a 20 week induction and 96 week maintenance period.⁵⁰ During induction, participants were given oral CAB 30 mg with ABC/3TC daily. At week 16, oral RPV 25 mg was added. At 20 weeks, 91% (n=282) of participants achieved virologic suppression. Patients who were virologically suppressed were then randomized to either continue oral therapy (n=56); change to CAB 400 mg with RPV 600 mg intramuscularly every 4 weeks (n=115); or to CAB 600 mg and RPV 900 mg intramuscularly every 8 weeks (n=115). At 96 weeks, rates

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of virologic suppression were 84%, 87% and 94% of patients in the oral, 4 week, and 8 week groups, respectively. These rates were not statistically significantly different between groups.⁵⁰ Intramuscular CAB and RPV are being studied in ART-naïve patients who maintained virologic suppression on ABC/3TC/DTG and in a switch study of virologically suppressed ART-experienced patients who switch to intramuscular CAB and RPV. Additional studies are underway to compare injections given every 4 or 8 weeks as well as for HIV prevention.^{13,51-53}

Conclusion

After over two decades of ART, the innovation of HIV therapeutic options continues to advance. Long-acting formulations, novel targets, and biologic agents will advent a new era of HIV treatment and prevention, with the hope of making strides towards a functional cure. Effective implementation of these medications should remain a priority; ensuring barriers to the HIV care continuum are addressed. **HIV**

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ABOUT THE AUTHORS

Jomy M. George is a Pharmacokineticist in the Clinical Pharmacokinetics Research Unit and Co-Director of the Pharmacokinetics Research Fellowship at the National Institutes of Health. Dr. George's areas of research include antiretroviral associated drug interactions and pharmacokinetics. She is a primary or associate investigator on various clinical and PK protocols, involving healthy participants and patients with HIV/AIDS with and without malignancies. She also currently serves on the Department of Health and Human Services (DHHS) Adult Opportunistic Infections Guidelines.



Neha Sheth Pandit is an Associate Professor and Vice Chair for Research and Scholarship at the University of Maryland School of Pharmacy, Department of Pharmacy Practice and Science. Dr. Pandit serves as a clinical pharmacist in an HIV primary care clinic in Baltimore, MD. Her patient care activities have included HIV inpatient and outpatient care, infected individuals with comorbidities including HCV, malignancies and primary care. Her research has focused on her patient care activities including drug-drug interactions, medication adherence, as well as pharmacy education. Dr. Pandit currently serves on the Advisory Board for the Maryland AIDS Drug Assistance Program.



Advances in Two-Drug

By AMESIKA N. NYAKU, MD, MS

OVER THE LAST 30 YEARS, there have been significant improvements in the efficacy and safety of antiretroviral therapy (ART). The current HIV treatment paradigm is to use three active antiretroviral agents. However, given the potency of new ART and the life-long duration that people living with HIV/AIDS (PLWHA) will require ART, there is a continued interest in 2-drug ART regimens. These interests include reducing costs and long term drug exposure with the associated cumulative renal, bone, and cardiovascular toxicities. In 2016, Achhra et al. conducted a systematic review and meta-analysis of 21 trials from 2008 to 2015 of the efficacy and safety of 2-drug ART as compared to standard 3-drug for ART-naïve patients or maintenance therapy.¹ Analysis of the studies showed that 2-drug ART failed to achieve or maintain virologic suppression HIV-1 RNA <50 copies/mL (cpm)) at a higher rate than standard 3-drug ART. When studies with maraviroc were removed, the relative risk of not achieving or maintaining VL <50 cpm on 2-drug ART as compared to 3-drug ART decreased but remained higher than 3-drug ART. This review serves to update the findings of Achhra et al. with the results of recent 2-drug ART trials.

The combination of dolutegravir plus lamivudine has generated attention as a potentially successful 2-drug combination given the potency of dolutegravir, minimal drug-drug interactions, and the safety profile of lamivudine. The AIDS Clinical Trials Group A5353 study was a Phase 2, multisite, open label, single arm study of dolutegravir 50 mg oral once daily plus lamivudine 300 mg oral once daily in ART naïve adults with HIV-1 RNA <500,000 cpm.² Participants who had any major resistance mutations, including integrase mutations, hepatitis B coinfection, or anticipated need for hepatitis C virus (HCV) treatment were ineligible to participate. The primary outcome was HIV-1 RNA <50 cpm at week 24. One hundred twenty-two participants were enrolled and 120 were included in the primary analysis. Participants were mainly male (87%) with a median age of 30 years and were racially diverse (40% black and 27% Latinx). At screening, 31% of participants had an HIV-1 RNA >100,000 cpm. At week 24, 90% of participants achieved virologic suppression. There was no statistically significant difference in virologic suppression when stratified by baseline HIV-1 RNA ≤100,000 vs HIV-1 RNA >100,000 cpm. Three participants had virologic failure (1 participant with screening HIV-1 RNA >100,000 cpm) and 1 participant developed the M184V mutation. Analysis of archived blood samples demonstrated that all



Antiretroviral Regimens

three participants had undetectable dolutegravir levels at least once during the study period. Dolutegravir plus lamivudine was well tolerated with few Grade 3 or higher adverse events (AEs). Given these promising results, there are two large Phase 3 clinical trials underway, GEMINI 1 and 2 (NCT02831673 and NCT02831764).

The ANRS 167 LAMIDOL study was a Phase 1 open label, single arm, multicenter study that assessed the efficacy of dolutegravir 50 mg oral once daily plus lamivudine 300 mg oral once daily to maintain HIV-1 RNA <50 cpm.³ Participants were 18 years or older and had been virologically suppressed for 2 years. Participants had no history of virologic failure or major drug resistance mutations. One hundred ten participants were enrolled and first switched to dolutegravir with lamivudine plus a third agent. After 8 weeks, 104 participants maintained virologic suppression and proceeded to the second phase of the study, simplification to dolutegravir plus lamivudine. Participants were mainly male (86%) with a median age of 45 years. At week 40 of the second phase 2, 97% of participants had maintained virologic suppression.

The Antiretroviral Strategy to Promote Improvement and Reduce Exposure (ASPIRE) study investigated the efficacy of dolutegravir plus lamivudine to maintain virologic suppression as compared to standard 3-drug ART.⁴ The study was an open-label, randomized, multicenter trial of participants who were 18 years or older, had been on standard 3-drug ART for at least 48 weeks, and had no history of virologic failure or any major resistance mutations. Like other studies, pregnancy, breastfeeding, hepatitis B coinfection, and need for HCV treatment during the study period were exclusionary. Ninety participants were enrolled and 89 participants were included in the analysis. Participants were 88% male, 60% white, and the median age was 47 years old. At week 24, 93.2% of participants on dolutegravir plus lamivudine

as compared to 91.1% of participants on standard 3-drug ART had HIV-1 RNA <50 cpm. The rate of virologic suppression was maintained throughout week 48 in both arms. Treatment failure at week 24 was 6.8% in the 2-drug arm and 6.7% in the 3-drug arm. Treatment with dolutegravir plus lamivudine was non-inferior to standard 3 drug therapy. Only one participant in the 2-drug arm had virologic failure and there were no major resistance mutations found. Both studies had few Grade 3 or higher AEs. Dolutegravir plus lamivudine appears to be efficacious for maintenance of HIV virologic suppression and the TANGO trial will be a large Phase 3 randomized trial to confirm this 2-drug strategy.

The ANDES trial is a Phase 4 open-label randomized, active-controlled trial of the virologic efficacy of generic fixed combination darunavir-ritonavir 800mg-100mg oral daily plus lamivudine 300mg oral daily as compared to darunavir – ritonavir plus tenofovir-lamivudine 300mg-300mg orally once daily in ART naïve participants. The week 48 primary endpoint data was recently presented at CROI 2018.⁵ One hundred forty-five participants were randomized and 93% participants in the 2-drug and 94% of participants in the 3-drug arm achieved HIV-1 RNA <50 cpm. Two-drug therapy was non-inferior to standard 3-drug therapy. Therapy was well tolerated in both arms but there was a statistically significant increase in total cholesterol in the dual therapy arm as well as a non-statistically significant trend toward increases in LDL-cholesterol and triglycerides. The lipid effects were likely due to the loss of the beneficial effects of tenofovir on lipids.

SWORD-1 and SWORD-2 are two identically designed, Phase 3, open-label, randomized, multicenter, parallel group, active-controlled, non-inferiority studies of 2-drug therapy with dolutegravir 50 mg orally once daily plus rilpivirine 25 mg orally once daily compared to standard three drug ART for the maintenance of virologic suppression.⁶ Participants

were eligible if they were 18 years or older, not pregnant, had an HIV-1 RNA <50 cpm for 6 months prior to screening, and did not have a history of any VL blips ≥ 200 cpm during the 6-12 months prior to screening. Participants were excluded if they needed HCV treatment, had hepatitis B coinfection, had any drug resistance mutations, or a history of virologic failure requiring ART switch to second line therapy. The primary outcome was maintenance of HIV-1 RNA <50 cpm at week 48. The two studies enrolled a total of 1028 participants and 1024 participants were included in the primary endpoint analysis. Study participants were mainly white (80%) and male (78%) with a median age of 43 years. In the pooled analysis, 95% of participants in the 2-drug arm and 95% of participants in the standard three drug ART arm maintained virologic suppression.

Treatment guidelines are rapidly evolving and given the increasing potency of newer ART and decreased costs of 2-drugs as compared to 3-drugs, a shift in the HIV treatment paradigm to 2-drug regimens is on the horizon.

The study was fully powered and confirmed that dolutegravir plus rilpivirine was non-inferior to three drug ART. There were 3 participants who experienced virologic failure in the dolutegravir plus rilpivirine group and resistance testing was successfully performed on 1 participant. That participant had a K101K/E mutation which did not affect the susceptibility to rilpivirine. Regarding secondary outcome measures, CD4 T-lymphocyte count increases were similar between the 2 groups and there were similar rates of AEs with few events leading to study withdrawal. Of note, neuropsychiatric AEs (insomnia, depression, and anxiety) were reported more frequently in the dolutegravir plus rilpivirine arm as compared to the 3-drug arm, 12% vs 6%, respectively; however, only 1% of neuropsychiatric AEs lead to withdrawal from the study in the 2-drug arm vs <1% in the 3-drug arm. The results of this trial led to the FDA approval of the single tablet formulation of dolutegravir plus rilpivirine (Juluca) for maintenance therapy in PLWHA who are virologically suppressed.

Many 2-drug studies exclude individuals with resistance mutations; however, ART resistance and need for second and third line regimens is an important treatment consideration for PLWHA. A retrospective analysis by Häggblom et al., reported that 14.2% of PLWHA in Sweden failed first-line ART with drug resistance mutations requiring a switch to second line

ART.⁷ A paradox often exists for these individuals because their subsequent regimens become more complex and thus adherence and polypharmacy become further barriers to ART adherence. At CROI 2018, Pierone et al. presented the virologic outcomes between 2-drug and 3-drug regimens in the OPERA observational cohort.⁸ In the OPERA cohort, patients who received 2-drug regimens were older, had more comorbid conditions, and 41.7% had experienced 5 or more ART regimens as compared to patients on 3-drug regimens. Fifty-five percent of the 2-drug regimens were protease inhibitors plus integrase strand transfer inhibitors (INSTI) based regimens with ritonavir-boosted darunavir plus dolutegravir being the most common regimen. In patients who were viremic at the time of ART switch, 61% and 67% achieved HIV-1 RNA <50 cpm on 2-drug and 3-drug regimens, respectively. In patients who were suppressed at the time of ART switch, virologic suppression was maintained; 10% of patients on 2-drug regimens and 11% of patients on 3-drug regimens experienced virologic failure. Data on drug resistance was not provided but drug resistance was inferred to be present as the patients were heavily treatment experienced.

