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HIV Specialist

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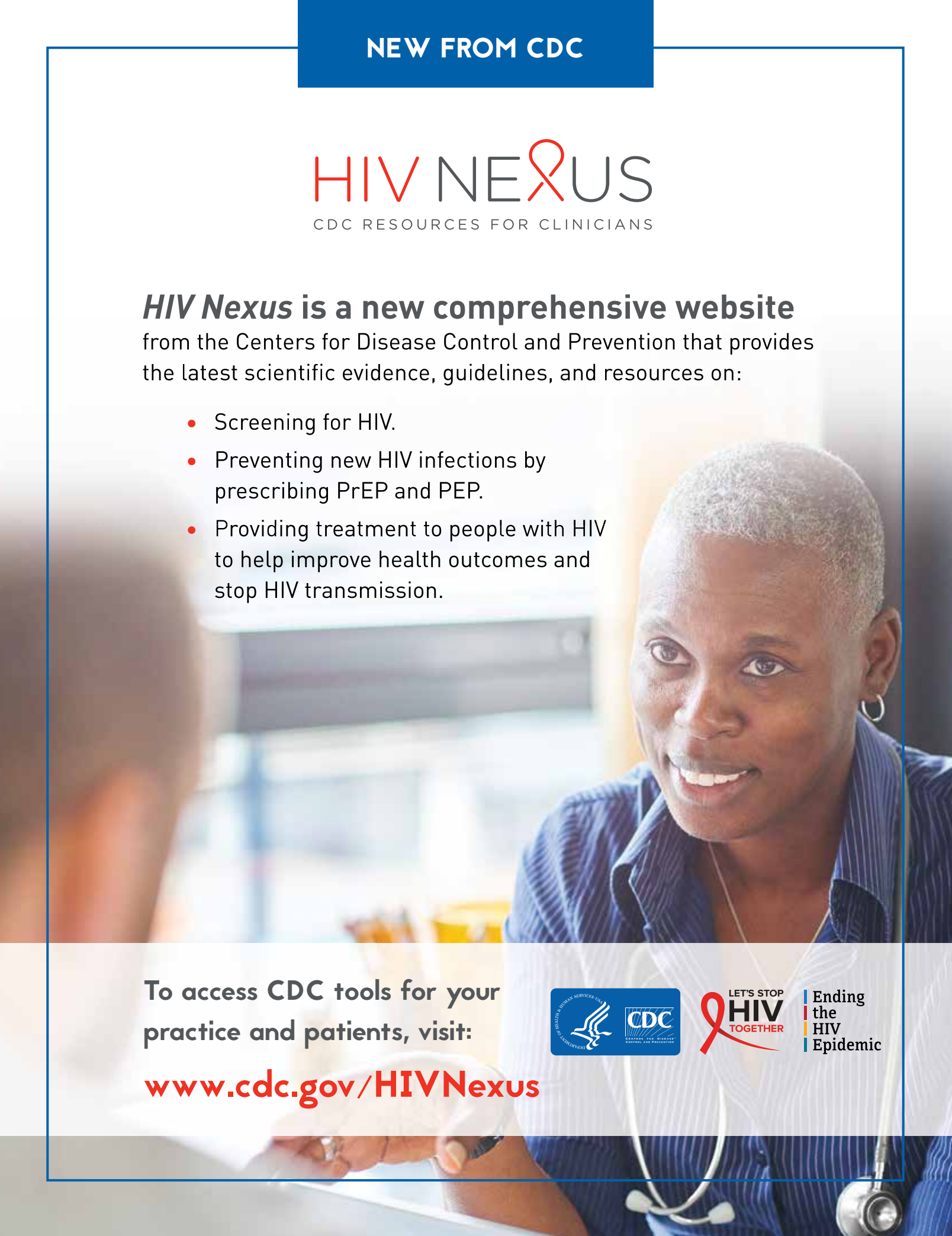

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LET'S STOP HIV TOGETHER

Ending the HIV Epidemic

THE AMERICAN ACADEMY OF HIV MEDICINE
HIV Specialist
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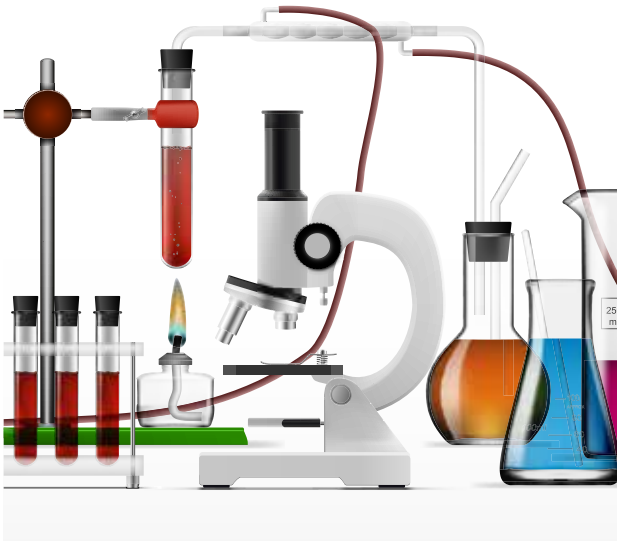


DEPARTMENTS

By BRUCE J. PACKETT II
Executive Director, AAHIVM

Tackling Cost Challenges

AN ISSUE ON THE "COST OF CARE" IN HIV MEDICINE is bound to bring controversy and political and corporate finger pointing, and it is not without some trepidation that I draft my introductory column here. We know that branded antiretroviral drugs are some of the costliest on the market today across disease states. Simultaneously, the epidemic is hitting some of the most socio-economically disadvantaged groups in the country with the least ability to pay and sometimes without health insurance. This formula of poorer people shouldering expensive healthcare burdens means that HIV is financially stressing the entire system, especially in light of the national efforts to eliminate new infections.

Pharmacy Benefit Managers (PBMs) and payers are perennially looking for novel ways to mitigate these cost factors, which inevitably translates to efforts towards implementing utilization management strategies. These solutions are ultimately tantamount to a reduction of access to some of the best ART options for individual patients. This is the situation we are all aware of, yet there are no easy solutions given the complexity of our "patchwork" health payer systems.

It becomes even more complicated when looking at some of the co-formulations and generic drugs coming to market, and what options may be the most efficacious and safe for specific patients versus the cost savings of switching to non-branded alternatives. Add to that the imminent introduction of novel treatment paradigms like long-acting agents and injectables (which may be the best options for some), and the cost versus outcomes impacts become incredibly difficult to quantitatively study and predict the true costs to the healthcare system. (Tim Horn and Amy Killelea expertly tackle these issues in their article.)

At the Academy, we strongly believe in the experience and wisdom of our members and HIV specialists to make the best decision for their patients, not only from a clinical perspective, but considering cost as well. Our providers have a long and outstanding history of navigating and utilizing the breadth and depth of complicated overlapping systems, including insurance formularies, prior authorizations, maximizing safety net payers, 340B pharmacies, co-pay coupons from manufacturers and other novel ways to obtain access to the optimal ART regimen for each of their patients at an affordable cost.

Advocating for enhanced access on the national level (and in state and local governments) is an ask that carries more uncertainty. From my time spent participating in budget and appropriations meetings on Capitol Hill on behalf of HIV providers, I've seen that the "you save more money in the end by keeping people healthy and preventing disease" argument isn't as compelling to policymakers and legislators as you would hope it would be. They are currently under immense political pressure to save money on healthcare, but often with a very myopic view of the larger national health picture. Without a uniform national health payer, such as "Medicare for All," or another system of universal coverage, there will always be a complicated patchwork to navigate, with much of that burden falling on providers to maneuver on their patients' behalf.

The role of the Academy will always be one of advocating for enhanced access to prevention, care and treatment. This remains true whether it is by protecting and/or expanding entitlements, pushing back against coverage restrictions, or joining the chorus for lower drug pricing, including enhanced access to generic and bioequivalent options. Despite the difficulty with this argument, we will continue to underscore the fact that patients with HIV and those at risk for acquiring the disease must have affordable access to options for prevention and treatment, and will therefore remain healthy while putting the least financial burden on our health care system. From my perspective, this is the only way to end the epidemic of HIV in the US. HIV

In the NEWS

American Academy of HIV Medicine Backs New Legislation Providing Loan Repayment for Health Professionals Providing HIV Care

THE ACADEMY OFFERED SUPPORT for the newly introduced HIV Epidemic Loan-Repayment Program (HELP) Act. The bill, introduced by Congressman John Lewis (D-GA), would offer up to $250,000 in loan repayment over five years to physicians, nurse practitioners, physician assistants and dentists for providing HIV care and treatment-related services. The health professionals must be practicing in an area with a recognized provider shortage or within a Ryan White funded clinical site.

The bill was introduced to address the critical shortage of clinicians and allied health professionals required to meet the needs of a growing population of people living with HIV.

"Our patient population is growing, but the number of medical professionals specializing in HIV care is not keeping pace," says Academy Executive Director Bruce Packett. "Many of the clinicians who entered the field in the 80s to help combat the once deadly epidemic are retiring. Attracting new providers into HIV care is difficult when there is no financial incentive unlike in many other specialty areas."

The Academy has been actively working for many years on bringing greater visibility to the provider shortage. In a 2008 survey, the Academy found that one third of its members plan to retire within the next 10 years.

"As the Administration rolls out its Ending the HIV Epidemic plans, we anticipate finding more people living with or at risk for HIV that will need care and prevention. At this crucial time, any substantial efforts to increase the number of providers in HIV care, treatment, and prevention will be welcomed," stated Dr. Margaret Hoffman-Terry, the Academy's Board Chair. "We commend Congressman Lewis for introducing this important legislation as we celebrate National Black AIDS Awareness Day and hope that we can encourage more providers to enter the field, especially providers that demographically mirror the epidemic and understand the needs of their patents."

In August 2016, the Academy was the first to publish the long-awaited Health Resources and Services Administration (HRSA) workforce study in its quarterly magazine, *HIV Specialist*. The study concluded that "the Nation faces severe workforce capacity challenges to effectively treat people living with HIV/AIDS. The demand for HIV and primary healthcare services, in particular, continues to increase as treating people living with HIV becomes more complicated and new cases arise."

"Since the HRSA report, we have seen the situation grow even more dire as a result of the uptick in cases in underserved areas," continued Packett. "This bill provides incentive to retain and attract medical talent to this ever-evolving clinical community. Our Academy members and credentialed providers successfully treat the vast majority of people living with HIV, allowing them to lead long, healthy lives. We have the clinical tools to manage and prevent the spread of HIV. We are at the cusp of ending the epidemic, but we can't do it without providers in the needed areas."

SHUTTERSTOCK/ AFRICA STUDIO

In the NEWS

Experimental HIV Vaccine Regimen Ineffective in Preventing HIV

No Safety Concerns Found; NIH and Partners Discontinue Vaccinations

THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID), part of the National Institutes of Health, has stopped administration of vaccinations in its HVTN 702 clinical trial of an investigational HIV vaccine. This action was taken because an independent data and safety monitoring board DSMB, found during an interim review that the regimen did not prevent HIV. Importantly, the DSMB did not express any concern regarding participant safety.

The Phase 2b/3 study, named HVTN 702 or Uhambo, began in 2016 and is taking place in South Africa. It was testing an investigational prime-boost vaccine regimen based on the only vaccine regimen ever to show protection from HIV—the regimen tested in the RV144 clinical trial in Thailand led by the U.S. Military HIV Research Program and the Thai Ministry of Health. For HVTN 702, the vaccine regimen was adapted to the HIV subtype Clade C most common in southern Africa, where the pandemic is most pervasive.

"An HIV vaccine is essential to end the global pandemic, and we hoped this vaccine candidate would work. Regrettably, it does not," said NIAID Director Anthony S. Fauci, M.D. "Research continues on other approaches to a safe and effective HIV vaccine, which I still believe can be achieved."

The HVTN 702 study enrolled 5,407 HIV-negative volunteers at 14 sites across South Africa. The study population consisted of sexually active men and women aged 18 to 35 years. The study volunteers were randomly assigned to receive either the investigational vaccine regimen or placebo injections. Study participants received six injections over 18 months. As with all NIAID-sponsored HIV prevention trials, the safety of HVTN 702 study participants was closely monitored throughout the trial, and participants were offered the local standard of care for preventing HIV, including access to oral pre-exposure prophylaxis (PrEP).

In the January 23, 2020 interim analysis, the DSMB examined data from 2,694 volunteers who received the investigational vaccine regimen and 2,689 volunteers who received the placebo injection. The analysis looked at how many participants were diagnosed with HIV after at least 60 percent of the participants had been in the study for more than 18 months—enough time for the vaccine regimen to stimulate an immune response. In this analysis, 129 HIV infections occurred among the vaccine recipients, and 123 HIV infections occurred among the placebo recipients.

Based on these findings, the DSMB concluded that the investigational vaccines had not shown any efficacy. The DSMB recommended that no further vaccinations be administered and that participants remain in the study for follow-up. The report noted there was no significant evidence of either decreased or increased infection rates with vaccination.

NIAID, the trial sponsor, concurred with the DSMB's recommendation, and stopped the vaccinations. Participants are being informed, and study investigators will continue following study participants over time.

"The people of South Africa have made history by answering this important scientific question. Sadly, we wish the answer was different," said HVTN 702 Protocol Chair Glenda Gray, M.B.B.C.H., F.C.Paed. (SA). "We will continue to explore promising avenues for preventing HIV with other vaccines and tools, both in South Africa and around the world." Dr. Gray is president and chief executive officer of the South African Medical Research Council; research professor of pediatrics at the University of the Witwatersrand, Johannesburg; and a founding director of the Perinatal HIV Research Unit at Chris Hani Baragwanath Hospital in Soweto, South Africa.

NIH is investing in multiple approaches to prevent HIV with the goal of delivering new options that are safe, effective, desirable to diverse populations, and scalable worldwide to help end the global pandemic. These efforts include two other late-stage, multinational vaccine trials, Imbokodo and Mosaico, both testing a novel mosaic vaccine regimen and being sponsored by Janssen Vaccines & Prevention, B.V., part of the Janssen Pharmaceutical Companies of Johnson & Johnson. The vaccine concept being tested in these trials is different than the one under investigation in HVTN 702.

In addition, the proof-of-concept AMP trials are testing an intravenously delivered investigational antibody for preventing HIV. Other cutting-edge studies, including the AMP trials, are investigating if broadly neutralizing antibodies (bNAbs) can protect against HIV. Two other large-scale trials are testing an investigational long-acting injectable antiretroviral drug, cabotegravir, for HIV prevention. Additional novel, long-acting HIV prevention products are also under study, including implants, vaginal rings, combinations of bNAbs, and multi-purpose products that offer contraception along with HIV prevention.