The Italian TIVicay plus PrezISTA Observation cohort (Tivista) followed patients from several Italian centers who were ART experienced and switched to ritonavir-boosted darunavir with dolutegravir.⁹ Ninety-one percent of the cohort had resistance to at least 1 class of ART, including 15% with reduced susceptibility to darunavir and 9% with reduced susceptibility to INSTIs. Depending on the patient's resistance mutations, their regimens were a combination of once or twice daily ritonavir-boosted darunavir plus once or twice daily dolutegravir. At the beginning of the study, 60% of participants had an HIV-1 RNA <50 cpm. At week 48, 91% of participants had virologic suppression. Six percent of participants had HIV-1 RNA ≥ 50 cpm, of which 3 had persistent viremia but slow virologic decline. Currently, the DUALIS study (NCT02486133), a Phase 3, randomized switch study is ongoing to confirm this 2-drug strategy.

The Long-Acting Antiretroviral Treatment Enabling (LATTE-1) trial was a Phase 2b, dose-ranging, parallel group, randomized trial to assess the efficacy of cabotegravir (a novel INSTI) with a standard ART backbone to achieve virologic suppression and to assess the efficacy of cabotegravir plus rilpivirine to maintain virologic suppression.¹⁰ Two hundred forty-four treatment-naïve participants were enrolled and randomized to receive either cabotegravir 10 mg, 30 mg, or 60 mg versus efavirenz 600 mg orally once daily combined with a standard 2 drug nucleos(t)ide reverse transcriptase inhibitor (NRTI) backbone. At week 24, participants in the cabotegravir arms who achieved HIV-1 RNA <50 cpm had their NRTI backbone replaced with rilpivirine 25 mg once daily and were maintained on their cabotegravir dose. Participants

were 96% male, 62% white, with a median age of 33 years. At week 48, 82% of participants in the cabotegravir plus rilpivirine arm and 71% of participants in the efavirenz arm had maintained an HIV-1 RNA <50 cpm. Through week 96, the cabotegravir arms continued to have slightly higher rates of virologic suppression compared to the efavirenz arm with lower rates of discontinuation due to AEs, 13% in the efavirenz arm vs 3% in the cabotegravir arms, and lower rates of virologic non-response, 16% in the efavirenz arm vs 10% in the cabotegravir arm. Three participants in the cabotegravir 10 mg arm experienced (or were suspected to have) virologic failure. Resistance genotyping demonstrated the development of significant non-nucleoside reverse transcriptase inhibitor (NNRTI) mutations (K101K/E and E138E/A/K/Q) and INSTI mutations (Q148R).

Currently, oral ART must be taken daily to maintain appropriate therapeutic drug levels in the blood. Adherence to daily ART remains a challenge. Ortego et al. estimated that only 62% of PLWHA had >90% adherence.¹¹ Long acting injectable ART may offer a solution to some barriers to ART adherence. In the LATTE-2 trial, long-acting injectable cabotegravir (LA CAB) plus rilpivirine (LA RPV) were evaluated for the maintenance of virologic suppression.¹² The study was a Phase 2b, randomized, parallel group, open label study. Participants were eligible if they were 18 years or older, ART naive, and had no major drug resistance mutations. Participants first underwent a 20-week oral lead-in phase: 16 weeks of oral cabotegravir 30 mg plus abacavir-lamivudine 600-300 mg followed by an additional 4 weeks with oral rilpivirine 25 mg added to the regimen. If participants achieved an HIV-1 RNA <50 cpm, they were randomly assigned to LA CAB 400 mg plus LA RPV 600 mg every 4 weeks (4W), LA CAB 600 mg plus LA RPV 900 mg every 8 weeks (8W), or to continue oral 3 drug therapy with cabotegravir plus abacavir-lamivudine. Three hundred nine participants were enrolled. They were 91% male with an average age of 36.6 years. Two hundred eighty-six participants completed the oral lead-in phase, achieved an HIV-1 RNA <50 cpm, and entered the long-acting injectable phase of the study.

At week 32, virologic suppression was 94%, 95%, and 91% in the 4W, 8W, and oral arms, respectively. Long-acting treatment was non-inferior to oral therapy and the efficacy of long-acting treatment was maintained through week 96. Nearly all participants experienced AEs with the most common being mild injection site reactions. There were few Grade 3 or higher AEs. Despite the injection site reactions, participants reported high levels of treatment satisfaction. Three participants had virologic failure, 2 in the 8W arm and 1 in the oral arm. There were no drug resistance mutations detected for the participant in the oral arm. The two participants on the 8W arm were found to have NNRTI (K103N, E138G, and K238T) and INSTI (R269R/G and Q148R) mutations. The second participant's mutations resulted in phenotypic resistance to all NNRTIs, except etravirine and all INSTIs (including cabotegravir), except dolutegravir.

The life expectancy of someone diagnosed with HIV is estimated to be as high as 78 years, which could potentially translate to 50 years of ART exposure.¹³ Newer 2-drug ART approaches are well tolerated and achieve and maintain virologic suppression at rates comparable to 3-drug regimens. Several national guidelines offer 2-drug regimens as alternates in certain clinical circumstances but this recommendation preceded the data from the studies in this review. Treatment guidelines are rapidly evolving and given the increasing potency of newer ART and decreased costs of 2-drugs as compared to 3-drugs, a shift in the HIV treatment paradigm to 2-drug regimens is on the horizon. These 2-drug regimens may not only be for individuals who have contraindications to NRTIs (those who require “nuke” sparing regimens”) but also as first line, switch strategies, and salvage treatment. However, research gaps remain regarding the efficacy of 2-drug ART in PLWHA with HBV coinfection, women, and during pregnancy and breastfeeding. Two-drug ART is a viable treatment strategy and novel drug delivery strategies, such as long-acting injectable ART, will further strengthen the therapeutic armamentarium. **HIV**

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ABOUT THE AUTHOR

Amesika N. Nyaku, MD, MS, is an Assistant Professor at Rutgers New Jersey Medical, Department of Medicine, Division of Infectious Diseases. She is also an investigator of the ACTG New Jersey Medical School Clinical Research Center CRS.

Nontraditional Delivery

By KRISTEN MOODY, PharmD and
ANGELA D. KASHUBA, BSCPHM, PharmD, DABCP, FCP

COMBINATION ANTIRETROVIRAL (ART) THERAPY is one of the major medical breakthroughs of the 20th century, transforming HIV from a high morbidity and mortality disease to a chronic condition, and increasing patient life expectancy to that of HIV-uninfected individuals.¹ Despite the success of ARTs, strict adherence to daily therapy remains a significant barrier to the maximally effective treatment and prevention of HIV. Medication non-adherence is a frequent cause of HIV treatment failure, es-



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pecially in adolescent patients.² Non-adherence also results in lack of protection against HIV in clinical trials of pre-exposure prophylaxis (PrEP).^{3,4} Possible approaches to overcome the challenge of daily adherence for HIV treatment and prevention are long-acting injectables (LAIs), implants, and certain topical formulations of HIV medications, which require less frequent dosing. These nontraditional delivery systems provide unique pharmacokinetic advantages and disadvantages, as well as regulatory and financial challenges.⁵

Long-acting injectables

LAIs have proven effective in treating other conditions affected by non-adherence, such as schizophrenia. The first antipsychotic LAI formulation, risperidone, was introduced in 2003 and has been successfully integrated into clinical practice.⁶ To date, five additional antipsychotic LAIs have entered the market, with indications spanning across various mental health conditions.⁷ Two forms of LAIs for HIV treatment and prevention have proven successful in Phase II clinical trials, and are currently undergoing Phase III clinical trials: rilpivirine (RPV) and cabotegravir (CAB). RPV is a potent nonnucleoside reverse transcriptase inhibitor (NNRTI) with a structure that enables tight binding to the reverse transcriptase enzyme.⁸ This agent is as effective as efavirenz with CNS tolerability advantages.⁸ Cabotegravir is an integrase strand transfer inhibitor (INSTI) and a structural analogue to dolutegravir.⁹ CAB is not metabolized through the cytochrome P450 enzyme system, and thus presents no significant drug interactions through this hepatic pathway.⁹ Both formulations are a nanosuspension with a particle size of 200 nm that provides a depot effect when injected intramuscularly (IM).^{8,9}

Rilpivirine LA

RPV is being investigated for HIV prevention as a 1,200 mg IM injection dosed every eight weeks, and for HIV treatment concurrently administered with CAB dosed every 4 or 8 weeks (RPV 600 mg/CAB 400 mg and RPV 900 mg/CAB 600 mg, respectively). Healthy volunteers who received a RPV IM loading dose of 1,200 mg followed by 600 mg on days 28 and 56 had plasma concentrations

sustained above the 90% effective concentration (EC_{90} ; 12 ng/mL) for 3 months.¹⁰ RPV concentrations were also detected in rectal fluid (RF) up to 84 days post-dose, with concentrations lower than plasma (geometric mean RF, 1.6 ng/mL; plasma, 15.9 ng/mL).¹¹ Rectal tissue (RT) concentrations at 14 days post-dose were similar to those in plasma (geometric mean RT, 70.3 ng/mL; plasma, 78.2 ng/mL).¹¹ RPV was also detected in cervicovaginal fluid (CVF) up to 84 days post-dose, with concentrations comparable to plasma (RPV 1,200 mg: geometric mean CVF, 36 ng/mL; plasma, 30 ng/mL).¹¹

RPV LAI has a half-life of approximately 30.5 days in males, and 39 days in females, which facilitates the extended dosing interval.¹¹ However, due to its long half-life, the potential for developing viral resistance during the sub-therapeutic drug concentrations found in the pharmacokinetic “tail” (where concentrations fall below a therapeutic concentration for a long period of time) is of concern.¹² One case report describes a woman who received a single RPV 300 mg injection and reported unprotected vaginal intercourse on day 41 post-dose. She seroconverted on day 84 (estimated concentration at the time of HIV exposure; plasma, 10.5 ng/mL; CVF, 18.3 ng/mL), and developed a resistant mutation (K101E/K) by day 115.¹² This risk will likely need to be mitigated by adding oral ARVs when discontinuing this therapy.¹³

RPV-LAI as a PrEP strategy was investigated in HPTN 076 (NCT02165202), a Phase II study assessing safety and acceptability over 40 weeks.¹⁴ RPV-LAI 1,200 mg was administered every 8 weeks, for 6 doses, and participants were followed for 52 weeks, with an additional 24 weeks of

follow-up to monitor the pharmacokinetic “tail” phase. In general, this drug was well accepted and considered easier to use than other prevention options (80% of participants considered RPV-LAI easier to use)¹⁵.