The HVTN 702 vaccine regimen consisted of two experimental vaccines: a canarypox vector-based vaccine called ALVAC-HIV and a two-component gp120 protein subunit vaccine with an adjuvant to enhance the body's immune response to the vaccine. Both ALVAC-HIV (supplied by Sanofi Pasteur) and the protein vaccine (supplied by GSK) were modified from the versions used in RV144 to be specific to HIV subtype C. Additionally, the protein subunit vaccine in HVTN 702 was combined with MF59, a different adjuvant than the one used in RV144, in the hope of generating a more robust and durable immune

Alarmingly Low Rates of HIV Testing Among At-risk Teenage Boys

Lack of testing feeds growing epidemic of undiagnosed HIV infections in the U.S.

THE MAJORITY OF teenage boys most at risk for developing HIV are not being tested for the disease, reports a new Northwestern Medicine study. This lack of testing feeds the growing epidemic of undiagnosed HIV infections in the United States.

An estimated 14.5 percent of HIV infections in the U.S. are undiagnosed, but among 13- to 24-year-olds, the undiagnosed rate is more than 3.5 times greater (51.4%).

This group of boys is disproportionately at risk to acquire HIV but faces many structural barriers that hinder testing, such as simply not knowing they can legally consent to getting an HIV test, where to get tested and fears of being outed. This is true even for those who want to check their status, the study found. This new study identified factors that increase the likelihood of testing, including parents talking about sex and HIV prevention, knowing basic facts about HIV, and feeling that testing is important and they are empowered to do it.

SHUTTERSTOCK/ MARTIN ALLINGER

SHUTTERSTOCK/ VCHAL

Mayo Clinic Assesses Rising Stress Levels among Physicians

A RECENT STUDY of 15,000 physicians indicated that nearly half of the "Generation X" participants (ages between 40 and 54) had higher rates of burnout than their older or younger peers. Research conducted at the Mayo Clinic last year suggests physicians experience higher rates of burnout than other full-time workers in the U.S. The "Gen Xers" displayed the highest rates; a phenomenon that Gary Price of the Physician's Foundation potentially attributes to the fact that they "are in the prime of their professional careers, at their busiest… and perhaps with more family competing pressures than younger physicians."

The survey also showed higher stress rates among women than men physicians. Price notes that, "societal factors, including time spent on domestic responsibilities, discrimination and harassment, likely play a role" in this trend.

response. Finally, the HVTN 702 vaccine regimen included booster shots at the one-year and 18-month timepoints in an effort to prolong the early protective effect observed in RV144. HVTN 100, a predecessor clinical trial using the HVTN 702 regimen, found that the new vaccine regimen was safe and induced high and boostable titers of antibodies to several HIV strains prevalent in southern Africa.

South Africa has one of the highest HIV rates in the world. According to UNAIDS, more than 20 percent of the adult population ages 15-49 in South Africa are living with HIV, and 240,000 people acquired HIV in 2018. Young people, like the volunteers who enrolled in the HVTN 702 study—and particularly young women—are at the highest risk for HIV.

HVTN 702 is part of a larger HIV vaccine research endeavor led by the Pox-Protein Public-Private Partnership, or P5—a diverse group of public and private organizations working to build on the RV144 trial. P5 members include NIAID, the Bill & Melinda Gates Foundation, and the South African Medical Research Council, which funded HVTN 702; the HIV Vaccine Trials Network (HVTN), headquartered at the Fred Hutchinson Cancer Research Center in Seattle, which conducted HVTN 702; Sanofi Pasteur and GSK, which provided study materials; and the U.S. Military HIV Research Program.

"We appreciate the trust and effort from our participants, and the tremendous effort expended by our staff at all of our South African sites," said Larry Corey, M.D., Principal Investigator of the HVTN.

"We commend all the sites, the South African communities and each participant for their tireless commitment to finding solutions to the HIV epidemic," added HVTN 702 Protocol Co-Chair Linda-Gail Bekker, M.D., Ph.D., deputy director of the Desmond Tutu HIV Centre at the University of Cape Town and chief operating officer of the Desmond Tutu HIV Foundation in Cape Town, South Africa.

In the NEWS

AAHIVM Warns Against the Adoption of Block Grants for State Medicaid Programs

THE ACADEMY called the Centers for Medicare & Medicaid Services' (CMS) recommendation for states to adopt block grants for their Medicaid programs misdirected and warned that the health and welfare of millions—including people living with HIV—will be in jeopardy.

"Ironically named the Healthy Adult Opportunity Initiative, the CMS guidance on block grants threatens the health of the most vulnerable among us," says Executive Director Bruce Packett. "People with HIV, those with disabilities, children—these people are all at risk to lose access to needed healthcare and coverage through Medicaid."

Since its inception, the Medicaid Act has provided for unlimited federal matching dollars for state funds spent under Medicaid's rules. By switching to a block grant, a state would accept a cap to federal support in exchange for the freedom to disregard Medicaid rules on mandatory benefits, such as prescription drug coverage.

An estimated 42 percent of adults with HIV in care in the United States receive their health care coverage from Medicaid. Critical services that Medicaid beneficiaries rely on like mental healthcare, prescription drug coverage, transportation assistance, and dental coverage can be indiscriminately cut from the Medicaid program with no oversight and no consequences.

Block grants encourage states to take actions that include restricting enrollment for legally eligible beneficiaries, limiting mandatory and optional benefits, decreasing already low reimbursement rates (which may lead providers to abandon the program), a combination of all three, and more.

"A state that allows prescription drug coverage but severely limits the drug formulary to only a handful of antiretroviral drugs would have a devastating effect on the progress we've made in treatment and prevention over the past two decades," said Academy Board Chair Dr. Margaret Hoffman-Terry. "This practice would limit the ability of the healthcare provider to tailor treatment options for their patients."

For Americans with HIV, there is a direct link to Medicaid access and the HIV epidemic. Eight of the ten states with the highest rates of HIV diagnoses in the United States are states that have not expanded Medicaid in accordance with the Affordable Care Act, and all eight of those states are in the southern United States. The South currently bears the largest burden of the domestic epidemic and has the least access to medical care.

"If the President is serious about ending the HIV epidemic in 10 years as he stated in his State of the Union Address just last year, then allowing states to block grant Medicaid will be in direct opposition to this goal," says Bruce Packett. "The administration tried to enact Medicaid block grant legislatively in 2017 and millions of Americans lifted their voices in opposition and that attempt failed. With this guidance, CMS is trying to administratively accomplish what it could not do in Congress. The reality is, we can end this epidemic, but only if we expand access to care, not restrict it."

Options for HIV treatment and prevention have grown exponentially over the past decade, giving practitioners the tools needed to effectively manage current cases, while reducing HIV incidence. However, access to these clinical options is paramount.

"Continuity of care is essential in HIV treatment in order to keep the patient healthy and the virus untransmittable to others," stated Dr. Hoffman-Terry. "Block grants will allow states to arbitrarily determine the quality of services and treatment healthcare professionals will be able to provide. This is not in the best interest of the patient or public health overall."

FDA Defers its Decision on the First Long-Acting Injectable ARV

ON DECEMBER 23, the US Food and Drug Administration (FDA) deferred its decision on approving Cabenuva, a long-acting, injectable ARV developed by ViiV Healthcare. Reuters reported that ViiV received a "complete response letter (CRL) from the FDA in which the regulator questioned the treatment's chemistry, manufacturing and controls process, but not its safety."

Cabenuva, a combination of long-acting rilpivirine and cabotegravir, is designed to be administered intra-muscularly once a month by a health care provider. It is designed as an alternative for people with HIV who prefer monthly injection to taking a daily pill. ViiV has been asked to further explain their data related to product testing and manufacture. No timeline has yet been announced.

To date, 40,000 Cabenuva injections have been administered in clinical trials and people currently getting the regimen are being assured that it is safe to continue their normal dosing.

POZ reports that over 1,100 people with HIV in 16 countries participated in two large-scale clinical trials of Cabanuva. The results showed viral suppression equivalent to those achieved with daily oral triple-ARV treatment. POZ notes that "the trial participants reported high levels of satisfaction with the regimen, greatly preferring it to taking daily pills." Only 1% of participants withdrew from the trials, most of them due to discomfort/pain at the injection site.

NIH-Funded Clinical Trial to Test PrEP, Dapivirine Ring for Safety in Pregnant Women

Study Also to Examine Whether Pregnant Women Accept, Use These HIV Prevention Tools.

THE FIRST clinical trial specifically designed to test the safety of the monthly dapivirine vaginal ring in pregnant women has begun in southern and eastern Africa. The National Institutes of Health-funded study also will test the safety of a daily oral antiviral tablet for HIV pre-exposure prophylaxis (PrEP) in pregnant women and will assess how much they accept and use these two HIV prevention tools. The study will complement an ongoing NIH-funded trial of PrEP in adolescents and young women during pregnancy and the first six months after birth. PrEP is available in some countries and is being rolled out in others, while the dapivirine ring is under regulatory review by the European Medicines Agency for potential use in sub-Saharan Africa.

"Women need reliable HIV prevention methods that they know are safe during pregnancy for themselves and their babies," said Anthony S. Fauci, M.D., director of the National Institute of Allergy and Infectious Diseases (NIAID), part of NIH. "This new clinical trial will provide important data on the safety of PrEP and the dapivirine ring during pregnancy and will help expectant parents make well-informed HIV prevention choices."

Studies have found that for women of reproductive age, the risk of acquiring HIV is two to four times greater during pregnancy and the first six months after childbirth than at other times. In sub-Saharan Africa, women tend to be pregnant for a substantial portion of their reproductive years, with an estimated 5.1 births per woman.

Limited evidence from earlier clinical trials and reports suggests that PrEP and the dapivirine ring are safe for pregnant women and their fetuses, but the safety of these tools during pregnancy has not yet been proven in a clinical trial designed specifically to address this question.

The new trial is called DELIVER: A Phase 3b Safety Study of the Dapivirine Ring and PrEP in Pregnant Women. NIAID is sponsoring the DELIVER trial and co-funding it with the Eunice Kennedy Shriver National Institute of Child Health and Human

Development and the National Institute of Mental Health, both part of NIH. The study, also known as MTN-042, is being conducted by the NIH-funded Microbicide Trials Network (MTN) at four sites in Malawi, South Africa, Uganda and Zimbabwe. Gilead Sciences, Inc., and the International Partnership for Microbicides, which developed the dapivirine ring, are donating PrEP medication and rings for the study, respectively.

The DELIVER study team plans to enroll 750 healthy, HIV-negative women aged 18–40 who have an uncomplicated singleton pregnancy. The women will be assigned at random to receive either the dapivirine vaginal ring or PrEP in a 2-to-1 ratio and will be asked to use their assigned product until the end of their pregnancy or 42 weeks gestation, whichever comes first. The study team subsequently will enroll the mothers' newborn infants.

Out of an abundance of caution, the study team will enroll participants in four stages, beginning with women latest in pregnancy, and will pause to conduct a safety analysis before enrolling the next group. The first enrollment group, consisting of 150 women, will begin using their assigned product at 36 to 37 weeks gestation. The study team will follow these women through the end of their pregnancy and enroll their newborns for additional safety assessments. Then a panel of international experts unaffiliated with the trial will conduct an independent, interim safety analysis to determine if the next group of women can be enrolled or the study needs to stop early. If it is safe to proceed, this process will be repeated with a group of 150 women at 30 to 35 weeks gestation, 150 women at 20 to 29 weeks gestation, and 300 women at 12 to 19 weeks gestation. The participating women will be followed until approximately six weeks after their pregnancy ends, and the infants will be followed until they are approximately one year old.

The study team will record any medical problems and deaths among the women and infants, as well as birth defects in the infants. In addition, the team will track the frequency of full-term live births, premature live births and pregnancy losses. Investigators also will record pregnancy complications associated with exposure to PrEP or the dapivirine ring, measure levels of study drugs in the infants, and determine the extent to which women accept and use their assigned study product. Questionnaires will be used to assess the acceptability of the study products. Finally, the team will evaluate changes in women's genital microenvironment associated with the use of PrEP or the dapivirine ring during pregnancy.

A related NIH-funded clinical trial that is expected to begin in the coming months will test the safety of PrEP and the dapivirine ring in HIV-negative breastfeeding women and their infants. The trial, called B-PROTECTED or MTN-043, will enroll 200 women and their infants aged six to 12 weeks in Malawi, South Africa, Uganda and Zimbabwe. As in DELIVER, the data gathered during the B-PROTECTED study will help countries decide whether and how to roll out PrEP and the dapivirine ring, if approved, among breastfeeding women and will help these women make informed choices about HIV prevention.

SHUTTERSTOCK/ PROSTOCK STUDIO

BY RANDALL MCDAVID, MS, NP-C, FNP-BC, AAHIVS

Rapid Initiation of Antiretroviral Therapy in Acute HIV-1

DESPITE COMPREHENSIVE INTERVENTIONS FOR THE PREVENTION OF HIV INFECTIONS and the positive impact of antiretroviral therapy (ART), per the most recent Centers for Disease Control and Prevention (CDC) data from December 2019, there were 38,739 new cases of HIV in the United States.[1] Men who have sex with men (MSM) continue to be the populations most affected by HIV and account for 66 percent of all HIV diagnoses.[1] By race/ethnicity, African Americans and Hispanics/Latinos are disproportionately affected by HIV. African Americans accounted for 43 percent and Hispanics/Latinos accounted for 26 percent of new HIV diagnoses.[1]

In an estimated 40 percent to 90 percent of individuals, HIV seroconversion is associated with a clinical syndrome known as acute HIV acquisition or acute retroviral syndrome. Many patients with acute HIV acquisition are symptomatic and seek medical care, but frequently are not diagnosed.[2] In one prospective study, 95 percent of individuals with symptoms at the time of seroconversion sought medical care, but only one-fourth were diagnosed at the first visit.[2] Acute HIV infection is rarely diagnosed, mainly because the signs and symptoms are very nonspecific. Common symptoms include fever, rash, lymphadenopathy, non-exudative pharyngitis and myalgias/arthralgias (Table 1).[3] The onset of illness seen with acute HIV infection occurs after viral transmission and the symptoms are believed to correlate with peak viremia, which is often in excess of one million copies/mL.[4] This early stage usually lasts for approximately two to four weeks from initial infection. During acute HIV acquisition, these individuals are highly contagious as the virus is disseminating and replicating rapidly. Recognition of this syndrome has implications for patient care as well as disease transmission and public health.

To diagnose acute HIV infection, the current CDC testing algorithm recommends using the fourth generation immunoassay that detects HIV-1 and HIV-2 antibodies, as well as the HIV-1 p24 antigen in serum or plasma. If the initial test is reactive, a confirmatory test is needed to differentiate HIV-1 from HIV-2. If the HIV-1/HIV-2 antibody differentiation assay is intermediate or negative, further testing with an HIV-1 nucleic acid test (NAT) is performed and a reactive NAT confirms the diagnosis of HIV-1 infection.