Cabotegravir LA

Long-acting injectable cabotegravir (CAB-LAI) is being pursued for HIV prevention as a 600 mg IM injection administered every 8 weeks, and for HIV treatment concurrently administered with RPV-LAI. In healthy volunteers who received a single CAB IM injection of 400 mg or 800 mg, plasma CAB concentrations were maintained above the protein-adjusted concentration that inhibits viral replication by 90% (PA-IC₉₀; 0.166 µg/mL) for 28 weeks.¹⁶ More specifically, the CAB IM 800 mg injection resulted in a concentration 4-times the PA-IC₉₀ (the concentration determined to be protective in animal models¹⁷) for 16 weeks.¹⁶ Additionally, CAB was detected in vaginal tissue at concentrations above the PA-IC₉₀ at 8 weeks post-injection but was undetectable in rectal tissues.¹⁶ Ongoing studies are currently being completed to further investigate the tissue concentrations of a single dose of CAB 600 mg IM, the dose proposed for PrEP (NCT02478463)¹⁸. Results are expected in late 2018.

Similar to RPV-LAI, CAB also has a long half-life of approximately 40 days, which facilitates the characteristic pharmacokinetic “tail” that may make patients susceptible to viral resistance.¹⁶ Dosed every 12 weeks, IM CAB was investigated for PrEP in the Phase II study, ÉCLAIR.¹⁹ One study participant receiving the active drug, CAB 800 mg IM, reported condomless sex 12 to 24 weeks after the final injection, and had a confirmed HIV infection at 24 weeks. At the 12-week post-injection visit, the plasma CAB concentration was below the PA-IC₉₀ (CAB plasma concentration, 0.122 µg/mL; PA-IC₉₀, 0.166 µg/mL), and HIV RNA was undetectable. By 36 weeks after the final injection, there was no evidence of viral resistance, suggesting that no viral resistance was conferred during the pharmacokinetic “tail” phase.¹⁹

CAB is being evaluated for PrEP in women. There is currently a Phase III double-blind trial evaluating its efficacy compared to oral tenofovir disoproxil fumarate/emtricitabine that plans to enroll 3,200 at risk women in Africa (NCT03164564).²⁰ Results are expected in 2022. It is also being studied for PrEP in men and transgender women who have sex with men (NCT02720094), with results expected in 2021.²¹

Combination LA Therapy

The combination of RPV-LAI and CAB-LAI for HIV treatment, dosed every 4 or 8 weeks, in treatment-naïve adults was studied in LATTE-2; a Phase II, randomized controlled trial to evaluate the safety and efficacy for maintenance of viral suppression through 96 weeks.²² Both 4-week (RPV 600

mg/CAB 400 mg) and 8-week (RPV 900 mg/CAB 600mg) dosing maintained viral suppression comparable to an oral 3-drug regimen (abacavir/lamivudine + CAB) for 96 weeks with viral suppression rates of 84% with the oral regimen, 87% with RPV/CAB 4-week dosing and 94% with RPV/CAB 8-week dosing.²² The RPV-LAI/CAB-LAI combination regimen was well tolerated; the most common treatment-related adverse event reported was injection-site pain (reported by 97% of patients dosed every 4-weeks, and 96% dosed every 8-weeks). However, this was categorized as mild for 84% of the events observed.²²

Additionally, RPV-LAI 600 mg/CAB-LAI 400mg combination dosed every 4 weeks is currently being studied in virally suppressed adults on an ART regimen containing two nucleoside reverse transcriptase inhibitors (NRTI), plus an INSTI, NNRTI, or protease inhibitor (PI).²³ The study aims to identify the efficacy, safety, and tolerability of switching participants from their current ART to RPV-LAI/CAB-LAI (NCT02951052).²³ Results are expected in 2022. Combination treatment of HIV with RPV-LAI and CAB-LAI continues to progress through clinical trials demonstrating safety and efficacy, while providing a promising outlook to overcome the barrier of daily adherence.

Topical ARV Formulations

Antiretroviral Gels

Topical microbicides have been evaluated for HIV prevention for over 15 years, but many early formulations failed to protect against HIV.²⁴ Microbicide formulations demonstrated local mucosal toxicity that led to irritation and epithelial disruption, and increased the risk for HIV acquisition.²⁴ Iso-osmolar products at a physiologic pH provide the best safety profile and do not increase the risk of infection.²⁴

A pivotal study in South Africa (CAPRISA 004) demonstrated that 4 mL of a 1% tenofovir (TFV) gel administered vaginally before and after sex was 30% effective in reducing HIV transmission.²⁵ A post-hoc analysis demonstrated that in women with >80% adherence, efficacy increased to 54%.²⁵ The VOICE trial measured the protective effect of daily 1% TFV gel in women in South Africa.⁴ The study found no protective effect of this intervention, which was likely due to low adherence to daily dosing (estimated less than 40%).⁴

In 2016, a different formulation of TFV gel, a reduced-glycerin 1% TFV gel, was explored for safety and acceptability among rectal administration in men who have sex with men (MSM) and transgender women (TGW). Both daily and episodic (pre- or post-receptive anal intercourse) administration was well tolerated, with patient acceptability highest in the on-demand dosing group.²⁶ In an effort to continue exploring the utility of topical gels, the Microbicide Trials Network (MTN) is currently enrolling participants into MTN-026, a Phase I study to evaluate the safety of rectal administration of 0.05% dapivirine (DPV) gel, with



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initial results expected in late 2018.²⁷ In general, topical microbicides can make an impact on HIV acquisition, if they are adequately formulated to reduce mucosal damage and facilitate adherence.

Vaginal Rings

Vaginal rings have been successfully used for contraception and are being explored for delivery of ARVs. They provide sustained local concentrations to vaginal and cervical tissues without the use of an applicator or gel leakage. Additionally, they may be co-formulated with hormonal contraceptives. In 2009, ART-loaded rings were investigated for the prevention of HIV transmission.²⁸ A vaginal ring containing DPV 25 mg resulted in concentrations in the lower genital tract >1,000 times the 50% effective concentration (EC_{50} ; 0.3 ng/mL) against wild-type HIV virus, with very low systemic exposure.²⁸ ASPIRE, a Phase III clinical trial conducted in Africa, demonstrated a 27% protective effect from the DPV ring.²⁹ The low protective effect was further investigated by stratifying the populations by age. Among younger populations of women (aged 18-21), there was low efficacy (10%), which was attributed to non-adherence.²⁹ However, in older women (aged 21+), increased protection (56%) was observed.²⁹ DPV has recently been co-formulated with a contraceptive, levonorgestrel, and is currently being studied in a Phase I trial in the United States to assess pharmacokinetics and safety.³⁰ Results are expected later in 2018.

Implants

Implantable drug delivery formulations have been utilized across many therapeutic areas for over 25 years. Norplant, a subdermal implant, was introduced in 1990 and slowly releases the contraceptive levonorgestrel over five years³¹. Norplant is 99% effective at preventing pregnancy, compared to traditional oral contraceptive pills, which provide only 91% efficacy, with proper adherence.³² Implantable formulations have high acceptability and remove the concern for adherence in PrEP. A number of implants formulated

with antiretrovirals are being investigated for PrEP, with or without contraceptive co-formulation.

A subdermal implant providing sustained release tenofovir alafenamide (TAF) has been studied in beagles. Concentrations of TAF, TFV, and the metabolite tenofovir diphosphate (TFV-DP) were maintained for 40 days at concentrations similar to a single 25 mg dose in humans.³³ The implant is designed to facilitate controlled release of TAF from a reservoir. The implant degradation is independent of drug release, allowing the implant to be removed at any time if warranted. In vitro studies demonstrate a linear release profile over 3 months. The implant is currently being evaluated *in vivo* in exploratory animal PK studies.³⁴ Additionally, a biodegradable thin-film polymer device has been fabricated to provide subcutaneous delivery of TAF.³⁴

Regulatory Challenges

Each of the alternative ART delivery formulations discussed above present regulatory challenges. Utilizing nonhuman primate studies in HIV prevention can help inform dose selection and provide threshold concentrations at which infection occurs.⁵ However, scaling these data to predict the protective dose in humans is challenging, as pharmacokinetic distribution may differ between species. For LAIs or implantable devices, an oral lead-in phase is necessary to assess for toxicity or allergic reactions.⁵ Furthermore, long-acting ART formulations have a characteristic long pharmacokinetic “tail”, which may facilitate the emergence of viral resistance and require coverage with another oral antiretroviral until the LAI-derived concentrations dissipate⁵. Also, adequately designing clinical trials to support approval of LAI formulations for PrEP, which includes an active comparator, is challenging, as is identifying the site of action, and the window of protection.³⁵ Lastly, implementing injectable formulations into clinical practice may prove challenging as they will require clinic visits for injections. However, established clinical flows for other long acting injectables currently in use (e.g., Depo-provera, antipsychotics)

provide a framework for antiretroviral LAI administration. Additionally, the approval of these therapies may pose an opportunity for pharmacists to engage in patient care and administer these injections.

Major advances with ART have continued to inform and shape HIV treatment and prevention. Despite this, adherence remains a major obstacle to efficacy. Novel and alternative formulations seek to address these adherence

concerns. LAIs are well-tolerated, accepted, and may improve adherence with every 4 (treatment) or 8 (prevention) week dosing. Vaginal rings are unique in their ability to provide local concentrations of drug to vaginal and cervical tissues, while minimizing systemic exposure and side effects. The least frequent dosing may be achieved with implantables; however, drug choices will need to have high potency in order to be formulated in small quantities. **HIV**

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ABOUT THE AUTHOR

Kristen Moody, PharmD, received her degree from the University of North Carolina, Eshelman School of Pharmacy. She is a post-doctoral Medical Affairs Fellow with the University of North Carolina, Eshelman School of Pharmacy and GlaxoSmithKline. She is currently working on HIV treatment and prevention adherence research in the laboratory of Dr. Angela Kashuba.

Angela D. Kashuba, BSCPHM, PharmD, DABCP, FCP, serves as Director of the UNC Center for AIDS Research Clinical Pharmacology and Analytical Chemistry Core. She joined the UNC-Chapel Hill faculty in 1997.

On Demand PrEP



Does it
work
when
you
want it?

By JACOB A. LANGNESS, PharmD, BCPS, and
CHRISTINA KOUTSARI, PharmD, PHD, BCPS

DESPITE EXPANDING PREVENTION EFFORTS, increased access to care, improvements in medication efficacy and tolerability, and health education efforts, HIV continues to spread across both the developed and developing world. In the United States in 2016, 39,782 individuals received a new HIV diagnosis. The main route of transmission is sexual contact, and predominantly in men who have sex with men (MSM).¹ It is well documented that the risk of viral transmission is virtually zero when the virus is undetectable in a person living with HIV/AIDS (HIV-1 RNA <200 copies/mL). Unfortunately, only 61% of Americans living with HIV/AIDS have a consistent undetectable viral load.² Approximately 91.5% of new HIV infections are transmitted by people who are either undiagnosed or not engaged in care.³ This illustrates the need for additional HIV prevention tools.