The newer fourth generation tests are notably different from the previously used HIV enzyme-linked immunosorbent assay (ELISA) and confirmatory Western blot tests. The new laboratory testing algorithm (Figure 1) has advantages over the previous two-step test including the ability to diagnosis acute or early HIV-1 infection, more accurate diagnosis of HIV-2 infection, fewer indeterminate test results and typically a faster turnaround time.[5]

Current CDC recommendations do not include the rapid HIV-1/HIV-2 antigen/antibody combination test that was approved by the Food and Drug Administration (FDA) in August 2013 because of insufficient evidence. The recommendations also do not include non-FDA approved HIV-2 nucleic acid tests. A positive result on the rapid combination test always requires further serologic confirmation with the algorithm below.

Benefits Initiating ART

Clinical trial data regarding the treatment of acute HIV are limited. However, a number of studies have found that individuals treated during early acquisition may have virologic and immunologic benefits.[6-18] In addition, as early HIV acquisition is associated with

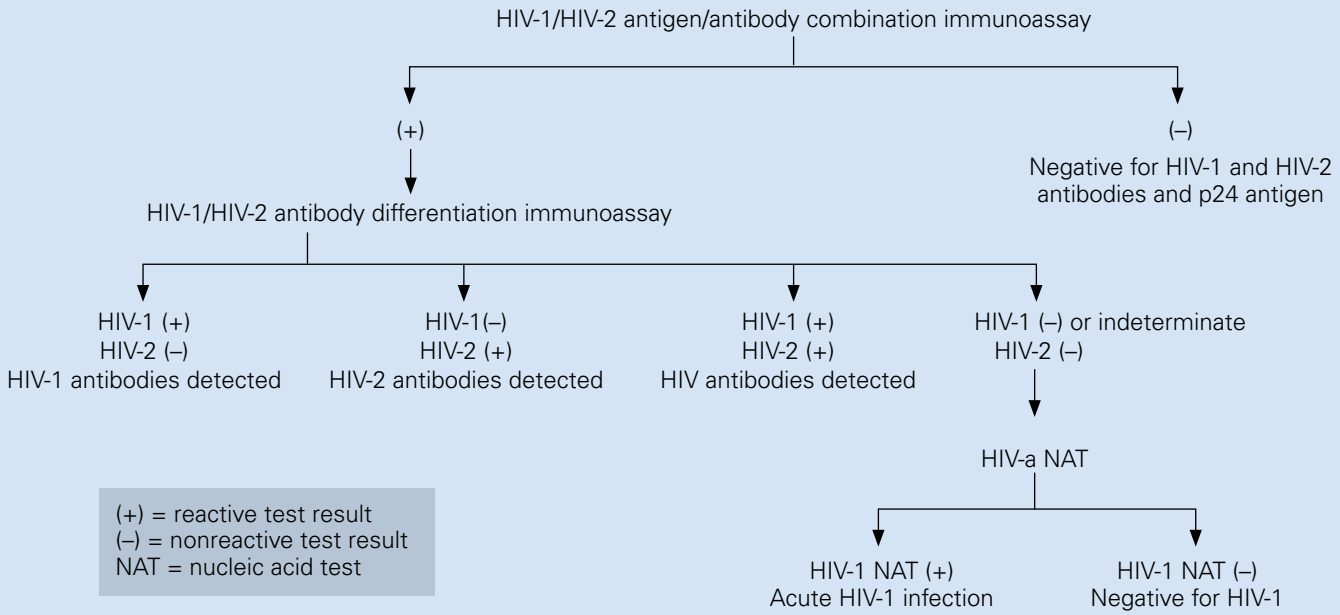
TABLE 1. Acute HIV Acquisition: frequency of signs and symptoms[3]

Sign or Symptom	Frequency (%)
Fever	75
Fatigue	68
Myalgia	49
Rash	48
Headache	45
Pharyngitis	40
Cervical adenopathy	39
Arthralgia	30
Night sweats	28
Diarrhea	27

SHUTTERSTOCK/ SEASONTIME

The newer fourth generation tests are notably different from the previously used HIV enzyme-linked immunosorbent assay (ELISA) and confirmatory Western blot tests.

FIGURE 1. Recommended diagnostic laboratory HIV testing algorithm for serum or plasma specimens.[5]



high viral loads and increased infectiousness, the use of ART at this stage to achieve and maintain viral suppression substantially reduces the risk of HIV transmission.[19-23]

The START and TEMPRANO trials evaluated the timing of ART initiation. Although neither trial collected specific information on participants with acute or early acquisition, the strength of the overall results from both studies strongly suggest that, whenever possible, persons with HIV should begin ART upon diagnosis of acute HIV.

ART Selection in Acute HIV

ART is the mainstay of HIV treatment although selection of ART has become increasingly complex with multiple first- and second-line regimens available. These recommendations are constantly changing as new classes and agents become available. Antiretroviral resistance limits future ART options. Thus, it is recommended that the provider refer to the Department of Health and Human Services (DHHS) guidelines when selecting ART.

The DHHS updated their ART treatment guidelines in December 2019. They now include treatment of acute HIV infection and emphasize the importance of initiating ART as soon as possible after diagnosis.[24] Bictegravir 50mg/tenofovir alafenamide 25mg/emtricitabine 200mg (BIC/TAF/FTC) has been added as a treatment option for persons with acute or recent HIV infection in cases where ART will be initiated before genotypic drug resistance testing results are available.[24]

Current recommended therapy for a treatment-naïve individual consists of a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third drug from one of the following classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) with a pharmacokinetic enhancer (cobicistat or ritonavir) as outlined in Table 2.[25]

Case Report

A 23-year-old Mexican male patient presented with fevers ranging from 101°F-102°F, sore throat, nausea, headache, dizziness, vomiting, diarrhea and a rash on his face and trunk. His last HIV negative test was in the spring 2018. On physical examination, he had an erythematous posterior pharynx with ulcers present. There were discrete, erythematous macules and papules on the anterior and posterior trunk and face.

An HIV viral load obtained and reported the same day was greater than 10,000,000 copies/mL. The actual value could not be calculated due to the limitations of the assay but the result essentially confirmed the diagonals of acute HIV infection. The baseline genotypic test does not show mutations (Table 3).

TABLE 2: Recommended regimens for initial therapy in acute HIV patients[25]

Integrase Strand Transfer Inhibitor-Based Regimens
Bictegravir (BIC)/tenofovir alafenamide (TAF)/emtricitabine (FTC)
Dolutegravir (DTG) with (TAF or tenofovir disoproxil fumarate [TDF])a plus (FTC or lamivudine [3TC])
Protease Inhibitor-Based Regimen
Boosted darunavir (DRV) with (TAF or TDF)a plus (FTC or 3TC)

a TAF and TDF are two forms of tenofovir that are approved in the United States. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and accessibility are among the factors to consider when choosing between these drugs.

In this context, I decided to rapid start ART with (BIC/TAF/FTC) (Table 4)[26] once daily, which is a three-drug regimen approved by the FDA for the treatment of HIV-1 acquisition in treatment naïve adults. The patient evolves favorably, with constitutional symptoms and rash resolving with four daily doses of BIC/TAF/FTC. After 72 days, an excellent virologic response was observed with a decrease in viral load to 70 copies/mL and an increase in CD4 lymphocyte count from 400/uL at baseline to 572/uL.

Rapid Initiation with Integrase Strand Transfer Inhibitors

Persons with acute HIV usually have a higher viral load than those with chronic HIV, and therefore are at a higher risk of sexual transmission to others. Rapid initiation of ART and subsequent viral load suppression can substantially reduce HIV transmission. Sustained viral suppression to less than 200 copies/mL can prevent transmission to sexual partners. Individuals starting ART should use another form of prevention with sexual partners (e.g., condoms or pre-exposure prophylaxis (PrEP) for partners who are HIV negative) until they have a documented viral load less than 200 copies/mL.

Prior to the widespread use of INSTIs, data from the United States and Europe demonstrated that transmitted virus may be resistant to at least one antiretroviral (ARV) drug in up to 16 percent of persons with HIV.[27-28] In one study, 21 percent of isolates from persons with acute HIV acquisition demonstrated resistance to at least one ARV drug, with transmitted resistance consistently most common to NNRTIs.[29-31] Therefore, before initiating ART in a person with acute HIV, a specimen should be sent for drug resistance testing, though treatment should not be delayed pending resistance test results. The test results should be used to modify the ARV regimen if necessary.

The Panel on Antiretroviral Guidelines for Adults and Adolescents does not currently recommend routine genotype testing for INSTI resistance in treatment-naïve persons given the low rate of transmitted INSTI resistance and high barrier to resistance of BIC and dolutegravir (DTG), unless transmitted INSTI resistance is a concern.[26] However, with the increasing use of INSTIs in recent years, the rate of transmitted INSTI resistance has increased (from 0.8% to 1.1%),indicating a need for ongoing population monitoring. [32-34] BIC and DTG are good treatment options because transmission of BIC- and DTG-resistant HIV is rare, and BIC and DTG have higher barriers to resistance than raltegravir (RAL) and elvitegravir (EVG).

Cost and Confidentiality of ART

In my case report, I was able to rapid start my patient with BIC/TAF/FTC due to my clinic accepting pharmaceutical samples. The cost of BIC/TAF/FTC is approximately $3,154.05 for a 30-day supply. The patient, being 23 years old, was on his parents' insurance and requested to keep his new HIV diagnosis confidential from his parents. The samples allowed me to treat the patient immediately while keeping his health information confidential. I did not want to submit a prescription to create an insurance claim until the insurance carrier received notification at the patient's request to keep his health information confidential.

TABLE 3. Evolution of laboratory parameters in a patient who starts ART with bictegravir during acute HIV acquisition

	Day 1	Day 11	Day 72	Day 164
HIV Antigen	Reactive			
HIV-1 AB	Negative			
HIV-2 AB	Negative			
CD4 (cel/uL)	400			572
Viral load (copies/mL)	>10,000,000		70	30
Viral load (log10)	Unmeasurable due to high viral load		1.845	1.477
Hemoglobin (g/dL)	14.7			
Hematocrit (%)	41.8			
WBC (10e3/uL)	3.0			6.4
Neutrophils (%)	35			64
Lymphocytes (%)	45			29
Platelets (10e3/uL)	135			245
GenoSure Prime®		No resistance		

Minors and young adults who are covered by their parents' health insurance worry about breaches of confidentiality if insurance companies mail an explanation-of-benefits (EOB) or other documents to their parents. This is particularly relevant because the Affordable Care Act (ACT) permits young adults up to age 26 to remain on their parents' health insurance plans.

As part of its law, Colorado has specific statutes governing EOBs, which are relevant to confidentiality related to HIV access for young adults. The Colorado Division of Insurance has issued regulations requiring an insurance carrier in the state to ensure confidential communication between the carrier and a covered adult child of a policyholder. The regulations state that information may not be sent to the policyholder without prior consent of the covered adult child (18- to 26-year-olds). This is a striking development to give young adults on their parents' insurance plans control over access to EOBs and other confidential information. The adult child can request the insurance carrier to mail EOBs to an address of choice.

The Colorado Insurance regulation is not without its shortcomings. First and foremost, the regulation only applies

TABLE 4. Identifying, Diagnosing, and Treating Acute and Recent HIV Infection[26]

Suspicion of Acute HIV Infection:

- Health care providers should consider the possibility of acute HIV infection in individuals with the signs, symptoms, or laboratory findings described below, and recent (within 2 to 6 weeks) high risk of exposure to HIV.a
- Signs, symptoms, or laboratory findings of acute HIV infection may include but are not limited to one or more of the following: fever, lymphadenopathy, skin rash, myalgia, arthralgia, headache, diarrhea, oral ulcers, leucopenia, thrombocytopenia, and transaminase elevation.
- High-risk exposures include sexual contact with a person who has HIV or a person at risk of HIV infection; sharing needles and syringes to inject drugs, as well as equipment used to prepare drugs for injection; or any exposure in which an individual's mucous membranes or any breaks in the skin come in contact with bodily fluid that potentially carries HIV.

Differential Diagnosis:

- The differential diagnosis of acute HIV infection may include but is not limited to viral illnesses such as EBV and non-EBV (e.g., CMV) infectious mononucleosis syndromes, influenza, viral hepatitis, streptococcal infection, or syphilis. Diagnosis of any STI should prompt HIV testing and consideration of acute or early HIV infection.

Testing to Diagnose/Confirm Acute HIV Infection:

- Acute HIV infection is defined as detectable HIV RNA or p24 antigen (the specific antigen used in currently available HIV-1/2 Ag/Ab combination assays) in the setting of a negative or indeterminate HIV antibody test result.
- A reactive HIV antibody test result or Ag/Ab combination test result must be followed by supplemental confirmatory testing.
- A negative or indeterminate HIV antibody test result in a person with a reactive Ag/Ab test result or in whom acute HIV infection is suspected requires plasma HIV RNA testing to diagnose acute HIV infection.
- A positive result on a quantitative or qualitative plasma HIV RNA test in the setting of a negative or indeterminate antibody test result indicates that acute HIV infection is highly likely. In this case, the diagnosis of HIV infection should be later confirmed by subsequent documentation of HIV antibody seroconversion.

ART After Diagnosis of Early HIV Infection:

- ART is recommended for all individuals with HIV, including those with earlya HIV infection (AI). ART should be initiated as soon as possible after HIV diagnosis (AII).
- Once initiated, the goals of ART are to achieve sustained plasma virologic suppression and to prevent HIV transmission (AII).
- All individuals of childbearing potential who receive a diagnosis of early HIV infection should have a pregnancy test (AIII).
- Pregnant individuals with early HIV infection should begin ART as soon as possible for their own health and to prevent perinatal transmission of HIV (AI).
- Pregnant individuals with early HIV infection should begin ART as soon as possible for their own health and to prevent perinatal transmission of HIV (AI).
- A blood sample for genotypic drug resistance testing should be obtained before initiation of ART to guide the selection of the regimen (AII), but ART should be initiated as soon as possible, often before resistance test results are available. If resistance is subsequently identified, treatment should be modified as needed.
- ART can be initiated before the results of drug resistance testing are known. In this setting, one of the following ART regimens is recommended (AIII):
  - DTG with (TAF or TDF)b plus (FTC or 3TC)
  - BIC/TAF/FTC
  - Boosted DRV with (TAF or TDF)b plus (FTC or 3TC)
- Pregnancy testing should be performed in individuals of childbearing potential before initiation of ART (AIII).
- Preliminary data from Botswana suggested that there is an increased risk of NTDs (0.9%) in infants born to women who were receiving DTG at the time of conception.45 Follow-up data, however, showed that the prevalence of NTDs in association with DTG exposure at conception is lower (0.3%), but still slightly higher than with non-DTG containing ARV regimens (0.1%).46,47 Before initiating an INSTI-based regimen in a person of childbearing potential.