In July 2012, the Food and Drug Administration (FDA) approved tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) taken daily as pre-exposure prophylaxis (PrEP) for individuals at an increased risk for HIV infection. This was the first instance of a non-barrier method of HIV prevention becoming FDA-approved. Subsequent to FDA approval, numerous studies have shown PrEP to be >95% effective when used daily.⁴ Retrospective studies on real-world use have shown that patients on daily PrEP initially have high

adherence and high motivation for continuing PrEP.⁵ However, PrEP implementation has been slow due to concerns for decreased condom use leading to increased sexually transmitted infections, possible low adherence leading to reduced efficacy, and difficulties related to retention in care. Data on PrEP uptake presented in 2017 showed that approximately 100,000 individuals have started PrEP since 2012.⁶ This number is less than 10% of the individuals the Center for Disease Control (CDC) estimates fit the criteria for being

at a high risk of HIV infection. Though the data show that PrEP implementation is expanding, few of the individuals receiving PrEP are younger than 25 years old or people of color, two populations at very high risk for HIV acquisition.⁶

On-demand, or event driven PrEP, is the practice of spacing medication use around a risk for transmission such as a sexual encounter. Daily PrEP is ideal for patients with frequent episodes of risk and for patients able to adhere to a daily regimen. However, there are others who have less frequent episodes of HIV exposure and are unwilling to commit to daily oral therapy. These individuals may not need continuous exposure to PrEP, though they are at risk for acquiring HIV at certain times. Potentially the 1.1 million Americans who are estimated to be at an increased risk for HIV infection but not on daily PrEP could benefit from another option. Researchers are investigating what modes of delivery might lead to safer, more effective, but also efficient, forms of HIV prevention.



The 1.1 million Americans who are estimated to be at an increased risk for HIV infection but not on daily PrEP could benefit from another option. Researchers are investigating what modes of delivery might lead to safer, more effective, but also efficient, forms of HIV prevention.

The IPERGAY Study Group's randomized trial and the follow-up observational cohort study provide the most comprehensive evidence to date that on-demand oral PrEP is highly effective at preventing HIV infection in MSM.^{7,8} The IPERGAY Study was a multicenter, double-blind, randomized trial in 414 HIV-negative MSM who were randomly assigned to a fixed combination dose of TDF/FTC or placebo before and after sexual activity. Participants were instructed to take a loading dose of two pills with food 2 to 24 hours before sex, followed by a third pill 24 hours after the first dose and a fourth pill 24 hours later. In the case of multiple consecutive episodes of sexual intercourse, participants were instructed to take one pill per day until the last sexual intercourse and then to take the two post-exposure pills. All participants received a comprehensive package of prevention services, including patient-centered, risk-reduction counseling, free condoms and gel, regular testing for HIV-1 and 2, and diagnosis and treatment of sexually transmitted

infections. Participants took a median of 15 pills of TDF/FTC or placebo per month. After a median follow-up period of 9.3 months, a total of 16 new HIV-1 infections occurred, two in the TDF/FTC group and 14 in the placebo group. This represented a relative reduction in the TDF/FTC group of 86% ($P=0.002$).⁷

The two participants in the TDF/FTC group in whom HIV-1 infection was diagnosed were non-adherent by pill count and had undetectable plasma levels of TDF/FTC at the time of HIV diagnosis. One area of concern was the complexity of the dosing schedule, highlighted by the self-reported use of PrEP at the time of the most recent sexual intercourse. Only 43% of participants reported taking the assigned drug correctly, whereas others reported taking the assigned drug incorrectly (29%) or not at all (28%). This study showed that event driven PrEP with oral TDF/FTC (on average approximately 4 pills per week) is an efficacious strategy for preventing HIV among MSM at high risk.⁷

The short follow-up for the IPERGAY Study may have increased the likelihood of a positive outcome due to high initial adherence.⁷ As a result the investigators subsequently extended the original randomized controlled trial to offer on-demand oral PrEP to all participants in an open-label fashion.⁸ A total of 361 participants were followed for a median period of 18.4 months. Instructions for on-demand PrEP were similar to those provided in the randomized phase of the study. Participants took a median of 18 pills of TDF/FTC per month. HIV-1 seroconversion was observed in only one participant during follow-up. The overall HIV incidence in the open-label extension phase was reduced by 97% compared to the placebo group during the randomized phase of the study.^{7,8} The participant who seroconverted reported non-adherence to PrEP. Similar to the randomized phase of the IPERGAY study, only 50% of participants self-reported correct use of PrEP at the time of the most recent sexual intercourse, whereas some reported taking suboptimal (24%) or no doses (26%). At the 6-month visit, tenofovir was detected in 71% of participants. Frequency of condomless receptive anal sex at the last sexual intercourse increased from 77% at baseline to 86% at 18 months' follow-up ($p=0.0004$). This study confirmed the efficacy of sexual-activity-dependent PrEP with oral TDF/FTC as a strategy for preventing HIV among MSM.

The IPERGAY studies represent the largest and most comprehensive sample of event-driven PrEP patients.^{7,8} However, due to some limitations of the studies, the CDC does not endorse PrEP used intermittently. Individuals studied were MSM with a risk of rectal transmission. Heterosexual men and women and injection drug users were not part of the study population and therefore it is unknown if PrEP used intermittently would be effective for these populations. As noted above, the median number of tablets used in the IPERGAY studies was 15-18 tablets a month, corresponding

to approximately four pills (one exposure) per week. Did the IPERGAY studies adequately test event-driven PrEP given that many participants had sex frequently enough to receive PrEP most days of the week? Would it be as effective if the exposure only occurred once or twice per month or a few times per year? This question remains to be investigated. Also of concern was the fact that in both studies only half of participants used the correct dosing regimen at the last exposure. If the use was more infrequent, would mistakes in dosing reduce efficacy? Lastly, potential exposures may be unpredictable or unexpected, leading to an inadequate loading dose.

The high efficacy (86%-97%) in the IPERGAY studies is in line with pharmacology modeling analyses that have predicted 96%-99% protection in rectal tissue after only four tablets of TDF/FTC.⁹ In addition, the inferred risk reduction remained $\geq 90\%$ for seven days after discontinuation of a 30-day regimen of daily TDF/FTC PrEP.⁹ Pharmacologic analyses have shown that TDF and FTC have different tissue distribution patterns, with TDF favoring colorectal tissue and FTC favoring vaginal tissue.¹⁰ The concentration of competing endogenous nucleotides (dATP and dCTP) in colorectal tissue was shown to be 7 to 11 times lower compared to that in vaginal tissue, favoring the pharmacologic activity of TDF/FTC in colorectal versus vaginal tissue. The study suggests that more consistent dosing is required to achieve

sufficient drug concentrations in vaginal than in rectal tissue.¹⁰ It is likely that daily rather than event-driven PrEP is required for adequate protection from HIV infection in women. Whether the high efficacy shown in the IPERGAY studies that has also been predicted in modeling studies would apply to men or women who have sex less frequently requires further investigation.

On-demand, or event driven PrEP, is an exciting potential dosing strategy to arm more people with the tools needed to prevent HIV. Further studies are needed in heterosexual men and women, injectable drug users, and MSM with infrequent exposures to HIV to validate the safety and efficacy of on-demand PrEP. Additionally, innovative formulations and routes of administration of PrEP that do not rely on daily dosing or advanced planning for sexual encounters would offer further options for HIV protection. Intravaginal rings and long-acting injectable antiretroviral agents are currently under investigation in clinical trials.^{11,12} Subdermal implants have been designed but not yet tested in clinical trials.^{13,14} There remains a great deal of interest in rectal or vaginal microbicides for HIV prevention, although to date these have not been very efficacious. With these progressive innovations, the landscape for HIV prevention is expanding. More options will hopefully lead to better patient care and ideally reduce the number of HIV infections in the United States and globally. **HIV**

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ABOUT THE AUTHORS

Jacob A. Langness, PharmD, BCPS, is a clinical pharmacist focusing in infectious disease and internal medicine at Abbott

Northwestern Hospital in Minneapolis, MN. He completed his Doctorate of Pharmacy at the University of Minnesota and pharmacy residency at University of Colorado Hospital. Jacob focuses on improving patient's health through optimal medication therapy management.



Christina Koutsari, PharmD, PhD, BCPS, is a PGY2 infectious diseases pharmacy resident at Abbott Northwestern Hospital in Minneapolis, MN. She earned her

PharmD degree at Creighton University in Omaha, NE and completed her PGY1 pharmacy residency at Abbott Northwestern Hospital. She also earned a PhD degree at Loughborough University, UK and completed post-doctoral research in the Division of Endocrinology at Mayo Clinic in Rochester, MN. Christina is committed to providing excellent patient care through integrated clinical practice, education, and research.



Test and Treat

A New Model for Better Patient Outcomes

By BROOKE STEVENS, PharmD, BCPS, AAHIVP, and BLAKE MAX, PharmD, AAHIVP

THE SUCCESS OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (ART) of decreasing AIDS-related morbidity and mortality is well recognized. However, identifying persons who are living with HIV, engaging them in medical care, and retaining them in care so that the benefits of ART can be attained are issues that need to be addressed. Data from the Centers for Disease Control (CDC) HIV Continuum of Care show that 85% of people living with HIV are diagnosed, 62% have received medical care, 48% have been retained in care, and 49% of persons in care are virologically suppressed.¹ A new model of care to help improve these numbers is “Test and Treat.” The goal of this intervention is to improve engagement in care and initiate antiretroviral therapy as soon as possible. The model aims to improve engagement and retention in care, increase the numbers of individuals living with HIV who are virologically suppressed, and decrease rates of transmission.

The practice of the “Test and Treat” model is currently being assessed in multiple ongoing studies. In a traditional HIV clinical care model, the healthcare provider will order a series of baseline laboratory tests that may take days to weeks for results, the newly diagnosed patient often meets with other members of the health care team, which may not be the same day, and drug and insurance coverage need to be determined. These factors and other patient specific factors result in the patient having to make multiple clinic visits before ART can be initiated. This series of events can disrupt the care continuum and result in individuals not returning to clinic to receive ART. The “Test and Treat” model proposes the immediate availability of ART for those persons newly diagnosed and willing to start therapy at the same clinical encounter when the HIV diagnosis is made.

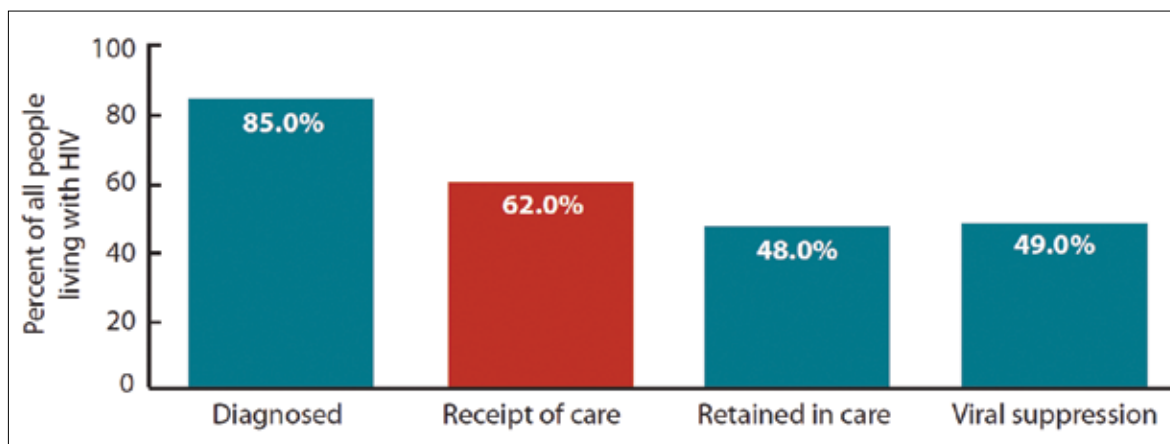
Review of Test and Treat Studies

The RAPID (Rapid ART Program for Individuals with an HIV Diagnosis) clinical program was piloted the San Francisco General Hospital HIV Clinic from July 2013 to December 2014 and was ultimately expanded citywide in 2015.² The goal of this program was to provide complete evaluation and initiation of ART on the same day as HIV diagnosis. Patients were able to secure a medical appointment with an HIV specialist and complete a 3–4 hour appointment consisting of general disease and medication education, after which the patient either accepted or declined treatment with a pre-approved ART regimen. Insurance approval and/or patient assistance program applications were initiated and the patient was provided with a 5-day supply of medication, if necessary. All patients were offered directly observed therapy for their first dose, and then received a follow-up phone call from a clinic nurse within the first week of their initial visit.