[a]In some settings, behaviors that increase the risk of HIV infection may not be recognized or perceived as risky by the health care provider or the patient, or both. Thus, even in the absence of reported high-risk behaviors, symptoms and signs consistent with acute retroviral syndrome should motivate practitioners to consider a diagnosis of acute HIV infection.

[b]TAF and TDF are two forms of TFV that are approved in the United States. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and accessibility are among the factors to consider when choosing between these drugs.

Key: 3TC = lamivudine; Ag/Ab = antigen/antibody; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; CMV = cytomegalovirus; DRV = darunavir; DTG = dolutegravir; EBV = Epstein-Barr virus; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; NTD = neural tube defect; STI = sexually transmitted infection; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed non-randomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

to adult children of policyholders and provides no confidentiality protections for those under the age of 18-years-old. While minors in Colorado can consent to HIV treatment, they still face the risk that an insurer could mail an EOB to their parents. Second, since many covered adult children may have the same address as their parents, there is some possibility that breaches could occur even if the EOB is not addressed to parents. Please reference your state laws for minors and young adults regarding health insurance confidentiality. **HIV**

ABOUT THE AUTHOR

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At What PRICE?

Ending the HIV epidemic in an era of prescription drug cost containment

By TIM HORN and AMY KILLELEA, JD

THE HIGH COST OF ANTIRETROVIRAL THERAPY (ART), for HIV treatment and prevention, is an important issue considering there are 1.2 million U.S. residents living with HIV and an additional 1.2 million HIV-negative individuals who are candidates for pre-exposure prophylaxis (PrEP).[1,2] The issue is particularly salient in the context of the White House administration's "Ending the HIV Epidemic: A Plan for America," which aims to reduce the number of new HIV infections by at least 90 percent within the next 10 years by maximizing the number of people living with and vulnerable to HIV infection who are in care and receiving ART or PrEP.

Cost should not be a factor for clinicians in making treatment recommendations for their patients living with or vulnerable to HIV infection. However, the high cost of antiretroviral (ARV) drugs–against the backdrop of ART continuation now measured in decades, the expansion of generic ART options, and efforts to rein in prescription drug spending–may ultimately provide an important consideration with respect to meeting and sustaining the goals of the "Ending the HIV Epidemic" initiative.

The Challenge of High HIV Drug Costs

The cost-effectiveness of ART, including its significant role in treatment, prevention ("Undetectable=Untransmittable") and as PrEP, is well established.[3,4,5,6,7,8,9] Yet being cost effective does not necessarily mean these medications are associated with short-term cost savings for payers or patient affordability. Indeed, ART is expensive. The mean yearly price (wholesale acquisition cost, or WAC) for the recommended initial regimens for most people living with HIV, as per the DHHS *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV*, has increased 77 percent over the past 10 years: $24,696 in 2009 vs. $43,872 in 2019. Compared with an annual list price of $19,884 for co-formulated efavirenz/emtricitabine/tenofovir in 2009, the DHHS guidelines recommended single-tablet regimens in 2019 had a mean annual list price of $43,044, a 116 percent increase.

Total annual undiscounted spending on ART in the U.S. has doubled since 2010, reaching $20.4 billion in 2017.[10,11] Consequently, ART was among the top five therapeutic classes in non-discounted spending on medicine in 2017, after medications for diabetes and autoimmune diseases, cancer drugs and respiratory agents.[11] Yet only 62.7 percent of people diagnosed with HIV in the U.S. were virologically suppressed in 2017.[12] To achieve 90-90-90 goal (90 percent of people with HIV are aware, 90 percent of people diagnosed with HIV are in care and 90 percent of those in care are virally supressed) based on 2017 expenditure and surveillance data, an additional $9.9 billion in undiscounted spending on ART would have been required. To achieve 95-95-95, an additional $11.6 billion in undiscounted spending would have been necessary.

ISTOCK/ DIGITAL SKILLET; SHUTTERSTOCK/ M TANAGON

As for PrEP, annual WAC prices for the brand-name version of emtricitabine (FTC) co-formulated with either tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) were $20,100 in 2018, with utilization limited to just 18.1 percent of the 1.1 million people with indications for PrEP in 2018.[12] To achieve a coverage rate of just 50 percent, an additional $7 billion dollars in undiscounted PrEP medication spending would have been required.

Is drug pricing truly a barrier to HIV treatment and prevention in the U.S.? Fortunately, the vast majority of U.S. residents living with HIV are able to access ART, often without significant out-of-pocket costs, thanks to a complex patchwork of public and private programs. This includes one of the only federal disease-specific payer-of-last-resort programs in the country: the AIDS Drug Assistance Programs (ADAP), funded through the Ryan White Care Act. Additionally, ART generally has not been subject to payer formulary restrictions given the challenges of implementing population-level cost containment when generics are limited and individualized therapy requires access to costly brand-name drugs.

Over the past several years, efforts to limit access to expensive ART, incentivize access to cheaper options, and maximize out-of-pocket spending on people living with HIV, illustrate the intent among payers to curb spending on brand-name ART.[13,14,15,16] As the medication landscape becomes more competitive and generic agents become more prevalent while novel drug administration routes emerge (e.g. injectable, subcutaneous), payers and providers will be required to make difficult choices concerning how to ensure and sustain access to clinically appropriate treatment.

With respect to PrEP, the failure to expand Medicaid in states disproportionately impacted by HIV and the absence of a federal safety net program synonymous with the Ryan White Care Act, lays bare the high cost of comprehensive biomedical prevention.[17] Cost will be a significant issue as many Medicaid programs and commercial payers begin implementing the U.S. Preventive Services Task Force Grade A recommendations for PrEP. The Affordable Care Act (ACA) provisions require most private insurance plans and Medicaid expansion programs to cover all USPSTF A and B rated services with no cost sharing. An important consideration is the pending generic TDF/FTC launch in late 2020/early 2021, which is expected to be associated with a significantly lower price compared with brand-name TDF/FTC and TAF/FTC. With lingering questions regarding the clinical benefits of TAF over TDF for PrEP, some Medicaid and commercial payer formularies are expected to implement utilization management (e.g., prior authorization) to prefer generic TDF/FTC over brand-name products (Truvada® and Descovy®).[18]

Entering the Era of Generic Antiretrovirals

A number of generic ARVs are commercially available in the U.S., including co-formulated abacavir/lamivudine (ABC/3TC), atazanavir (ATV), efavirenz (EFV), lamivudine (3TC), nevirapine, ritonavir (RTV) and TDF. There are also "quasi-generic" branded products: co-formulations of antiretrovirals that are no longer patent protected but were originally developed by other manufacturers. These are cheaper than their branded comparators, but more expensive than generic products. Examples include co-formulations of EFV/TDF/3TC (Symfi Lo®) and TDF/3TC (Cimduo® and Temixys™).

Substantial improvements in the safety and effectiveness of contemporary ART has resulted in a number of DHHS guideline-recommended regimens remaining listed beyond their patent protection date as they become available as lower-cost generic options. For example, 3TC can be substituted for FTC and TDF and TAF are generally considered comparable agents.

A key question remains: are generics necessarily cheaper? Generic drug prices are inversely proportional to competition: the greater the number of manufacturers with a competing product, the lower the cost.[19] There are significant differences between brand-name and generic ARV drug prices. According to data from the National Drug Acquisition Cost (NADAC) database, a 30-day supply of generic ABC/3TC costs $72, compared with $1,254 for the brand-name version. A 30-day generic TDF is $29, compared with $1,161 for the brand-name product. RTV plus ATV costs about $300 versus nearly $1,700, respectively.

Looking at cost differences concerning the DHHS guidelines' recommendations for initial ART regimens, an important consideration is that high-cost brand-name products are still recommended. However, there remain appreciable pharmacy acquisition cost differences, with branded dolutegravir (DTG) or raltegravir (RAL) combined with generic TDF plus generic 3TC costing between $1,600 to $1,800/month compared to branded bictegravir/TAF/FTC and DTG/ABC/3TC with acquisition costs of approximately $2,800.

Potential cost savings associated with generic ART utilization have also been subject to academic analysis. In one study, the savings associated with a transition to a hypothetical lower-cost generic ART could potentially help cover the

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TABLE 1. Insurance and Health Program Prescription Drug Pricing and Access

Medicaid	Drug manufacturers must participate in MDRP for their drugs to be covered by Medicaid and under Medicare Part B.
	Manufacturers are required to pay Medicaid programs a rebate of at least 23.1% of the average price paid to manufacturers by wholesalers (AMP) for most brand-name drugs sold to retail pharmacies (13% for generics). Manufacturers pay additional rebates if this confidential AMP increases faster than the CPI-U rate of inflation.
	States are permitted to require "nominal" cost-sharing for medical and pharmacy benefits for some beneficiaries though many elect not to do so. States can obtain a waiver to allow them to apply higher cost-sharing.
Medicare	ARVs are one of six "protected drug classes" under Medicare Part D. Part D plans must provide access to all, or substantially all, FDA-approved ARVs without prior authorization or step therapy. Part D plan sponsors, or PBMs on their behalf, negotiate rebates on outpatient drugs with manufacturers; the extent of rebating is unclear.
	Most physician-administered drugs and biologics are covered under Medicare Part B at a set cost: ASP plus 6%. This pricing mechanism controls spending by narrowing the spread between what is actually paid for the drug and what is actually billed to Medicare.
	Premiums and cost-sharing payments may be significant for both services and prescription drugs; there is no cap on out-of-pocket spending under Part A (hospital care) and Part B.
	Some subsidies and supplemental coverage are offered for low-income beneficiaries. Manufacturer copay assistance programs cannot be applied to Part B or Part D cost sharing; cost sharing support is available from ADAPs, foundations, and other sources, based on financial eligibility criteria.
Commercial Insurance	Private insurance plans, or PBMs on their behalf, negotiate rebates on inpatient and outpatient drugs with manufacturers; the extent of rebating is unclear.
	Formulary restrictions and utilization management (prior authorization, step therapy, higher cost sharing) are possible as cost-containment measures.
	Cost sharing can be highly variable. Manufacturer copay assistance programs can be applied in most cases but may not count toward annual Affordable Care Act cost sharing limits; cost sharing support is also available from ADAPs, foundations and other sources based on financial eligibility criteria.
ADAPs	Significant discounting on most ARVs negotiated by the ADAP Crisis Task Force is allowed under the 340B Drug Pricing Program.
	There is usually no cost sharing for ADAP clients who are uninsured. ADAP can assist with commercial or public insurance out-of-pocket costs.
Veterans Affairs	The FCP is the maximum price manufacturers may charge the four largest federal purchasers of pharmaceuticals (the "Big Four"): The Department of Veterans Affairs, the Department of Defense, the Public Health Service (including the Indian Health Service), and the Coast Guard. The FCP of a drug includes a 24% discount on a drug's average price paid by non-federal purchasers. Additional discounts may be applied if non-federal purchase prices increase faster than the CPI-U inflation rate.
	Big Four prices may be 40% to 50% below list prices. VA may negotiate further price reductions.
	Prescription drug cost sharing is generally nominal; medications are not withheld from those who cannot afford cost sharing expenses.
Community Health Centers	Many community health centers are enrolled in the 340B Drug Pricing Program, which allows for discounted drug purchasing using the MDRP formula.
	Discounts start at 23.1% off AMP, with additional discounts if the AMP increases faster than the CPI-U rate of inflation.
	Cost-sharing in community health centers is first driven by payer source. For clients who are uninsured, cost-sharing, if required, is typically based on a sliding fee scale.

Abbreviations. ADAP = AIDS Drug Assistance Programs; AMP = average manufacturer price; ARV = antiretroviral; ASP = average sales price; CPI-U = consumer price index-urban; FCP = Federal Ceiling Price; FDA = Food and Drug Administration; MDRP = Medicaid Drug Rebate Program; PBM = pharmacy benefits manager; VA = Veterans Affairs

Originally published in the Health and Human Services' Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV, December 2019, https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/459/cost-considerations-and-antiretroviral-therapy

20-year, $480 billion projected costs to reach national treatment targets.[20] Among the various cost-effectiveness evaluations that have been published, an analysis involving DTG plus generic 3TC for initial therapy projected that if 50 percent of patients with newly diagnosed HIV initiated a two-pill regimen consisting of branded DTG plus generic 3TC, cost savings could reach $550 to $800 million over a five-year period.[21]

Cost Savings to the U.S. Healthcare System: It's Complicated

Prescription drug pricing in the U.S. involves an incredibly complex patchwork of systems with varying requirements for mandatory and voluntary discounts, rebates and reimbursement rates. Much of the pricing information is shrouded in secrecy, further complicating matters. Prescription drug prices and costs can vary depending on the state, purchaser, the type of public or private insurance coverage in use and the number of generic competitors to branded drugs (see Table 1). Consequently, when comparing costs of brand-name drug products and generic ARVs, savings may vary across public and private payer systems. Moreover, providers may find it difficult to navigate payer cost-containment practices, such as formulary restrictions, prior authorization and cost-sharing arrangements. The latter may include patient co-payments, co-insurance and insurance deductible payments and programs to mitigate their impact as barriers to treatment and prevention.

There is also reason to believe that the high cost of ARVs has fueled dependence on manufacturer assistance programs, both to help provide

medications to uninsured individuals and to offset high cost sharing for those with commercial insurances. Manufacturer assistance programs, while an important lifeline for individuals, also mask high costs of drugs and exacerbate a fragmented system of services and access for consumers. Similarly, the high cost of ARVs has also increased reliance on financing systems that perversely tie high list prices to the ability of safety net 340B providers to generate and reinvest savings into vital public health infrastructure and programs.

Supporting policies that achieve the scale-up of access to meet national targets to end new HIV infections involves interrogating each piece of this patchwork. It also involves advancing policy changes supporting access to ART based on an ethical, clinically appropriate and sustainable framework. Making changes to any of these systems is a difficult task, with potential unintended consequences and trade-offs.