During the original study period, 39 patients were managed by the RAPID protocol including several with historical adherence barriers including lack of insurance coverage, homelessness, illicit substance use, and mental health disorders. Of those included, 35 patients took their first dose of

ART while in clinic and an additional 2 patients took their first dose within 24 hours of their clinic appointment, indicating a high level of patient acceptability. Within 30 days after the initial clinic visit, 100% of patients in the RAPID group had initiated ART compared to 68% of patients receiving standard care. No treatment regimens were changed due to virologic failure or the presence of transmitted resistance after baseline HIV genotype results were available. Loss to follow-up was not significantly different between patients following the RAPID protocol and those receiving standard of care. The time to viral suppression was significantly faster in the RAPID protocol patients (56 vs. 79 days, $p = 0.009$). The RAPID protocol was also compared to the pre-RAPID, “universal ART” period, and the time to viral suppression was also significantly shorter (1.8 vs. 4.3 months, $p < 0.001$).

An unblinded, randomized, controlled trial completed at the Haitian Group for the Study of Kaposi’s Sarcoma and Opportunistic infections (GHESKIO) Clinic in Port-au-Prince, Haiti compared same day ART initiation versus standard ART initiation over a 2 year study period.³ Patients enrolled in the standard of care arm returned to clinic on day 7 after diagnosis, but did not start ART until day 21. Patients were originally included if their CD4 T-lymphocyte count was <350 cells/mm³, which was later changed to <500 cells/mm³ due to a change in local standard of care guidelines. The number of physician visits and the counseling received were identical between the two groups, the only difference was the timing of the appointments and when ART was initiated. At the end of 12 months, significantly more patients were retained in care and had a HIV-1 RNA <50 copies/mL in the same-day ART group compared to the standard ART group (53% vs. 43.8%, $p=0.008$). The difference was also statistically significant when looking at HIV RNA <1000 copies/mL (61.1% vs 51.7%, $p=0.008$). Additionally, the mortality rate was significantly higher in the standard ART group (5.6% vs. 2.9%, $p=0.033$). Although the inclusion criteria of this study does not align with the current standard of care in the United States, the positive clinical implications of early initiation are still applicable.



The Rapid Initiation of Treatment (Rap-IT) study was an unblinded, randomized, controlled trial completed at two outpatient clinics in Johannesburg, South Africa.⁴ Patients were included if their CD4 T-lymphocyte count was <350 cells/mm³ or classified as WHO HIV/AIDS clinical stage 3 or 4. Patients were randomized to either rapid initiation of ART (i.e. at the first clinic visit) or initiation based on standard of care, which was on the sixth clinic visit. For patients unable to complete all steps on day of enrollment, there was a 30 day window that allowed them to complete these steps and still be included in the rapid initiation arm. All patients had several clinic visits following initiation (1, 2, 3, 6, and 12 months), and HIV RNA was obtained at 6 months.

There were 377 ART naïve patients that were randomized and completed the study procedures. In the rapid initiation group, significantly more patients had initiated ART within 90 days and achieved viral suppression by 10 months (RR

There were 137 individuals randomized to each study group. Within the first 90 days, significantly more patients were linked to care, defined as attending at least 1 facility visit, in the same day group compared to the standard of care group (68.6% vs. 43.1%, $p < 0.001$). In addition, more patients achieved viral suppression by 12 months in the same day group (50.4% vs. 34.3%, $p < 0.007$). Retention in care was also higher at 12 months in the same day group.

Discussion

The concept of “Test and Treat” is not new, but has taken on new meaning. The impact of universal HIV testing was attempted over a decade ago when the CDC revised their recommendation to all persons aged 13-64 years in all health care settings should be routinely screened for HIV infection, and since 2016, there is a global consensus that all patients living with HIV, regardless of CD4 T-lymphocyte count, should initiate ART.⁶⁻⁹ This shift was based on two recently published randomized controlled studies (START and TEMPRANO) and the growing body of data supporting the benefits of ART.¹⁰⁻¹¹ These benefits include decreased risk of non-AIDS defining diseases such as HIV-associated nephropathy, cardiovascular disease, malignancies, neurologic complications, persistent inflammation, and a decreased risk of sexual and perinatal transmission.

In the US, the Department of Health and Human Services (DHHS) Treatment Guidelines have evolved over the years. The most recent DHHS treatment guidelines begin to discuss “Test and Treat” as data are emerging to answer the question regarding the benefit of very early initiation of ART. The new “Test and Treat” model may result in patients remaining engaged and retained in care and from a clinical standpoint this may result in better immune function and recovery leading to decreased risk of disease progression¹².

If the “Test and Treat” model of care becomes accepted by the DHHS, new treatment guidelines may present some potential problems for health care systems such as the feasibility of same-day treatment. Depending on patient volume and availability of a multidisciplinary team, some clinics may not be able to accommodate the “Test and Treat” model of clinical care. This new model is a change in the treatment paradigm and some providers may be hesitant to prescribe ART without laboratory results. Other potential factors to overcome will be provider acceptability, patient acceptability, and timely access to ART.

ART is lifelong and nonadherence may lead to development of resistance and a decrease in viable treatment options. The identification of patient-specific barriers and appropriate patient education addressing these barriers are warranted. Based on current models, this education may span over several clinic visits to ensure readiness to initiate ART. However, several studies have shown that the prevalence of



The “Test and Treat” model proposes the immediate availability of ART for those persons newly diagnosed and willing to start therapy at the same clinical encounter when the HIV diagnosis is made.

1.26, CI 1.05-1.50). In addition, more patients initiated ART within 90 days and were retained in care at 10 months in the rapid initiation arm (RR 1.27, CI 1.12-1.44). Of the patients included in the rapid initiation arm, 72% were able to complete study enrollment the same day, indicating the feasibility of this process in their clinics.

The CASCADE trial was a randomized, controlled trial completed in Lesotho, South Africa that investigated the utility of home-based HIV testing and same day ART initiation and the impact on linkage to care as well as sustained viral suppression.⁵ Patients were randomized to receive either same day initiation of ART, in which they were given a 1 month supply of ART at the time of their home-based testing visit with the expectation of follow-up in a clinic within 2 – 4 weeks, or standard of care, which involved at least 2 separate counseling sessions prior to initiation of ART to ensure appropriate labs were obtained and readiness was adequately assessed.

resistance mutations increases when ART is delayed.¹³⁻¹⁵ In addition, a study by Siedner et al. showed that there was no difference in average adherence, treatment gaps, or rates of virologic failure between patients who received pre-initiation adherence counseling and those that did not.¹⁶ Although adherence counseling is important to identify barriers to care and maximize long-term viral suppression it should not be a reason for delay in ART.

Several regimens could be chosen for early ART initiation based on high barrier to resistance, well tolerated, low pill burden, and treatment for hepatitis B co-infection. Antiretrovirals likely to be recommended will also be those that are associated with a low level of transmitted resistance, such as darunavir, tenofovir alafenamide, and integrase inhibitors. A single tablet regimen (STR) incorporating these agents (darunavir/cobicistat/emtricitabine/tenofovir alafenamide) is currently being studied for use in the “Test and Treat” model and others will likely follow.¹⁷

Another question is will facilities implementing this model have the ability to provide immediate ART to newly diagnosed persons who do not have insurance to cover ART? Ideally, patients would already have established healthcare coverage during their initial clinic encounter, however, this is often not the case. Patient assistance programs (PAP) through drug manufacturers are available, although some of these programs may take 2 – 3 weeks to obtain approval and procure drug. Fortunately, with the help of state-administered AIDS Drug Assistance Programs (ADAP), patients are more rapidly able to obtain medication coverage until enrolled in comprehensive insurance, but this process and utilization of funding differs based on local policies. Cost analysis and feasibility studies will be needed to help show the benefit of health care systems covering the cost of ART before insurance coverage/Medication Assistance Programs can be utilized.

Summary

HIV health care providers have witnessed many clinical benefits over the last 30 years. . The proposed clinical benefits of “Test and Treat” include preservation of the immune system, decreased risk of transmission to sexual partners, and decreased incidence and prevalence of HIV infection in a community or at a population level. However, there are obstacles to overcome before “Test and Treat” can become the standard of care. This model is predicated on transmitted drug resistance for ART remaining extremely low on a population level, and implementation of “Test and Treat” will require access to costly ART for individuals who are often under insured or lack drug coverage. Finally, both patients and health care providers will need more data to support the implementation, feasibility, and clinical benefits of this new treatment model before it becomes standard of care. **HIV**

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ABOUT THE AUTHORS

Dr. Brooke Stevens, PharmD, BCPS, AAHIVP, is an HIV clinical pharmacist at LifeCare located at Indiana University Health Methodist Hospital and The Ryan White Center for Pediatric Infectious Disease and Global Health located at Riley Hospital for Children at Indiana University Health. She currently serves as a clinical preceptor for APPE students, PGY1 residents, and PGY2 residents as well as serves as clinical faculty for the Midwest AIDS Training and Education Center (MATEC).

Dr. Stevens earned her PharmD from Butler University in Indianapolis, IN. She completed a PGY1 residency and Infectious Diseases PGY2 residency at Indiana University Health. Dr. Stevens is credentialed as a Board Certified Pharmacotherapy Specialist through the Board of Pharmacy Specialties as well as an HIV Specialist through the American Academy of HIV Medicine.



Dr. Blake Max, PharmD, AAHIVP, is a clinical Associate Professor at the University of Illinois at Chicago College of Pharmacy and an HIV clinical pharmacist for the Ruth M. Rothstein CORE Center, Cook County Health and Hospital Systems. Dr. Max also is the Pharmacy Discipline Coordinator for the Midwest AIDS Training and Education Center (MATEC).

Dr. Max earned his PharmD from the University of California at San Francisco. He completed a pharmacy general practice residency and HIV specialty residency at the University of Illinois at Chicago. Dr. Max is also credentialed as an HIV Specialist through the American Academy of HIV Medicine.