There is no shortage of evidence that reining in prescription drug pricing, egregious patient cost-sharing practices and discriminatory payer cost-containment measures are all critical to prescription drug access. Are there opportunities to reduce the costs associated with HIV treatment and prevention? Yes, and our ability to ensure equitable access to these public health tools is a public health imperative. The larger question, however, is how to ensure we are supporting ethical, clinically-based and sustainable access to ARVs given the dynamic treatment and biomedical prevention landscape. The overarching ethical question of "who gets access to what and under what circumstances" looms large as the ARV space becomes more competitive. Moreover, as we contemplate broader changes to our complex drug pricing system, including changes that affect the 340B Program, we must consider reinvestment of cost savings back into the HIV care and prevention services that are necessary to meet and exceed the goals of the federal "Ending the HIV Epidemic" initiative. Unfortunately, the complexity of our healthcare system will not make this easy. **HIV**

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THE COST OF PrEP

A Case Report

BY RICHARD PROKESCH, MD, FACP, FIDSA, AAHIVS

SHUTTERSTOCK/ ALEX SG/ ALIM YAKUBOV

ROBERT IS A 43-YEAR-OLD MALE who presented to our office with his husband, Mark, requesting to start pre-exposure prophylaxis (PrEP) therapy. They have been in a monogamous relationship for six years and married for three of those years. Mark is HIV positive and has been poorly compliant with taking antiretrovirals (ARVs) until approximately two months ago. At that time, he followed-up in our office after a two-year hiatus. He was started on bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF). His CD4 was 121 cells/uL with an HIV 1 RNA of 212,000 copies/mL prior to restarting therapy. HIV 1 genotype and integrase inhibitor genotype testing revealed minor viral mutations but no resistance to ARVs.

Robert is covered under Mark's commercial insurance. Appropriate pretreatment PrEP testing was ordered, at which time, Robert was found to be HIV negative. He was prescribed FTC/TAF for PrEP. However, when he went to obtain his prescription, the pharmacy tech told him that the cost would be "$1500" for a 30-day supply. Robert related this to our office and we subsequently submitted paperwork for a required prior approval.

Initially, Robert's insurance informed the office that FTC/TAF for PrEP was not covered. However, following further inquiries, his insurance explained that FTC/TAF is in fact covered but that Robert would need to pay his $1000 deductible and subsequently, need to pay a co-pay of $500 for the 30-day supply. Fortunately, our office was able to furnish Robert with a co-pay card from Gilead, the company that manufacturers FTC/TAF, which reduced his out-of-pocket expense to $0. In addition, our office provided additional information to Robert's insurance, concerning the Food and Drug Administration's (FDA) approval of FTC/TAF for PrEP in males. This enables him to obtain future prescriptions of FTC/TAF for PrEP with the same parameters (co-pay/deductible assistance).

This case illustrates the time-consuming process that offices like ours often encounter in trying to obtain appropriate therapies for patients. Thankfully, the majority of our efforts are successful as a result of various means including submitting prior approvals that commercial insurances may require and/or aiding patients in receiving co-pay assistance as per the illustrative case. **HIV**

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THE **IMPACT** OF LOCALIZ **IMPLEM**

SHUTTERSTOCK/ ZORAN MILLIC/ DJENT

ED
ENTATION

By EMANUEL KREBS, MA, LAURA DALE, BSC, MPH, and BOHDAN NOSYK, PhD, on behalf of the localized economic modeling study group

THE PRESIDENT OF THE UNITED STATES recently announced the intention to eliminate the domestic HIV epidemic within 10 years.[1] To achieve this goal, healthcare providers and public health departments will need to overcome political, legal and structural barriers, and make efficient use of funding.[2] Efficacious biomedical, behavioral and structural interventions are available; however, there is a paucity of evidence on real-world implementation of many of these interventions.[3] This is further complicated because the HIV epidemic is better categorized as a series of microepidemics dispersed across large urban centres.[4] Just as no two patients are exactly the same, requiring different treatment approaches and care plans, nor can two microepidemics be treated the same.

THIS ARTICLE DESCRIBES A SIMULATION MODELLING APPROACH grounded in implementation science that aims to determine the cost-effectiveness of HIV treatment and prevention interventions across six U.S. cities, providing evidence that can inform HIV health service delivery planning.[5] The implementation science approach, which enhances the model, is built on extensive real-world evidence and is a novel application to current knowledge.

OBJECTIVE: to determine the cost-effectiveness of HIV treatment and prevention interventions, offered at previously documented levels of scale in six U.S. cities with diverse HIV micro epidemics

METHODS:

Overview of the model (Figure 1, opposite)

The model described here was adapted from a previously published model[6,7] to replicate microepidemics for six U.S. cities: Atlanta, Baltimore, Los Angeles (LA), Miami, New York City (NYC) and Seattle. In each city, the adult population ages 15–64 was partitioned by sex at birth, race/ethnicity, HIV-risk behavior type and sexual risk behavior level (Figure 1a). HIV risk groups included men who have sex with men (MSM), people who inject drugs (PWID), MSM who inject drugs (MWID) and heterosexuals.

Consistent with other dynamic transmission models, the probability of HIV transmission was dependent on how many people were living with HIV across the different states of care engagement and disease progression (infection, diagnosis, treatment and out of treatment), and was impacted by the local context and transmission routes (Figure 1b).

The model outcomes included health benefits, total costs (2018 USD) and new HIV infections (Figure 1b). Health benefits were captured by quality-adjusted life years (QALYs), which is a single measure of disease burden that captures both morbidity and mortality (i.e. the quality and quantity of years lived). Using the latest available evidence, current health service levels in the model were held at their 2015 levels except for pre-exposure prophylaxis (PrEP) which was held at 2017 levels to account for its recent rapid growth in uptake among MSM.

Our model accounts for projected population growth and demographic shifts in race/ethnicity composition. Each intervention was sustained for a 10-year period, though the impacts were modeled over 20 years (Figure 1b). We assumed proportional scale-up of interventions across risk and ethnic groups, i.e., our model assumed that there would be no explicit effort to reduce racial/ethnic and risk disparities throughout the study period.

The model was calibrated and validated using a state of the art process following an extensive evidence synthesis, both documented elsewhere.[8,9]

Interventions analyzed

We considered 16 interventions, each categorized under three domains: protect, diagnose and treat (Figure 2).

All interventions were selected based on having established effectiveness data and promising scalability. They were identified from the Centers for Disease Control and Prevention, "Compendium of Evidence-Based Interventions and Best Practices for HIV Prevention"[10] and the recently published literature.

As part of the evidence review process, we used the Reach Effectiveness Adoption Implementation Maintenance (RE-AIM) framework[11] to define four components associated with the implementation of each intervention (Figure 3). The review of real-world evidence via RE-AIM represents the implementation science approach that is unique to this study.

Cost-effectiveness analysis

The cost-effectiveness analysis conformed to best practice guidelines.[12] Detailed information on the analysis is documented in the full manuscript.[5]

FIGURE 2. Interventions Analyzed

PROTECT

1. Syringe services program (SSP)
2. Medication for opioid use disorder (MOUD) with buprenorphine
3. MOUD with methadone
4. Targeted* PrEP for high-risk MSM & MWID

DIAGNOSE

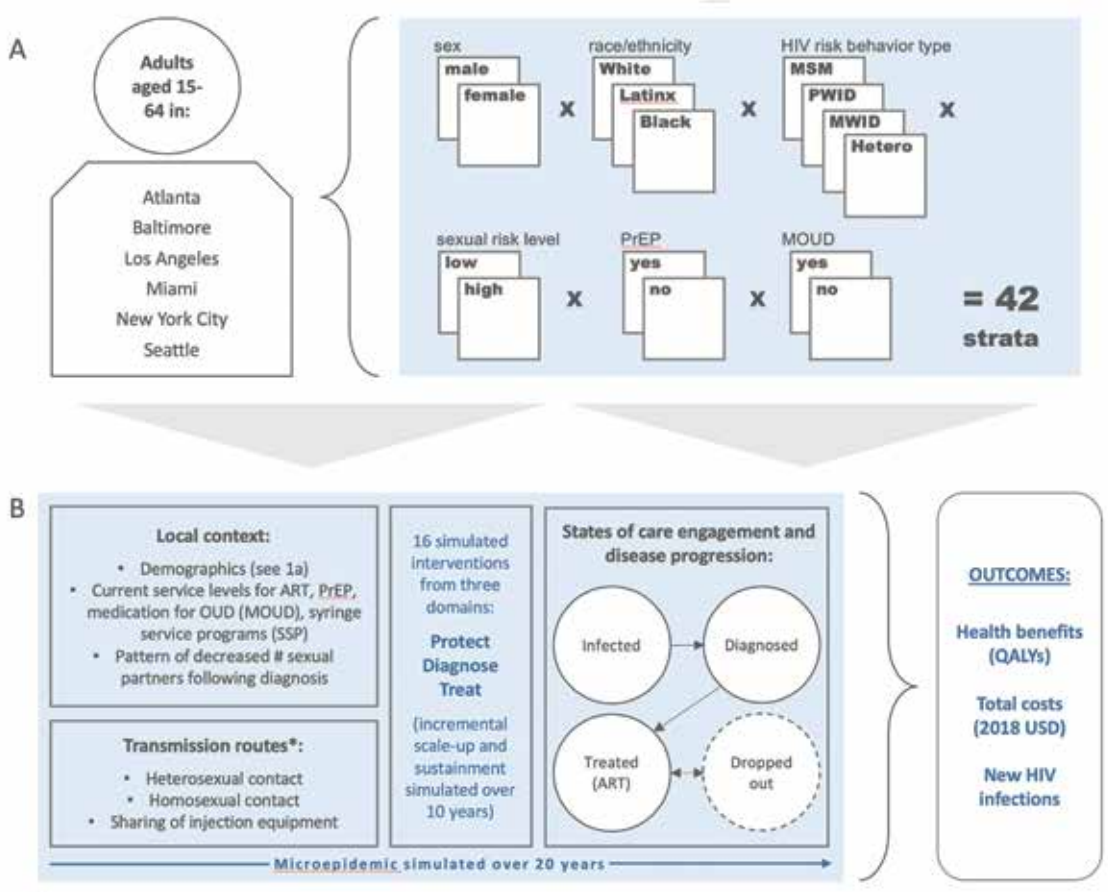
5. Opt-out testing in emergency room
6. Opt-out testing in primary care (PC)
7. EMR testing offer reminder
8. Nurse-initiated rapid testing
9. MOUD integrated rapid testing

TREAT

10. Case management for initiation
11. Care coordination for retention
12. Care coordination for retention, targeted to individuals with CD4<200 cells per μL
13. EMR alert of suboptimal ART
14. Same-day ART initiation
15. Enhanced personal contact
16. Re-linkage program

*We assume that 25% of MSM are indicated for PrEP in accordance with CDC guidelines.

FIGURE 1. Overview of the Model



*We assumed assortative and proportional sexual partnership mixing by race/ethnicity and sexual risk behavior level, respectively. Assortative sexual mixing means individuals are more or less likely to form partnerships within groups (e.g. race/ethnicity, risk behavior level), while proportional mixing accounted for individuals with many partners being more likely to select a partner who also had many partners. We also assumed proportional mixing among PWID (i.e., individuals who share many injections were more likely to select a partner who also shares many injections).

RESULTS:

The model outcomes included health benefits (QALYs), total costs (2018 USD) and new HIV infections. These outcomes are described under the two headings below: "New HIV Infections" and "Cost-effectiveness of Interventions" (QALYs and total costs).

New HIV Infections

Figure 4 outlines the percentage of total averted infections over 20 years (2020-2040) resulting from incremental increases in service delivery levels (over 10 years, 2020-2030) for 16 interventions in the six cities studied.

Our model estimated that for all cities but Miami, the maximum incidence reduction over 20 years compared to maintaining current service levels would result from **enhancing general population HIV testing**. In Miami, expanded access to targeted PrEP for high-risk MSM and MWID would have the greatest impact on the epidemic (Figure 4).

Specifically, the electronic medical record testing reminder would reduce incidence the most in Atlanta (7.6%), LA (6.6%), NYC (7.8%) and Seattle (7.6%), and both nurse-initiated testing and targeted PrEP would reduce incidence equivalently in Baltimore (10.0%).

Targeted PrEP would result in the greatest incidence reduction for Miami (10.1%), and relatively large reductions in Atlanta (6.0%), LA (3.4%), NYC (7.5%), and Seattle (5.3%).

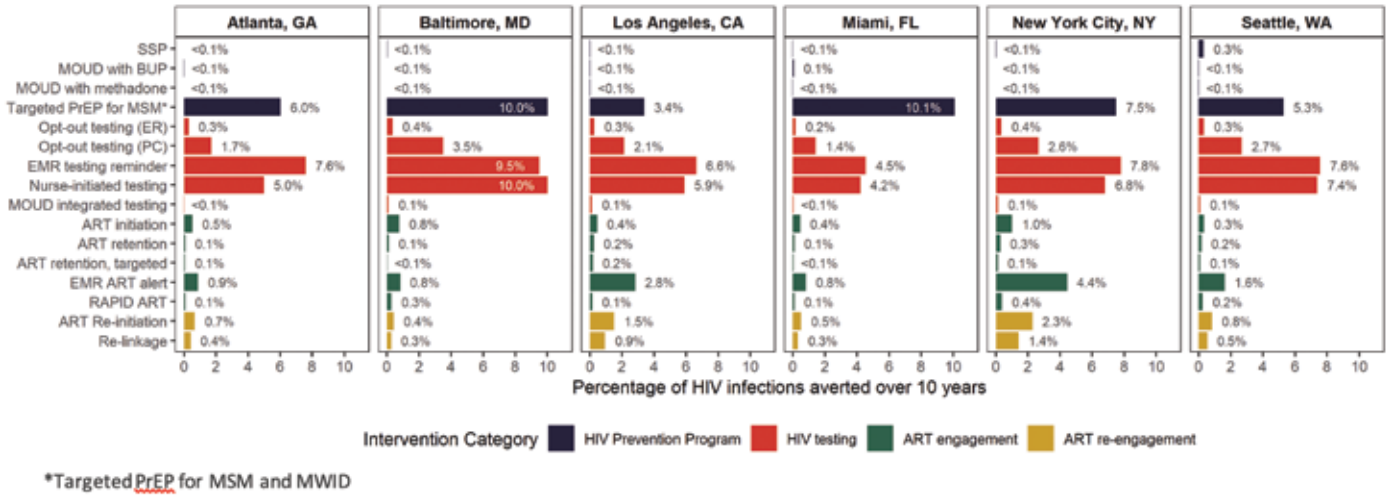
KEY FINDING: no magic bullet, but incremental scale-up provides benefit

As no single intervention was predicted to avert more than 10 percent of projected new HIV infections, our findings emphasize the need for combination implementation strategies.

FIGURE 3. RE-AIM FRAMEWORK COMPONENTS

Scale of delivery	Proportion of the target population that is provided with the intervention. (Dependent on how many people are reached by the intervention and how many care settings offer it.)
Population level impact	Proportion of HIV transmission prevented (protect) and proportion of HIV patients moved between health states (diagnose and treat). (Dependent on the scale of delivery and effectiveness of the intervention.)
Sustainment period	Impact of the intervention over 10 years. (The 10 years comprised an initial 18-month scale up period from current delivery levels, then a subsequent sustainment period over the remainder of the 10 years during which impacts were held constant.)
Costs of implementation, delivery and sustainment	Costs of implementation, delivery and sustainment over 10 years. (The implementation costs accrued during the initial 18-month scale-up period and sustainment costs accrued during the remainder of the 10-year period. Delivery costs accrued over the entire 10-year period.)