HIV PrEP

Role of the Clinical Pharmacist



**BY RENATA O. SMITH, PharmD, AAHIVP
and SARAH M. MICHENZI, PharmD, BCPS, AAHIVP**

I**N 2015, 1.2 MILLION PEOPLE in the United States were estimated to have an indication for HIV pre-exposure prophylaxis (PrEP) with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF).¹ Of these, African Americans comprised the highest number of persons with PrEP indications by race/ethnicity.² Encouragingly, PrEP utilization has increased every year since its Food and Drug Administration (FDA) approval in 2012.³ However, there is still progress to be made. As of the first quarter of 2017, there were only 120,000 people estimated to be taking FTC/TDF for PrEP.³ This means that just 10% of the population that could potentially have a need for PrEP is using PrEP. Furthermore, PrEP uptake remains lowest among the populations at the highest risk for HIV infection.³**

Although African Americans and Latinx make up the majority of new HIV diagnoses,^{4,5} they are not as likely as Whites to use PrEP.³ Of the unique individuals who started PrEP from 2012 through the third quarter of 2016, only 10% and 13% were African American and Latinx, respectively.³ Additional gaps in PrEP uptake exist among cis- and transgender women and younger individuals (< 25 years of age).³

Given the disparities in HIV incidence and PrEP uptake, novel approaches for PrEP care are needed. Expanding pharmacist roles in PrEP represents one approach to decrease new HIV infections and increase PrEP use. Even before the FDA approval of FTC/TDF for PrEP, roles for pharmacists in PrEP care were described.⁶ Since its approval, the body of literature surrounding pharmacists and PrEP has grown from defining roles⁷⁻¹¹ to descriptive reports of pharmacist PrEP clinic implementation and initial outcomes.^{12,13} The goal of this article is to review the pharmacist's role in the provision of PrEP care by highlighting examples from clinical practice and providing insight from our own experiences.

Pharmacist roles in PrEP include a range of involvement along the PrEP care continuum (awareness → uptake → adherence and retention)¹⁴ or taking responsibility of the process from start to finish in a pharmacist-run clinic. Nunn et al. proposed their PrEP continuum to standardize comparisons and progress of PrEP implementation programs. Their continuum can be further broken down into nine steps. Steps one to three (identify individuals at highest HIV risk, enhance PrEP awareness, facilitate PrEP access) relate to awareness, steps four to seven (facilitate PrEP access, link to care, prescribe PrEP, initiate PrEP) relate to uptake, and steps eight and nine (adhere to PrEP and retain in care) relate to adherence and retention.¹⁴ Although there are several published iterations of the PrEP care continuum, they generally follow similar principles.

Much like the HIV care continuum, it has been shown that engagement in care declines as patients move forward through the cascade.^{15,16} A recent example comes from a county health clinic in Atlanta, GA that implemented PrEP services in October 2015 and sought to investigate PrEP uptake and persistence through March 2017. Of the 367 patients determined to be eligible for PrEP, 41% did not return to start PrEP after screening and only 39% remained in PrEP care at the end of the study period.¹⁷ Another recent example comes from the RADAR study, which follows cohort of young MSM in Chicago, IL outside of clinical trials and demonstration projects. Of the 1031 participants from 2015 to 2017, 65 (33%) discontinued PrEP prior to their interview date. Primary reasons for PrEP discontinuation were issues attending doctor's appointments (~22%) and issues related to insurance (20%).¹⁸ Pharmacists may be able to improve persistence in PrEP care given our accessibility to the public and knowledge of medication assistance programs that can help fill the gap when insurance issues arise.

Notable examples of roles for pharmacists in PrEP care include: adherence counseling and monitoring, HIV prevention education, medication acquisition, co-pay assistance, identification and management of drug-drug interactions and adverse events, and dispensing FTC/TDF.⁶⁻¹¹ Additionally, there are multiple settings in which pharmacists can provide PrEP care. Examples include: community/dispensing pharmacies and outpatient clinics, from general medicine, such as internal or family medicine clinics, to specialty settings, such as sexual health or infectious diseases clinics. Local health departments are another setting to consider. Furthermore, pharmacists can be involved with community engagement and administrative aspects of PrEP, such as policy development.

Perhaps the most prominent example of a pharmacist-run PrEP clinic is, a community pharmacy in Seattle,

WA. Based on the success of pharmacist management of other disease states, pharmacists at Kelley-Ross set out to determine the feasibility of a pharmacist-run PrEP clinic in a community setting.¹² Pharmacists practice under physician oversight with a protocol and collaborative drug therapy agreement (CDTA).^{12,19} The protocol and CDTA were based on the US Public Health Service PrEP Clinical Practice Guideline.¹² A Medical Test Site Certificate of Waiver License (CLIA-waver) and Phlebotomy License were obtained to allow pharmacists to perform all aspects of PrEP care, including ordering labs.¹⁹ Furthermore, pharmacists are able to bill for their services.¹⁹ Within a single patient encounter (hence the name “One-Step PrEP”), pharmacists take a medical and sexual history, make a risk assessment, perform laboratory testing and patient education, and prescribe and dispense PrEP, as appropriate. Pharmacists also provide all recommended follow-up care for PrEP and test and treat sexually transmitted infections (STIs) per the Centers for Disease Control (CDC) Guidelines.¹² Retrospective data from their first year of operation was presented at the Conference on Retroviruses and Opportunistic Infections (CROI) in 2017.¹²

Clinical pharmacists are integral members of the patient care team. Responsibilities include: treatment evaluation and selection, management of drug-drug interactions, laboratory ordering and adverse effect monitoring, patient education, medication acquisition via the patient’s insurance required pharmacy, and adherence assessment and interventions.

From March 2015 to March 2016, 373 patients contacted the clinic, 251 were seen in the clinic, and 245 initiated FTC/TDF for PrEP. Of the 240 who initiated PrEP, 210 (83%) were MSM. Clinic retention (number in service at the end of the study period divided by the number that qualified for service) was 75%. Of the 63 patients (25%) that discontinued service, the main reason was insurance restriction or transfer of care (38/63 patients, 60%). The program concluded an unmet need was identified in their community based on the higher-than-expected response from MSM seeking PrEP care. They also concluded pharmacist-run PrEP was an acceptable care delivery model based on the high retention rate. Additionally, the program was found to be feasible and financially sustainable.¹²

Another example highlighting pharmacist provision of PrEP care from start to finish along the care continuum comes



from our own experiences. Our pharmacist-led PrEP service is provided within a multidisciplinary HIV and Infectious Diseases (ID) specialty clinic in Chicago, IL. As a comprehensive ID clinic, we have been providing PrEP care for many years. However, we did not have a formal service until 2015 when we received a grant from the American Society of Health-System Pharmacists (ASHP) Foundation (ASHPF).

Clinical pharmacists are integral members of the patient care team at our clinic. Responsibilities include: treatment evaluation and selection, management of drug-drug interactions, laboratory ordering and adverse effect monitoring, patient education, medication acquisition via the patient’s insurance required pharmacy, and adherence assessment and interventions. These established roles help set the framework for our pharmacist-led PrEP service.

There are several mechanisms for patient referral to our clinic. Potential patients may see our clinic advertisements around the medical center, community, or on social media. We are included in the local and national PrEP databases. Patients may be referred by other medical providers from within or outside of the medical center, our clinical research center, or the needle exchange staff from our community-based centers. Additionally, patients may be referred by family members, friends, or serodiscordant partners.

Once patients are referred to our clinic, there are two pathways for PrEP care - one by physicians and one by pharmacist consult. The physician pathway is representative of the typical patient care process for other medical conditions or concerns. In the pharmacist pathway, the clinical pharmacist is consulted by the primary or supervising physician and assumes full responsibility for the patient’s PrEP care. Our scope of practice and the care we provide as pharmacists is outlined in an institutional PrEP clinical care protocol.

Pharmacists serve as the leading content experts for the

PrEP clinical care protocol. The objective of the protocol is to delegate the clinical assessment and management of PrEP patients to clinical pharmacists under the supervision of the patients' primary physician. The PrEP clinical care protocol is approved for pharmacists across all ambulatory clinic sites within the medical center. In addition to our clinic, the Family Medicine Clinic is a large provider of pharmacist-led PrEP via this protocol.

Screening, counseling, and provision of PrEP under the clinical care protocol are in accordance with the 2014 US Public Health Service PrEP Clinical Practice Guideline and the 2015 CDC Sexually Transmitted Diseases Treatment Guideline.^{20,21} The protocol allows for pharmacists to be involved at every step of PrEP care and recommends indications/eligibility for PrEP, frequency of screening/monitoring tests, and education/counseling points. Additionally, the protocol outlines certain situations in which patients must be referred back to the physician. Examples include: positive screening tests, such as for HIV or pregnancy, and if the patient needs throat and rectal swabs for chlamydia and gonorrhea.

In addition to direct patient care activities as outlined by the protocol, pharmacists in our clinic devote a significant amount of time to community outreach to increase PrEP awareness and uptake. We distribute PrEP advertisements and information sheets, run a social media account dedicated to PrEP, participate in local health fairs, and engage with community partners via our state's PrEP workgroup. The goal is continued expansion of our pharmacist-led PrEP service with increased outreach and service provision to the areas of Chicago most affected by HIV (such as the South and West sides).

Preliminary data generated from the ASHPF grant were presented at the ASHP Midyear Clinical Meeting in 2018.¹³ A total of 38 patients were referred to a pharmacist for PrEP care in the Infectious Diseases Clinic and the Family Medicine Clinic at our medical center. Of these, the majority (90%) were MSM. As of October 2017, 20 of the 38 patients (53%) were retained in care. Of the 18 patients (47%) who discontinued PrEP medication or care at our medical center, only six had a reason documented in the medical record. Of those, the primary documented reason for discontinuation was change in self-perceived risk or behaviors. We concluded pharmacist-led PrEP services in a multidisciplinary clinic are feasible and pharmacists can be key contributors to developing guidelines and protocols for provision of PrEP services.¹³

As we look towards the future, we are developing a standardized note template and order set for PrEP to streamline and improve care. These will apply across all disciplines and

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clinics within the medical center. Like our PrEP protocol, pharmacists are taking a lead role in the design and implementation of these initiatives. We offer the following advice for those interested in becoming more involved with PrEP or starting PrEP services. Any pharmacist or pharmacy considering a PrEP program should ensure they are adequately staffed to accommodate the new service and staff are trained in HIV, hepatitis B and C, STIs, and cultural sensitivity/competency. The pharmacists and technicians (pharmacy staff) should receive ongoing training as guidelines change and new antiretrovirals are approved for PrEP. Pharmacy staff should be well versed in insurance formulary and pharmacy restrictions, as well as available patient assistance programs. For example, some Medicaid managed care plans in Illinois require that patients fill PrEP prescriptions via a designated specialty pharmacy. There is also a State of Illinois PrEP assistance program (PrEP4Illinois) that offers medication assistance to qualifying patients. Pharmacy staff should be aware of insurance requirements and assistance programs in their specific state to help patients navigate those systems.

Additionally, we recommend remaining up-to-date with state-specific laws and regulations regarding scope of practice and collaborative practice agreements. For example, the Kentucky Board of Pharmacy recently granted



authority to pharmacists to provide certain services under a specific board-authorized care protocol. There are a number of conditions for which procedures are being set forward. Conditions include allergic rhinitis, acute, uncomplicated urinary tract infections, and HIV PrEP (pursuant to CDC recommendations), among many others.²² The American Pharmacists Association (APhA) frequently provides updates on the progress of provider status for pharmacists in their publication *Pharmacy Today*. A recent example is their article titled “State-Level Provider Status Explained.”²³

Pharmacies should ensure they have adequate FTC/TDF in stock at all times to avoid treatment delays. Clinics should ideally have an electronic record system in place to ensure patients are not lost to follow-up. For example, the specialty pharmacy at our medical center created a computer program

that reminds pharmacists and technicians which patients are due for refills, delivery, and pickup. In our clinic, we do not have an automated reminder system, but we are able to track patients who miss follow-up appointments so we can contact them by phone to remedy barriers to follow-up and then reschedule.

There are various pros and cons to the different methods and levels of pharmacist involvement in PrEP care. As more data are generated, the most effective role for pharmacists in the provision of PrEP may come to light. Several studies, including our own experience, have shown pharmacists to be positioned to provide PrEP services. We remain hopeful this approach to PrEP care will expand the availability of PrEP and decrease new HIV infections in the populations most at risk. **HIV**

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ABOUT THE AUTHORS

Renata Smith is a Clinical Assistant Professor and the Co-Director for the HIV and Infectious Diseases Pharmacy Residency Program at the University of Illinois at Chicago College of Pharmacy. She provides HIV and infectious disease clinical pharmacy services at outpatient clinics located in Chicago neighborhoods with the highest prevalence of HIV.



Sarah Michienzi is a Clinical Assistant Professor at the University of Illinois at Chicago College of Pharmacy. She provides HIV and infectious diseases clinical pharmacy services at outpatient clinics in Chicago and for the Illinois Department of Corrections via telemedicine. Her research interests include HIV prevention and HIV-HCV co-infection.

How Depression and Other Mental Health Disorders Affect HIV Treatment:

What Can HIV Care Providers Do?

HIV INFECTION AND MENTAL DISORDERS often travel together and adversely influence each other's course. Co-occurring mental disorders in HIV-infected patients are associated with increased HIV transmission, poor prognosis, and inadequate adherence to antiretroviral therapy (ART) (Counos et al., 2005).

Higher Prevalence of Depression and PTSD in HIV-Infected Patients Than in the General Population

The most common mental illnesses we see in HIV practice are depressive disorders, anxiety disorders, posttraumatic stress disorder (PTSD), and alcohol/substance use disorders. The exact prevalence of these disorders is uncertain because studies are limited, and they often rely on convenience samples and/or lack methodological rigor. A group of researchers, led by scientists at the Centers for Disease Control and Prevention (CDC), conducted one of the best studies to assess the prevalence of depressive disorders among more than 4,000 people with HIV infection in medical care in the United States (Do, et al., 2014). The prevalence of a current episode of major depression was 12.4%, and the prevalence of other depressive diagnoses was 13.2%, yielding 25.6% with any current depressive disorder. These rates are three times higher than those seen in the general population. When considering both current and past episodes of moderate or severe depression, the rates are as high as 50%. This is important to bear in mind since depression tends to be a recurrent illness (McKinnon K, and Pinho, V, 2015).

Smaller studies (Brief, et al., 2004; Cohen et al., 2002; Kelly et al., 1998; Kimerling et al., 1999; Martinez et al., 2002) suggest that the lifetime prevalence of PTSD in people living with HIV ranges between 30% and 64%, again much higher than the general population. Early life traumas, often referred to as adverse childhood events, are associated with higher rates of unsafe sexual behaviors and alcohol/substance use during adolescence. Taken together, this combination of childhood trauma and adolescent risk-taking increase the likelihood of both developing PTSD and acquiring HIV infection (Hillis, et al.). A diagnosis of HIV infection then adds to these pre-existing traumas. Rates of anxiety disorders

are elevated among men with HIV infection, with perhaps a third suffering from these conditions within the past year, whereas the rates among women look similar to the general population, with about one fifth of women suffering from an anxiety disorder in the past year. Current rates of alcohol and substance use disorders among people with HIV infection attending medical care appear to be similar to the general population, but lifetime rates are considerably higher. There is significant comorbidity between all these conditions.

Importance of Tobacco Addiction

Depression and alcohol/substance use disorders are the mental illnesses with the strongest evidence for interfering with adherence along the entire HIV care continuum. These mental illnesses are in and of themselves associated

PROVIDER ACTION STEPS

- Assess and address medical conditions that could contribute to mental illness.
- Begin ART early to reduce the likelihood of cognitive problems.
- Use available screening tools for mental illness, such as The National HIV Curriculum, that provide guidance for how to ask questions about psychiatric symptoms. To access The National HIV Curriculum, visit: <http://www.hiv.uw.edu/go/basic-primary-care/screening-mental-disorders/core-concept/all>.
- Hold brief conversations with patients, using eye contact and expressing interest, to uncover symptoms of mental illness; look for missed appointments, changes in mood, or an unkempt appearance.
- Adopt an integrative care approach of having a single team for medical and mental health care that makes all of the treatment decisions collaboratively.

with increased risk for mortality. Tobacco smoking, which is elevated among people with depression and/or alcohol or substance use, makes an important additional contribution to the risk of early death. In the United States, close to half of cigarettes (44.3%) are smoked by people who have a mental illness besides tobacco addiction (Lasser et al., 2002). People with HIV infection who smoke tobacco die on average seven years earlier than people with HIV infection who don't smoke (Helleberg M., et al. 2013). A greater emphasis on smoking cessation, including the use of bupropion and varenicline, could increase the life span of our patients (Cahill et al., 2013).

What Can HIV Care Providers Do?

The close relationship between the brain and the body is reflected in the fact that medically ill people have much higher rates of mental disorders than people in good physical health. In the case of HIV infection, this comorbidity is compounded by the fact that people with mental illness are at increased risk for acquiring HIV infection in the first place. Fortunately, those of us caring for people with HIV infection have been remarkably accepting of complex patients with multiple medical and psychiatric comorbidities, suggesting we have already gone a long way toward overcoming mental illness stigma. Here are five suggested action steps providers can use to optimize care for people living with HIV infection and mental illness:

- 1 First, assess for the many medical causes of an altered mental status.** Foremost is ruling out delirium, a serious and potentially life-threatening medical condition often

seen in people with symptomatic HIV infection. Abnormal vital signs and a fluctuating level of consciousness strongly suggest delirium. Furthermore, endocrine conditions and prescribed medications are common causes of depression and anxiety. Treatment medical problems that alter mental status is vital to patient safety and improvement.

- 2 Begin ART early to reduce the likelihood of cognitive problems.** Cognitive disorders are common. Earlier and more effective ART is protective of the brain and has greatly reduced the prevalence of HIV-associated dementia. But milder forms of HIV-related asymptomatic and symptomatic cognitive impairment are present in about 50% of people with HIV infection, and there are no clear-cut treatments beyond viral suppression. Since these milder impairments may persist even then, the best strategy is to reduce the likelihood of cognitive problems by beginning ART as soon as possible. Hepatitis C infection, alcohol/substance use, and depression all compound cognitive impairment, and successful treatment of these conditions often contributes to cognitive improvement.

- 3 Administer screening tools with reasonably good sensitivity and specificity.** Mild symptoms of anxiety and depression are ubiquitous. As with measures of blood pressure and blood sugar, experts try to reach consensus on the threshold that defines where illness begins. Since we have few diagnostic biological measures in psychiatry, administering screening tools with reasonably good sensitivity and specificity is often the best way to identify those patients who are most likely to have a mental disorder. Usually further evaluation is needed for a definitive psychiatric diagnosis. Familiarity with screening tools for mental illness can provide guidance for how to ask questions about psychiatric symptoms. A very useful source for mental health screening tools is the National HIV Curriculum, developed by the AIDS Education and Training Centers with HRSA funding. A description of tools for anxiety disorders, depressive disorders, and PTSD can be found at <http://www.hiv.uw.edu/go/basic-primary-care/screening-mental-disorders/core-concept/all>. The National HIV Curriculum also offers tools for screening for alcohol/substance use disorders and cognitive disorders. Scoring can be completed online, and information is provided about the sensitivity and specificity of each instrument. Screening can be conducted at baseline and annually, or more often if a patient is showing signs of depression or other mental status changes.

- 4 Distinguish between mental illness and situational distress.** Many people with HIV infection are distressed by problems that can be conceptualized as the social determinants of health, including unemployment, poverty, food insecurity, homelessness, domestic violence, and social

RESOURCES

- Cournos F, McKinnon K, Wainberg M. (2017) Epidemiology of psychiatric disorders associated with HIV and AIDS, in *Comprehensive Textbook of AIDS Psychiatry*, Second Edition, Cohen MA, Gorman JM (eds.), New York, Oxford University, pp 29-45.
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- United States Preventive Services Task Force. Final Recommendation Statement. Depression in Adults: Screening 2017: www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatement/Final/depression-in-adults-screening
- SAMSHA's Patient Stress Questionnaire can be used to screen for behavioral health symptoms: www.integration.samsha.gov/Patient_Stress_Questionnaire.pdf
- Additional screening tools are available through SAMSHA: www.integration.samsha.gov/clinical-practice/screening-tools

isolation. Social workers and case managers on the treatment team may be in the best position to assist patients in responding to these stressors. Reducing distress is important to both the prevention of and recovery from mental illness. Brief conversations can uncover the symptoms of mental illness, as can observations of the patient's behavior, such as a distressed or unkempt appearance or missing recent appointments. When talking with patients, make eye contact and look genuinely interested when asking a patient how s/he is feeling. Otherwise you may only get a pro forma "fine" response.

5 The ability of HIV clinicians to respond to the mental health needs of their patients is greatly enhanced when health care settings work toward care integration. The collaborative care model has gotten particular attention, because case managers and non-physician members of the team do the bulk of the work of managing mental illness, saving physician time. When programs are large enough, integrated care models can incorporate team members who are trained to deliver evidence-based behavioral interventions, including cognitive, behavioral, interpersonal, and supportive therapies. There is a strong movement toward integrating treatments for alcohol/substance use disorders and other mental illnesses into medical care. At the lower end of the integration spectrum, providers in the medical setting screen patients for mental illness and refer those testing positive to off-site mental health services. Providing co-located mental health care at the same site as medical care offers a greater degree of integration, especially when there is a shared electronic medical record. Fully integrated care involves having a single team for medical and mental health care that makes all of the treatment decisions collaboratively. Telehealth and telemedicine can assist in improving mental health care in rural areas. Additionally, training in pain management is vital for all prescribers to reduce opioid addiction.

HIV Treatment and Care: A Focus on Mental Health and Substance Use

is a new web-based CME program from the Centers for Disease Control and Prevention and Medscape Education that discusses the impact that mental health and substance use disorders can have on HIV treatment and care. This CME activity demonstrates how HIV care providers can screen patients for mental health and substance use disorders, address factors related to mental health and substance use, and help patients adhere to HIV treatment and remain in care. Visit: <https://www.medscape.org/viewarticle/880901>.

Conclusion

Although the rates vary, the bulk of the available evidence shows that people living with HIV infection in the United States have rates of mental disorders that are considerably higher than the general population. Despite incredible scientific advances, the absence of a strong focus on mental disorders remains a glaring omission in our progress on HIV prevention, care, and treatment, especially for the special populations that most need our care. However, if providers can optimize care for people living with HIV infection by identifying and addressing common comorbid mental disorders early, they can reduce mortality, improve quality of life, and increase rates of viral suppression. **HIV**



ABOUT THE AUTHOR

Francine Coumos, M.D., is Professor of Clinical Psychiatry (in Epidemiology) at the Mailman School of Public Health at Columbia University and Principal Investigator of the Northeast/Caribbean AIDS Education and Training Center. She has worked nationally and internationally at the interface of HIV and mental illness since 1983. Dr. Coumos published early studies documenting the elevated rates of HIV infection and the associated risk behaviors among people with severe mental illness. She has participated in numerous clinical practice guidelines and policies on HIV-related mental health issues and has published more than 140 articles and book chapters, the majority of which are focused on mental health and HIV.