FIGURE 4. Percentage of total averted infections over 20 years resulting from expanded access to HIV prevention programs and HIV testing and care interventions implemented at scales of delivery documented in the public domain in six U.S. cities



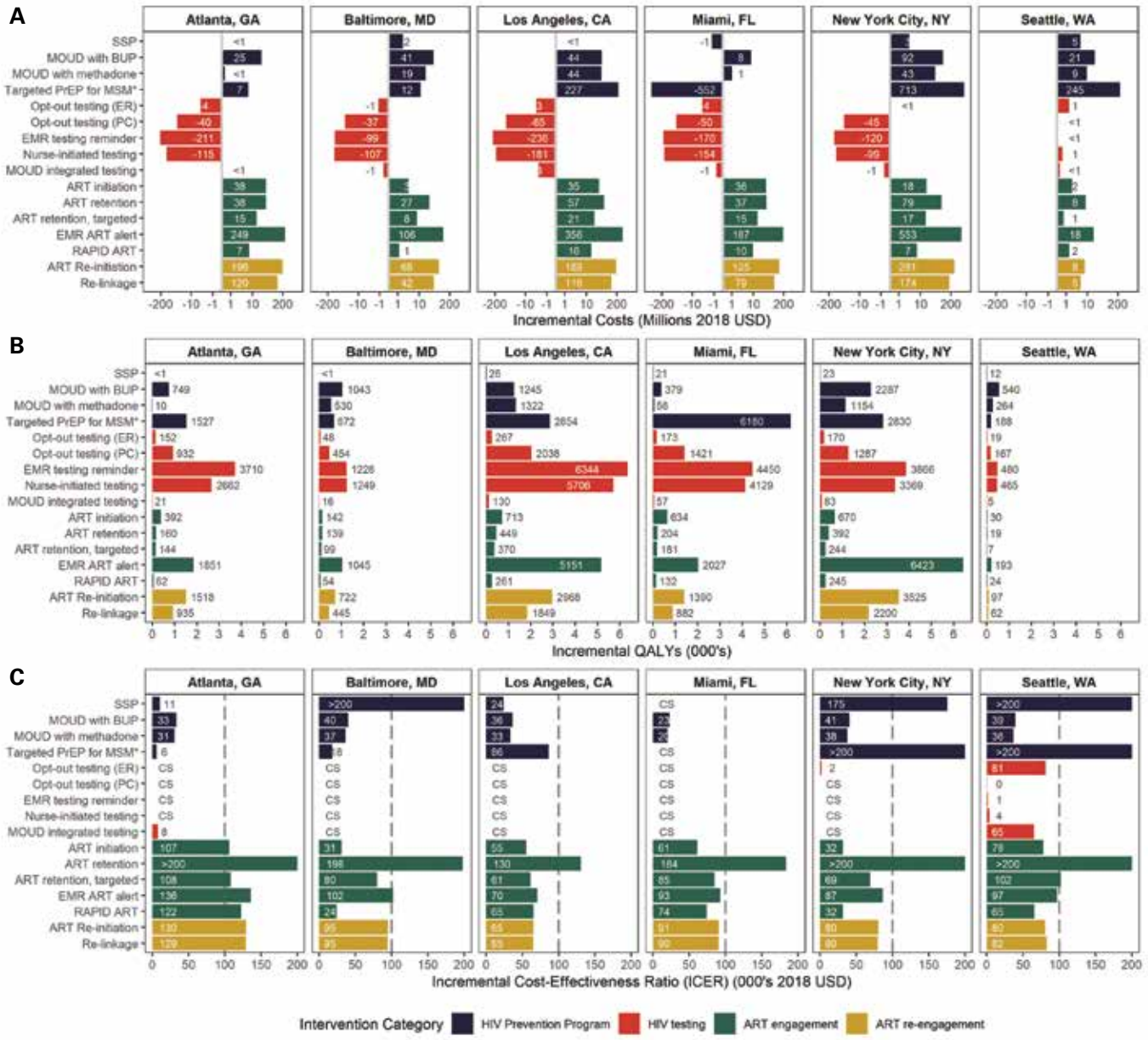
Cost-effectiveness of interventions

Figure 5 describes the results of the model on cost-effectiveness from 16 interventions modeled in the six cities. Modeling was done over a 20-year time horizon (2020-2040; based on interventions sustained over the first 10 years) to capture the long-term benefits on the individual and on others who are susceptible to being infected by them in turn:

- 5a describes the monetary costs (2018 USD) of expanding a given intervention above current service levels and includes costs of implementation, delivery and sustainment specific to each intervention.
- 5b describes the health benefits: QALYs gained or lost as a result of a given intervention.
- 5c describes incremental cost-effectiveness ratios (ICERs), a measure that combines total costs and QALYs. ICERs are the measure that give us an indication of cost effectiveness and cost-saving. We defined cost-effective interventions as those with an ICER below $100,000/QALY.

- **ICER:** incremental cost / incremental QALY gained, compared to current service levels.
- **Cost-effectiveness:** The dotted line in each plot indicates an ICER of $100,000/QALY. Results with an ICER less than $100,000/QALY (or to the left of the dotted line) are considered cost-effective.
- **Cost-saving:** We indicated interventions as cost-saving where projected costs were lower and effectiveness (measured as QALYs) was higher compared to maintaining current service levels. These are marked on the figure with "CS."

FIGURE 5. Incremental costs, QALYs and ICERs resulting from expnded access to HIV prevention programs and HIV testing and care interventions implemented at scales of delivery documented in the public domain in six U.S. cities



*Targeted PrEP for MSM and high-risk MWID

Results shown in Figure 5 indicate that depending on the city, the cost-effectiveness or "value" provided by a given intervention varies significantly, even with similar impacts on HIV incidence reduction.

For example, results from the expansion of SSP and PrEP highlight that **the value of a given intervention may depend on pre-existing service levels**:

- **SSP:** Syringe distribution expansion was cost-saving (Miami) or highly cost-effective (Atlanta, LA) when existing coverage was low, but additional expansion of SSP services in well-resourced cities that have already experienced the substantial public health benefits of high SSP coverage (Baltimore, NYC, Seattle) provided less value.[13]

- **Targeted PrEP:** Targeted PrEP for high-risk MSM/MWID provided good value for money in cities with relatively lower coverage and higher rates of HIV incidence among high-risk MSM (Atlanta, Baltimore, LA, Miami) but provided less value in NYC and Seattle where coverage levels were relatively higher.

Treatment interventions demonstrated that **the value depends on the accessibility of services to the target population**:

- **Treatment (ART engagement and re-engagement):** Of the ART engagement and re-engagement interventions, none were cost-effective in Atlanta. ART engagement interventions varied in their value across other cities and ART re-engagement interventions were cost-effective across all other cities. These findings reflect the disparity in access and quality of care for people living with HIV in Atlanta, a state that did not expand Medicaid under the Affordable Care Act. Our findings, consistent with prior evidence that found greater ART dropout for people living with HIV that are from the South,[14] further underline the need for multifaceted public health strategies to overcome social and structural barriers to care.

In contrast, scaling up access to **some interventions was cost-effective everywhere**:

- **MOUD:** Given the reduced risk of mortality, expansion of MOUD to PWID with an opioid use disorder was found to be cost-effective across cities regardless of existing coverage levels, even though the population-level impact on HIV incidence was relatively low (see Figure 4).

- **HIV Testing:** Increased HIV testing was found to be cost-saving or cost-effective across cities, despite extensive epidemiological and structural differences in their public health responses to HIV.[4] While nationwide expansion of HIV testing in the United States has previously been found to be cost-effective (but not cost-saving),[6,15–17] testing levels were typically based on national guidelines, without accounting for current service levels.

KEY FINDING: value from incremental scale-up can be influenced by local context

Local contextual factors, including existing service levels and accessibility, can vastly influence the value of incremental increases in service levels. Cost-effectiveness results reiterate that responses should be tailored to the different microepidemics.

DISCUSSION:

This article summarizes a novel simulation modeling approach to determine the cost-effectiveness of select interventions across six cities based on extensive real-world evidence. We reiterate that our analysis considered only increments in service provision–that is, additional scale-up beyond existing service levels.

Limitations:

As with any model, certain parameters (e.g. transmission dynamics associated with sexual behavior/injection networks and costs/impacts of implementing each intervention) were simplified by assumptions. As we used real-world evidence to inform the model, our model is also limited by the best available local evidence at the time.

As well, a key assumption of our model was proportional scale-up across risk and ethnic groups, i.e. we assume there is no explicit effort to reduce racial/ethnic and risk group disparities throughout the study period. This is an important limitation because it suggests that higher value may be observed for interventions that target these inequalities.

Conclusion:

As no single intervention was predicted to avert more than 10 percent of projected new HIV infections, our findings suggest the need for combination implementation strategies to reach the ambitious goal of ending the HIV epidemic.[1] Further investigation is needed to provide evidence on the sets of interventions that would optimize the value of responses across different cities. As the present model assumed scale-up of interventions under the condition that inequalities among race/ethnicity and risk groups would remain constant, interventions that can address inequalities in service access may provide further value still compared to that described here. Findings on the low value of treatment scale-up in Atlanta

HIV care providers interpreting this study should note that the need for HIV treatment, prevention and diagnostic services is not yet saturated and incremental scale-up of these services continues to provide value. Scale up of these services should be done with consideration to local contexts, including existing service levels and structural inequalities to access.

highlight a different type of accessibility issue but underscore the importance of accessibility on the value of interventions.

HIV care providers interpreting this study should note that the need for HIV treatment, prevention and diagnostic services is not yet saturated and incremental scale-up of these services continues to provide value. Scale up of these services should be done with consideration to local contexts, including existing service levels and structural inequalities to access.

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HIV

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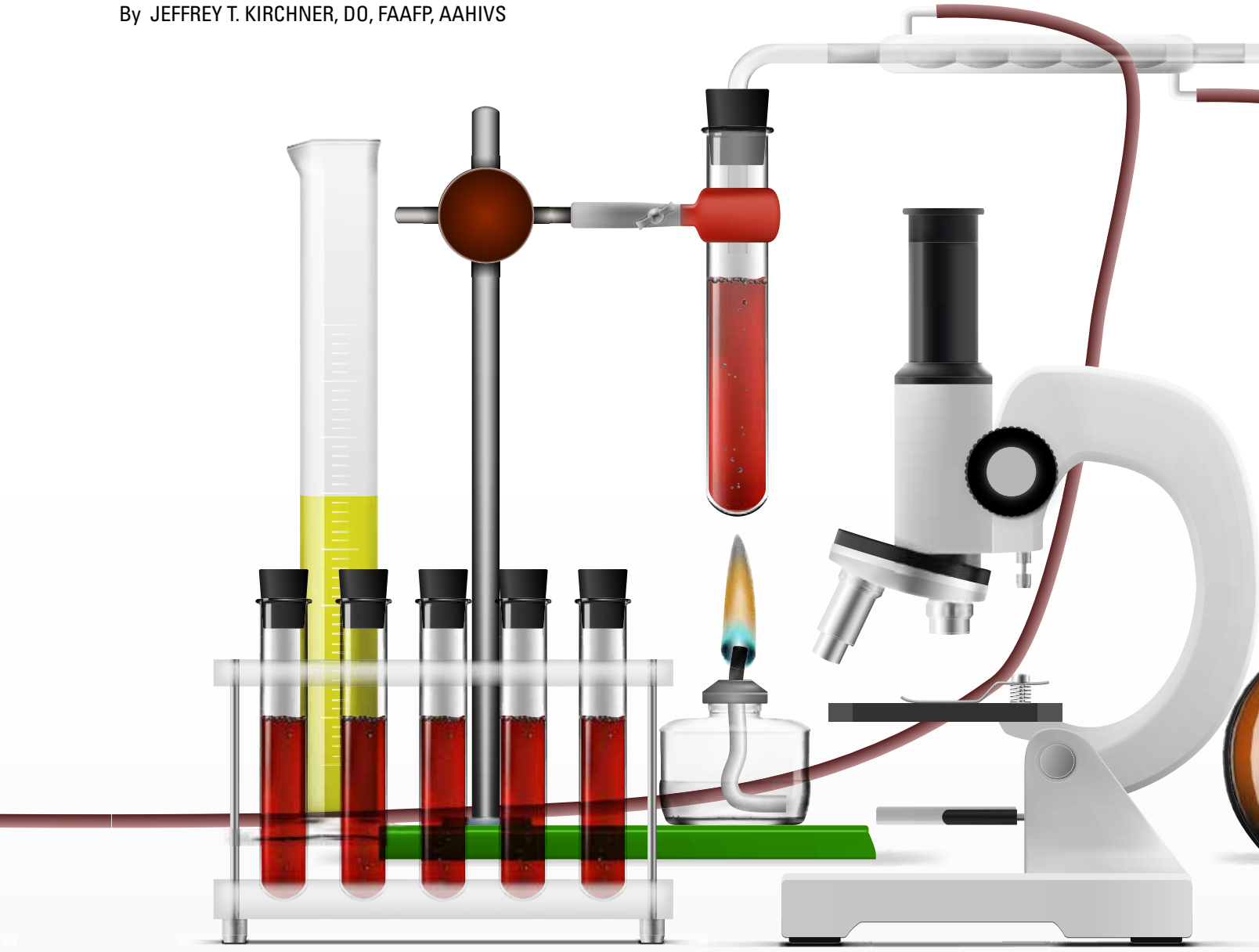
LABORATORY SERVICES

for Patients with HIV Disease

Addressing cost issues: a discussion from the DHHS guidelines.

By JEFFREY T. KIRCHNER, DO, FAAFP, AAHIVS

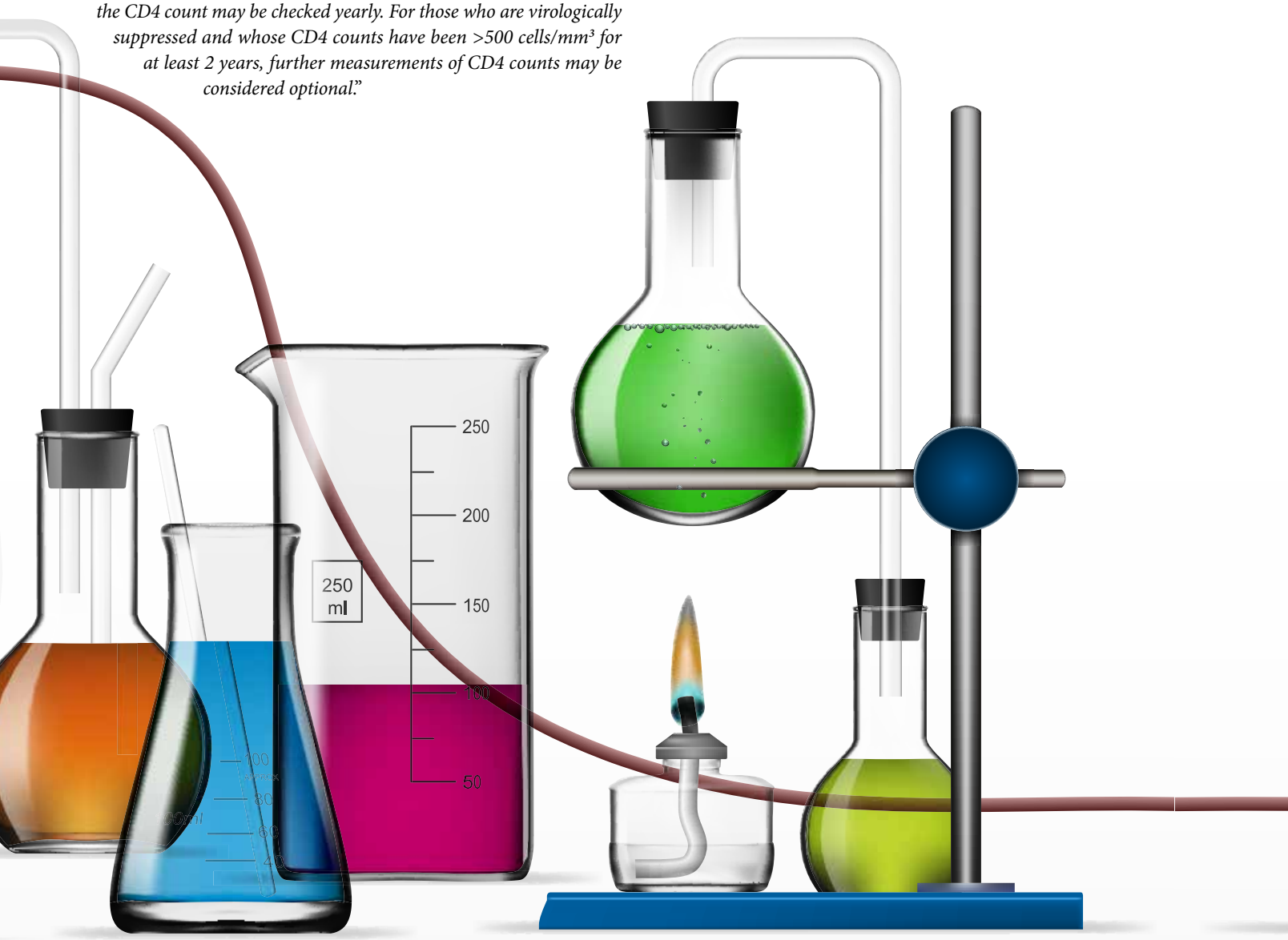


SHUTTERSTOCK/ VECTOR THINGS

HISTORICALLY, patients with HIV disease required frequent clinical and laboratory monitoring—usually on a monthly basis if not more often. As we moved into the "HAART" era of the late 1990's, it became apparent that most patients with good adherence to their HIV medications did well clinically and quarterly office visits became the standard of care. With the progressive improvement, tolerability, and safety of antiretroviral therapies (ART), when the DHHS guidelines were updated in May of 2014, the panel noted "*a viral load should be repeated every 3 to 4 months or as clinically indicated to confirm continuous viral suppression. This may be every 6 months for adherent patients whose viral load has been suppressed for more than 2 years and whose clinical and immunologic status is stable.*"[1] Many HIV providers began extending the time period for visits to every six months and two visits in a 12-month period has become the current standard of care for Ryan White-funded clinics.

Regarding CD4 T lymphocyte (CD4) cell counts, the panel noted in the 2014 revisions *"a repeat CD4 count 3 months after ART initiation will provide information regarding the magnitude of immune reconstitution. This is most important in patients who initiate ART with advanced disease and require Opportunistic Infection (OI) prophylaxis or treatment. During the first 2 years after ART initiation, CD4 counts can be monitored at 3– to 6– month intervals. For patients on suppressive ART and whose CD4 count has been between 300 and 500 cells/mm³ for at least 2 years, the CD4 count may be checked yearly. For those who are virologically suppressed and whose CD4 counts have been >500 cells/mm³ for at least 2 years, further measurements of CD4 counts may be considered optional."*

For many providers and patients, the uptake of these changes was not promptly instituted, with clinicians reluctant to change clinical practice protocols or habits. Moreover, many patients were focused, and appropriately so, on what their most recent T-cell count was, as a measure of how they were doing and if their HIV medications were still working. More than five years after these recommendations were published, may patients and providers continue regular monitoring CD4 counts—often at the patient request. However, as has been observed



over time there can be considerable fluctuation in a patient's CD4 count due to a multitude of reasons, the least not being that the "normal" range is typically reported as 500 to 1500 cells/mm^3. Many providers have likely had to assuage the fears of a patient who was quite worried because their CD4 count had "dropped from 752 to 510."

The most recent updates to the Adult DHHS guidelines have not changed the monthly or yearly time intervals for viral load and CD4 count monitoring.[1] However, the panel makes some specific comments and recommendations on the frequency and necessity of lab monitoring, including the need for more patient engagement. The DHHS panel notes "*judicious use of laboratory testing, without compromising patient care, can be an important way to reduce costs. For patients with deductibles for laboratory tests, decreasing the use of tests with limited clinical value could reduce patient costs and improve adherence to a care plan.*" Several studies are cited that examined the value of laboratory services in HIV care. One is a cost analysis which found no clinical benefit to continuing CD4 monitoring in patients with suppressed viral loads and CD4 counts >200 cells/mm^3 after 48 weeks of therapy.[2] A study published by Emily Hyle and colleagues in Boston, found that reducing from twice yearly to annual CD4 monitoring could save approximately $10 million per year in U.S. healthcare costs.[3]

Another study looked at 274 patients with HIV disease who were hospitalized in Texas over a six month period. A chart review found that 45 percent of laboratory tests ordered by attending and resident physicians were NOT medically-indicated. These included but were not limited to hepatitis serologies, toxoplasmosis serologies, and PCR testing for cytomegalovirus. During this six month period at this single site, the estimated cost of excess inappropriate laboratory testing totaled $92,000.[4] Anecdotally, at the teaching hospital where I work, I have witnessed quite often well-intended residents ordering unnecessary lab tests on HIV patients from our clinic when admitted to their service.

Regarding genotype resistance testing, two cost-effectiveness studies published in 2001 and 2005 demonstrated the value of these tests in ART-naïve and ART-experienced patients.[5,6] These studies became the basis for the DHHS guidelines' recommendation for performing HIV-genotype testing before ART initiation and at the time of virologic failure. However, more recent cost-effectiveness analyses have revisited the value of baseline, pre-treatment genotype testing in the setting of integrase strand transfer inhibitor (INSTI) plus two-nucleoside reverse transcriptase inhibitors (NRTIs) regimens. One study found that Integrase-specific genotype testing before initiation of dolutegravir (DTG) plus two NRTIs regimen was not cost-effective and may actually lead to underuse of INSTIs.[7] These results highlighted that some patients with reported INSTI-resistance would still become virologically suppressed on a DTG-based regimen.

A second study by Hyle and colleagues found that standard genotype testing for non-nucleoside reverse transcriptase inhibitor or protease inhibitor resistance before ART initiation was not cost-effective because it had little impact on virologic outcomes given the use of an INSTI plus 2 NRTIs as initial ART for the majority of patients.[8] Both studies only assessed genotype testing before initial ART but still presumed testing would be used after first-line ART failure.

The results of these studies suggest we need more clinical research to better define the role of resistance testing before initiation of an INSTI with a two-NRTI regimen. In addition, these data cannot be extrapolated for two-drug ARV regimens, which are increasingly being prescribed in clinical practice. For now, the DHHS guidelines still recommend baseline resistance testing for PI and NRTI mutations although this may change with more data and future updates. However, based on data above and clinical experience, one could make an argument for not ordering HIV-genotyping which usually cost $400 to $500, especially if the patient was responsible for the cost. As we move toward "rapid start" of newly diagnosed HIV patients, genotypic results are often ordered but take a week or longer to result and thus become a non-issue in regards to starting patients on ART.

This section of the DHHS guidelines on cost considerations concludes by stating *"Ideally, costs should not drive clinical care, yet they are a factor in contemporary health care."* I would agree with this in principle, but believe that costs often drive clinical care (especially for the uninsured or underinsured) and thus remain an important part of the care we provide for our HIV patients. There are recent data from the CDC's Medical Monitor Project which found medical costs significantly impact patients' ability to afford and adhere to ART and be retained.[9] In this CDC study, 14 percent of patients reported using a cost-saving strategy for prescription medications and 7 percent had cost saving–related nonadherence.

SHUTTERSTOCK/ ANGEL LODECO

KEY POINTS

- Viral load and CD4 cell count testing are appropriate for all patients at entry into care
- Patients who are clinically stable with virologic suppression for two years should have viral load testing done twice yearly and CD4-Tcell counts once a year
- For patients with CD4-Tcell counts > 500 cells/mm3 continued CD4 cell count testing is optional
- Chemistry panels should be obtained twice yearly and a CBC every 12 months when no longer monitoring CD4 counts.
- Baseline resistance testing is still recommended but may be optional for some patients based on costs, availability, and concerns for transmitted drug-resistance.
- Used shared-decision making with patients regarding the ordering of certain lab tests
- The cost of ART, especially costs to the patient should be one consideration in regimen selection as expenditures my directly impact adherence.

** adapted from Ref. # 1

Although not discussed in this article, a specific section (L) "Cost considerations and Antiretroviral Therapy" is also part of the recent DHHS guidelines. The estimated total direct expenditures for HIV/AIDS care and treatment between 2002 and 2011 was $10.7 billon which is at least 800 percent higher than similar expenditures for other chronic health conditions.[1] Specifically noted, are the rising costs of ART which in 2018 cost $22.5 billion in the U.S., more than double the cost in 2010. Worth noting however are similar cost increases with medications for cancer, diabetes, pulmonary diseases, and rheumatologic conditions. It is likely there will be more emphasis on cost-sharing with patients and the use of generic ART in the years ahead.

Despite the inherent belief that we are being good stewards of our healthcare dollars the data suggests otherwise. Total healthcare expenditures in the U.S. were projected to be $3.82 trillion for 2019.[10] A recent publication estimated the waste in our healthcare system to range from $760 to $935 million or about 25 percent of all healthcare expenses.[10] A substantial part of the 25 percent is on what is called "overtreatment or low-value" care. This is defined as "subjecting patients to care that according to sound science and the patients' own preferences cannot possibly help them…it is care rooted in outmoded habits, supply-driven behaviors, and ignoring the science." A recent example is routine screening for vitamin D deficiency which at a population level has no value, but millions of these tests are ordered annually. A payment reform policy in Canada which stopped reimbursement for screening was associated with a 93 percent reduction in vitamin D testing. An educational intervention in the U.S. during this same time only led to a 14 percent reduction in screening for Vitamin D deficiency.[11]

Not paying for specific lab tests appears to be heavy-handed but effective in changing the practice behaviors of physicians and other healthcare providers. Think of pre-authorizations for medications and testing, which are part of our professional life and although burdensome—they do serve a purpose. Also consider in the context of money wasted on low-value care, the number of Americans who remain without health insurance.

Going forward, I challenge and encourage my AAHIVM colleagues to adapt the best science contained in the DHHS guidelines while also considering well-informed patient preferences. A consistent goal should be to provide excellent but cost-efficient and appropriate care at our respective clinical sites. Before ordering any test, one should be asking "will this change the treatment plan for my patient"? I would also recommend looking at the "Choosing Wisely" campaign (https://www.choosingwisely.org) endorsed by ACP, AAFP, and other specialty societies to help eliminate low-value care.[12] We do not have endless dollars from the private or public insurance sectors nor from the Ryan White Care Act —the latter which provide $2.9 billion in funding for FY 2019.[13] With no short-term end to the HIV epidemic in sight, cost-conscience health care can equal excellent health care without putting undue burdens on our clinics, our patients, and the complex healthcare system we are all part of. **HIV**

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MITIGATING FINANCIAL TOXICITY

Through Cost of Care Conversations

Identifying the role of nonprofit organizations in addressing social determinants of health

By KATHLEEN GALLAGHER, MPH, ALAN RICHARDSON, and REBEKAH ANGOVE, PhD

DUE TO RISING HEALTHCARE COSTS, many Americans struggle to afford needed medical care alongside their day-to-day financial obligations. While a patient's financial status plays a significant role in the development of treatment-related financial hardship, health-system related factors such as lack of transparency about out-of-pocket (OOP) costs, lack of access to patient assistance resources and general lack of financial counseling or financial literacy resources may exacerbate the problem.

Out-of-pocket costs are the main driver of financial stress, regardless of the medical or surgical diagnosis, with 24.2 percent of patients with large employer coverage having spent at least $1,000 in 2015 compared to 17.1 percent in 2005 (inflation-adjusted).[1] Furthermore, 37 percent of Americans have unpaid debt associated with their medical expenses and 27 percent have skipped needed medical treatment due to cost. This data highlights the true impacts of OOP healthcare costs on patients' outcomes and lives.[2] Strategies to deal with these barriers may decrease patients' financial stress and burden.

SHUTTERSTOCK/ NAYPONG STUDIO

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The healthcare costs of treating HIV-infected individuals as they age includes both HIV- related and HIV-unrelated medical care. The estimated discounted lifetime cost for persons who is infected with HIV at age 35 is $326,500 (60% for antiretroviral medications, 15% for other medications, 25% non-drug costs).[3] The average annual cost of HIV treatment ranges from $14,000 to $20,000, with a monthly cost of $1,500-$2,000.[4] Taking into consideration that the median annual salary for a single 35-year-old was $49,500 in 2017, spending 28-40 percent of one's pre-tax income on medical care is a substantial burden and cost conversations with medical providers about treatments options quickly become a priority.[5] The need for cost information is even more pronounced among under-resourced individuals. This patient population also indicate they are less likely than higher-income individuals to receive the care and cost information they need to make informed medical decisions and to remain engaged in care.