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WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of BIKTARVY. Closely monitor hepatic function with both clinical and laboratory follow-up for at least several months in patients who are coinfecting with HIV-1 and HBV and discontinue BIKTARVY. If appropriate, anti-hepatitis B therapy may be warranted [see Warnings and Precautions].

INDICATIONS AND USAGE

BIKTARVY is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY.

DOSAGE AND ADMINISTRATION

Also see **Warnings and Precautions** and **Use in Specific Populations**.

Testing Prior to or When Initiating: Test patients for HBV infection.

Testing Prior to or When Initiating, and During Treatment: As clinically appropriate, assess serum creatinine, estimated creatinine clearance (CrCl), urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus.

Dosage: One tablet taken once daily with or without food.

Renal Impairment: BIKTARVY is not recommended in patients with CrCl <30 mL/min.

Hepatic Impairment: BIKTARVY is not recommended in patients with severe hepatic impairment.

CONTRAINDICATIONS

Also see **Drug Interactions**.

BIKTARVY is contraindicated to be co-administered with:

- dofetilide due to the potential for increased dofetilide plasma concentrations and associated serious and/or life-threatening events
- rifampin due to decreased BIC plasma concentrations, which may result in the loss of therapeutic effect and development of resistance to BIKTARVY

WARNINGS AND PRECAUTIONS

Also see **BOXED WARNING, Contraindications, Adverse Reactions, and Drug Interactions**.

Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV: Patients with HIV-1 should be tested for the presence of chronic hepatitis B virus (HBV) before or when initiating ARV therapy. Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfecting with HIV-1 and HBV and have discontinued products containing FTC and/or TDF, and may occur with discontinuation of BIKTARVY. Patients coinfecting with HIV-1 and HBV who discontinue BIKTARVY should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions: Coadministration of BIKTARVY with certain other drugs may result in known or potentially significant drug interactions; this may lead to loss of efficacy and development of

resistance to BIKTARVY or clinically significant adverse reactions from greater exposures of concomitant drugs. Consider the potential for drug interactions and review concomitant medications prior to and during therapy. Monitor for adverse reactions associated with concomitant drugs.

Immune Reconstitution Syndrome (IRS): IRS has been reported in patients treated with combination ARV therapy. During the initial phase of treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections, which may necessitate further evaluation and treatment. Autoimmune disorders have been reported to occur in the setting of immune reconstitution; the time to onset is variable, and can occur many months after initiation of treatment.

New Onset or Worsening Renal Impairment: Renal impairment, including acute renal failure and Fanconi syndrome, has been reported with the use of tenofovir prodrugs in animal studies and human trials. In clinical trials of BIKTARVY in subjects with no antiretroviral treatment history with eGFRs >30 mL/min, and in virologically suppressed subjects switched to BIKTARVY with eGFRs >50 mL/min, renal serious adverse events were encountered in less than 1% of subjects treated with BIKTARVY through Week 48. BIKTARVY is not recommended in patients with CrCl <30 mL/min. Patients taking tenofovir prodrugs who have renal impairment and/or are taking nephrotoxic agents including NSAIDs are at increased risk of developing renal-related adverse reactions. Discontinue BIKTARVY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome. **Renal Monitoring:** Prior to or when initiating BIKTARVY, and during treatment with BIKTARVY, assess serum creatinine, CrCl, urine glucose, and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus.

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including FTC and TDF. Treatment with BIKTARVY should be suspended in any individual who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity, including hepatomegaly and steatosis in the absence of marked transaminase elevations.

ADVERSE REACTIONS

Also see **BOXED WARNING** and **Warnings and Precautions**.

In Adults with No ARV Treatment History:

The safety assessment of BIKTARVY is based on Week 48 data from two randomized, double-blind, active-controlled trials: 1489 (n=314) and 1490 (n=320), in HIV-1 infected, ARV treatment-naïve adults. Through Week 48, 1% of subjects discontinued BIKTARVY due to adverse events, regardless of severity.

Adverse Reactions: Adverse reactions (all Grades) reported in ≥2% of subjects receiving BIKTARVY through Week 48 in Trials 1489 and 1490, respectively were: diarrhea (6%, 3%), nausea (5%, 3%), headache (5%, 4%), fatigue (3%, 2%), abnormal dreams (3%, <1%), dizziness (2%, 2%), and insomnia (2%, 2%). Additional adverse reactions (all Grades) occurring in less than 2% of subjects administered BIKTARVY in Trials 1489 and 1490 included vomiting, flatulence, dyspepsia, abdominal pain, rash, and depression. Suicidal ideation, suicide attempt, and depression suicidal occurred in <1% of subjects administered BIKTARVY; all events were serious and primarily occurred in subjects with a preexisting history of depression, prior suicide attempt, or psychiatric illness.

Laboratory Abnormalities: Laboratory abnormalities (Grades 3–4) occurring in ≥2% of subjects receiving BIKTARVY through Week 48 in Trials 1489 or 1490, respectively were: amylase >2.0 x ULN (2%, 2%), ALT >5.0 x ULN (1%, 2%), AST >5.0 x ULN (2%, 1%), Creatine Kinase ≥10.0 x ULN (4%, 4%), Neutrophils <750 mm³ (2%, 2%), and fasted LDL-cholesterol >190 mg/dL (2%, 3%).

Changes in Serum Creatinine: Increases in serum creatinine occurred by Week 4 of treatment and remained stable through Week 48. In Trials 1489 and 1490, median serum creatinine increased by 0.10 mg/dL from baseline to Week 48 in the BIKTARVY group and was similar to the comparator groups.

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Changes in Bilirubin: In Trials 1489 and 1490, total bilirubin increases were observed in 12% of subjects administered BIKTARVY through Week 48.

In Virologically Suppressed Adults: The safety of BIKTARVY in HIV-1 infected, virologically suppressed adults is based on Week 48 data from 282 subjects in a randomized, double-blind, active-controlled trial in which virologically suppressed subjects were switched from either DTG + ABC/3TC or ABC/DTG/3TC to BIKTARVY; and Week 48 data from 290 subjects in an open-label, active-controlled trial in which virologically suppressed subjects were switched from a regimen containing atazanavir (ATV) (given with cobicistat or ritonavir) or darunavir (DRV) (given with cobicistat or ritonavir) plus either FTC/TDF or ABC/3TC, to BIKTARVY.

Adverse Reactions: Overall, the safety profile in virologically suppressed adult subjects was similar to that in subjects with no antiretroviral treatment history.

DRUG INTERACTIONS

Also see **Indications and Usage, Contraindications, and Warnings and Precautions.**

Other Antiretroviral Medications: BIKTARVY is a complete regimen for the treatment of HIV-1 infection. BIKTARVY coadministration with other ARV medications for treatment of HIV-1 infection is not recommended. Complete information regarding potential drug interactions with other ARV medications is not provided.

Potential for BIKTARVY to Affect Other Drugs: BIC inhibits organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1) *in vitro*. Coadministration of BIKTARVY with drugs that are substrates of OCT2 and MATE1 (e.g., dofetilide) may increase their plasma concentrations.

Potential Effect of Other Drugs to Affect BIKTARVY: BIC is a substrate of CYP3A and UGT1A1. A drug that is a strong inducer of CYP3A and also an inducer of UGT1A1 can substantially decrease the plasma concentrations of BIC which may lead to loss of efficacy and development of resistance. The use of BIKTARVY with a drug that is a strong inhibitor of CYP3A and also an inhibitor of UGT1A1 may significantly increase the plasma concentrations of BIC. TAF is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Co-administration of drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentrations of TAF. Co-administration of drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of efficacy and development of resistance.

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

Established and Potentially Significant Drug Interactions: The listing of established or potentially clinically significant drug interactions with recommended prevention or management strategies described are based on studies conducted with either BIKTARVY, the components of BIKTARVY (BIC, FTC, and TAF) as individual agents, or are drug interactions that may occur with BIKTARVY. **An alteration in regimen may be recommended.**

- **Antiarrhythmics:** dofetilide. Coadministration is contraindicated due to potential for serious and/or life-threatening events.
- **Anticonvulsants:** carbamazepine, oxcarbazepine, phenobarbital, phenytoin. Coadministration with alternative anticonvulsants should be considered.
- **Antimycobacterials:** rifampin. Coadministration is contraindicated due to the effect on BIKTARVY. Rifabutin, rifapentine. Coadministration is not recommended.
- **Herbal Products:** St. John's wort. Coadministration is not recommended.
- **Medications/oral supplements containing polyvalent cations (e.g., Mg, Al, Ca, Fe):** **Antacids containing Al/Mg or Calcium:** BIKTARVY can be taken under fasting conditions 2 hours before antacids containing Al/Mg or calcium. Routine administration of BIKTARVY simultaneously with, or 2 hours after, antacids containing Al/Mg or calcium is not recommended. **Supplements containing Calcium or Iron:** BIKTARVY and supplements containing calcium or iron can be

taken together with food. Routine administration of BIKTARVY under fasting conditions simultaneously with, or 2 hours after, supplements containing calcium or iron is not recommended.

- **Metformin:** Refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use of BIKTARVY and metformin.

Consult the full Prescribing Information prior to and during treatment with BIKTARVY for important drug interactions; this list is not all inclusive.

USE IN SPECIFIC POPULATIONS

Also see Dosage and Administration, Warnings and Precautions, and Adverse Reactions.

Pregnancy: **Pregnancy Exposure Registry:** There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to BIKTARVY during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263. **Risk Summary:** There are insufficient human data on the use of BIKTARVY during pregnancy to inform a drug-associated risk of birth defects and miscarriage. BIC and TAF use in women during pregnancy has not been evaluated; however, FTC use during pregnancy has been evaluated in a limited number of women as reported to the APR. Available data from the APR show no difference in the overall risk of major birth defects for FTC compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The rate of miscarriage is not reported in the APR.

Lactation: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Based on published data, FTC has been detected in human milk; it is not known whether BIKTARVY or all of the components of BIKTARVY are present in human breast milk, affects human milk production, or has effects on the breastfed infant. BIC was detected in the plasma of nursing rat pups likely due to the presence of BIC in milk, and tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF. It is unknown if TAF is present in animal milk. Because of the potential for HIV transmission in HIV-negative infants, developing viral resistance in HIV-positive infants, and adverse reactions in nursing infants, mothers should be instructed not to breastfeed.

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

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

Renal Impairment: BIKTARVY is not recommended in patients with severe renal impairment (CrCl <30ml/min). No dosage adjustment of BIKTARVY is recommended in patients with CrCl >30ml/min.

Hepatic Impairment: No dosage adjustment of BIKTARVY is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. BIKTARVY is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C) as BIKTARVY has not been studied in these patients.

OVERDOSAGE:

If overdose occurs, monitor the patient for evidence of toxicity. Treatment consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

210251-GS-000 February 2018

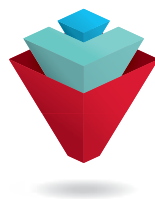


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Please see Brief Summary of full Prescribing Information for BIKTARVY®, including **BOXED WARNING**, on the following pages.