High drug prices and cost-sharing health plans are the most frequently associated drivers of financial stress for individuals diagnosed with HIV. Almost half of all individuals living with HIV in the United States are covered by federally funded programs including Medicare or Medicaid.[4] Medicare Part D, which was developed to cover medications (including HIV drugs), has a restriction in its annual benefit that's referred to as the "donut hole." Recipients are required to pay $3,051 out of pocket after their initial, basic coverage benefit is used up and before the catastrophic coverage kicks in to cover the rest of the year's medication needs.[4] Even private insurance coverage may require substantial co-pays forcing patients to juggle medical costs against other necessary expenses including rent, transportation, utilities and food. Therefore, from a consumer perspective, cost information is only meaningful in the presence of other information related to risks and benefits, which allows individuals to make a value-based rather than price-based decision. It is also important to understand how and where individuals prefer to receive cost information relative to healthcare services, as well as how they intend to use the information.

Understanding the Patient's Financial Experience

Patient Advocate Foundation (PAF) provides direct case management, financial support and educational services primarily for low-income patients and caregivers experiencing financial, employment, insurance coverage or household material hardships because of health conditions. PAF provides services to any patient with a chronic, life threatening and/or debilitating disease. In 2018, PAF served patients across 584 different diagnoses.

To better understand the patient experience around financial distress, care decisions and cost of care, and to address cost concerns of their patients, PAF conducted a survey to identify root causes of financial stress, treatment concerns, care goals and other unmet financial needs. PAF surveyed 642 HIV/AIDS patients who received financial or navigation services in 2018. Nearly all (92 percent) of the respondents were 36 years of age or older, 89 percent identified as male, 66 percent were non-Hispanic whites, 65 percent resided in the South, and 71 percent had an annual income less than $48,000. Seventy-one percent of respondents had been diagnosed with HIV for more than 10 years.

PAF survey data from HIV/AIDS patients indicated that availability of cost information was insufficient to assist them in making decisions consistent with their needs, preferences and values. The data relayed that they need curated information and personal assistance to guide them in making financial plans specific to their circumstances as well as help finding resources so as to avoid medical debt and other hardships during treatment and in its aftermath.

Distress & Financial Stress

The costs to both the patient and society of an HIV infection extend well beyond the medical domain. They can also include social services, housing, patient time, lost productivity and physical and emotional distress to patients and families.[1] At the individual level, this myriad of health and non-health related concerns can cause patients undue distress that may impact their ability to adhere to their healthcare goals. When asked about the level of distress experienced in the past seven days, 22 percent of respondents score seven or higher (zero = low; 10 = high). Specifically, the cost of HIV care and treatment causes many patients undue stress daily; 15 percent indicated their level of financial distress was "overwhelming" and an additional 33 percent stated "above average." Complicating matters is a lack of understanding around how medications and services are covered by insurance, how their deductible impacts their OOP cost responsibilities, coinsurance cost and the availability and eligibility requirements needed for safety net service assistance.

Treatment Concerns & Care Goals

Conversations with medical providers about treatment options and shared decisions to determine the course of HIV therapy are integral components to designing treatment plans that patients can adhere to. The survey found that while confidence in taking an active role in initiating and making decisions about care is high, perceived financial barriers to treatment also remain high. Seventy-seven percent of PAF patients were "very concerned" about the overall financial cost of their chosen treatment. Not surprisingly, 82 percent of those surveyed indicated that the biggest barrier to treatment adherence was the cost of medication, followed by costs of procedures, surgery, labs or scans (32%). While not a direct cost, lack of understanding regarding insurance coverage was also reported as a barrier to treatment adherence (32%). Personal care

goals are also important to consider within the context of coordinated HIV care. While avoiding financial distress was the top answer (64%), maintaining quality of life (58%) and being able to take care of one's self (51%) were top responses. Independence was a strong theme throughout these sections.

Identifying & Addressing Unmet Needs

While the impact of medical costs are important to address, patients diagnosed with an HIV infection are at a higher risk for material hardships including essential living expenses such as food, housing, utilities and transportation. These items become even harder to pay when financial resources are diverted toward essential healthcare costs. Financial support for daily living expenses (rent/mortgage/utilities) was listed as an important unmet need (41%), followed by nutrition/food security (10%). Both of these non-medical hardships play an important role in the management and adherence to antiretroviral therapy (ART), as some medications are better-tolerated when taken with food.

Health insurance premiums were also indicated as an unmet financial need. Employment is the gateway to insurance (and, therefore, access) for many low-income patients as well as the ability to qualify for government supported products (ADAP, ACA and Medicaid). When ask how PAF could help to mitigate financial burdens, almost half of those surveyed (49%) listed assistance with health insurance premiums as a way to increase access and retention in care.

Managing the comprehensive and increasing costs associated with an HIV diagnosis or obtaining preventative medications requires a strategic approach to ensure that these therapies are accessible to the people most likely to benefit from them. This process should rely on clinician-patient care planning, cost information and cost conversations. Individuals want information on their healthcare costs which often cause undue financial burden and force them to make harmful tradeoffs. In addition, patients want and need to understand how the financial risk associated with their medical care can be avoided, mitigated and managed. Fortunately, there are available resources to help patients with these cost conversations and with mitigating the impacts of financial toxicity.

MAKING AN IMPACT ONE PATIENT AT A TIME

Patient Advocate Foundation (PAF) is a non-profit organization which provides case management services and financial aid to patients across America with chronic, life-threatening or debilitating illnesses including HIV and access to HIV prophylaxis (PrEP). Services are free of charge to the patient and can be provided in both English and Spanish.

https://hivoraids.pafcareline.org/
https://www.copays.org/diseases/hiv-aids-and-prevention

Our website also hosts several useful tools that can be used by patients seeking information on access to HIV or prevention medication and facilitating cost of care conversations with their medical providers.

https://www.patientadvocate.org/explore-our-resources/common-barriers-affordability/

https://www.patientadvocate.org/explore-our-resources/interacting-with-physician/

Resources To Address Costs Of Care

For more than two decades, PAF has provided financial and insurance navigation, social services, financial support and educational services for primarily low-income patients and caregivers. Through this work, PAF has created and curated an extensive catalogue of resources to support financial navigation and promote the delivery of patient-centered care.

HIV care is expensive and all patients, regardless of income and insurance status, have at least some concerns regarding how they will cover the direct and indirect costs of receiving medical care. These indirect costs are not optional for patients and can cause significant burdens, even beyond deductibles and copays. Resources to address and mitigate these concerns are offered through case management and financial navigation programs provide by PAF. Beyond the linkage of patients to resources is the lack of communication between patients and providers about the costs associated with care. Providers need to feel confident in initiating these conversations to ensure that patients can access the information they need about costs before making financially

ISTOCK/ TERO VESALAINEN

binding decisions. Addressing barriers to medical care and treatment adherence, and linking patients to organizations that provide resources to mitigate these obstacles, can result in stronger clinician-patient relationships and ultimately better patient outcomes.

PAF has two programs that are available to patients with an HIV/AIDS diagnosis or are utilizing HIV treatment programs and are experiencing access issues.

HIV, AIDS & Prevention CareLine

The HIV, AIDS and Prevention CareLine helps patients who have been diagnosed with or are at risk for HIV infection and seeking education and access to care. Leveraging the lessons learned from over 20 years of case management across multiple disease states, the CareLine services are provided to patients who face obstacles to prescribed healthcare. Education, research and representation across a wide spectrum of services are provided for uninsured, underinsured and insured patients, their caregivers and providers. Skilled case managers have a myriad of backgrounds including nursing, social work, insurance industry, coding and billing expertise. PAF's case management services are broken down into three distinct levels of service:

Reduce Financial Burden

- Find local, regional and national resources for financial support for living expense support needs such as housing, utility, transportation, food
- Educational and emotional support resources: support groups, nutrition and wellness
- Education on ADA and FMLA rules and regulations

Enroll into Appropriate Insurance and Social Programs (as necessary)

- Eligibility and enrollment into Medicare, Medicaid, disability, ACA products, insurance, charity care, negotiation of payment plans or discounts for medical care
- A baseline level of employment related support as needed (COBRA, short- and long-term disability)

Insurance Navigation

- Insurance utilization assistance such as benefit review, preauthorization, clinical appeals, billing and coding issues, out-of-network, second opinions and treatment decisions, insurance plan interpretation

All CareLine services are provided at no cost to the patient.

Financial Assistance Programs

PAF Co-Pay Relief Program (CPR) provides financial assistance to financially and medically qualified patients. This includes those insured through federal health plans such as Medicare, for co-payments, co-insurance and deductibles required for pharmaceutical treatments and/or prescription medications. Patients, providers and pharmacists can initiate applications for assistance through our online portal. The program offers personal service to all applicants through our Approval Specialists, who are available to guide applicants through the enrollment process. PAF's CPR currently offers assistance for patients with HIV, AIDS and/or those patients at high risk for HIV/AIDS and who are accessing prevention medications. Patients are instantly approved, and their award amount is available for at 12-month period. For more information on CPR, visit www.copays.org. **HIV**

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Kathleen Gallagher, MPH is an epidemiologist and health services researcher who serves as the quantitative research lead at Patient Advocate Foundation. Prior research endeavors have focused on traditional and non-traditional underserved patient populations and the links between health access, service utilization and barriers to care. Her current research centers around financial toxicity, healthcare barriers and identifying unmet needs in low income chronically ill patients, including those living with HIV.

Rebekah SM Angove, PhD is a health services researcher and leader in patient engagement. She currently serves as the Vice President for Patient Experience and Program Evaluation at the Patient Advocate Foundation. Her work is focused on mapping the patient experience and uncovering unmet needs, translating those needs to direct service and policy recommendations and evaluating the impact of initiatives on patients and the patient community. Her expertise spans numerous clinical research programs and advisory groups with numerous projects focused on addressing health disparities.

Alan Richardson is the Executive Vice President of Strategic Patient Solutions at Patient Advocate Foundation where he is responsible for working with internal and external stakeholders on case management-based solutions for patients experiencing access and affordability challenges. These include general case management services, MedCareLine-PAF's disease-specific case management programming and Financial Aid Funds. He is also the community lead for oncology, virology and cardiology.

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SHUTTERSTOCK/ AFRICA STUDIO

By MILENA M. MURRAY, PharmD,
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Crushing ARVs

Recommendations for crushing oral formulations of antiretroviral therapy

ALTHOUGH the number of new human immunodeficiency virus (HIV) diagnoses have stabilized, there were an estimated 1.1 million adults and adolescents living with HIV in the U.S. at the end of 2017. Of these individuals, only 49 percent have achieved viral suppression.[1] While antiretroviral therapy (ART) is very efficacious, interruptions in therapy may lead to drug resistance, viral rebound and disease progression.[2] Adherence to ART for patients living with HIV (PLWH) is a key factor to the long-term success of treatment and reduction of disease-associated morbidity and mortality.

PLWH may have comorbid conditions which affect their ability to swallow medications. Causes of swallowing disorders in PLWH include infection of the esophagus with herpes simplex virus, cytomegalovirus, cryptosporidiosis and most commonly, esophageal candidiasis.[3] Dysphagia may also result from a number of etiologies secondary to central nervous system (CNS) damage or problems affecting the head and neck. Stroke, traumatic brain/spinal cord injury, dementia, Parkinson's disease, multiple sclerosis, Lou Gehrig's disease and muscular dystrophy may all result in CNS damage-related dysphagia.[4] Dysphagia may also result from cancer, chemotherapy, surgery, dental problems, pulmonary disease and gastroesophageal reflux disease. A 2012 survey reported that one in 25 adults reported a swallowing problem and many do not seek care despite the negative health impacts.[5]

Adherence in PLWH can be severely hindered by dysphagia due to their inability to swallow tablets, capsules and other oral formulations of medications. Unfortunately, limited options for drug therapy exist when treating patients with swallowing disorders. Not all ART come in liquid form, have adult dosing for formulations other than capsules/tablets and may not have a desirable taste. In addition, not all formulations may be readily available to a patient. This article discusses a compilation of recommendations for crushing ART medications and subsequent administration to patients with swallowing difficulties.

The potential to crush, open, split, add to water or food for each antiretroviral therapy was reviewed in the full prescribing information from the manufacturer. In addition, a MEDLINE search was performed using "antiviral," "crush," "enteral," "dysphagia" and "split." In the event information was unavailable, the manufacturer of the medication was contacted for additional information. Recommendations are listed in Table 1. A brief overview of select data and recommendations are presented below.

Drug properties must be considered when changing the intended route and formulation of a medication such as crushing a tablet. The solubility of the agent may change such as with rilpivirine (RPV). As a result of its insolubility over a wide pH, it is not recommended for RPV or any formulation containing RPV to be crushed.[6] Similarly, cobicistat (COBI) is practically insoluble in water.[7] Therefore, crushing or splitting COBI or any medication containing COBI is not recommended, except for darunavir/cobicistat (DRV/COBI) due to its specific formulation. Flavor may play a factor in determining if a drug can be crushed. Although there are no pharmacokinetic studies on crushing tenofovir alafenamide (TAF), it is not recommended to crush or split certain formulations containing TAF due to its bitter and burnt aromatic flavor.[8] In addition, antiretroviral dosing may change when switching between formulations. Emtricitabine (FTC) liquid and capsule doses are not equivalent.[9] Clinicians should be aware of this issue if switching from one form to another is necessary.

Furthermore, chemical interactions may occur between the administered drug and tubing used for administration. The available oral solution of ritonavir (RTV) contains 27 percent propylene glycol and 43 percent ethanol.[10] Propylene glycol and ethanol may be incompatible with polyurethane

Antiretroviral Crush/Do Not Crush List

Agents	Open Capsule	Crush Tablet	Liquid Form	Other Formulations	Notes
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)					
Abacavir (ABC / Ziagen)[1]	—	Yes	Yes	No	Add to small amount of semi-solid food or liquid; Consume immediately
Didanosine (ddI / Videx EC)[2]	No	—	Yes	—	
Emtricitabine (FTC / Emtriva)[2]	No	—	Yes	No	Liquid dose not equivalent to capsule dose
Lamivudine (3TC / Epivir)[1]	—	Yes	Yes	No	Add to small amount of semi-solid food or liquid; Consume immediately
Stavudine (d4T / Zerit)[1]	Yes	—	Yes	No	Mix with 5-10 mL cool tap water
Tenofovir (TDF / Viread)[1]	—	Yes	No	Powder	Mix in water, grape juice, or orange juice
Zidovudine (ZDV / Retrovir)[2]	—	No	Yes	IV	Add to small amount of semi-solid food or liquid; Consume immediately
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)					
Efavirenz (EFV / Sustiva)[1]	Yes	No	No	No	Add to small amount of semi-solid food; Consume immediately
Etravirine (ETR / Intelence)[2]	—	Yes	No	No	
Doravirine (DRN/Pifeltro)[1]	—	No data	—	—	
Nevirapine (NVP / Viramune / Viramune XR)[1]	—	No	Yes	No	Do not crush XR formulation
Rilpivirine (RPV / Edurant)[2]	—	No	No	No	Tablets do not readily disperse in water
Protease Inhibitors (PIs)					
Atazanavir (ATV / Reyataz)[1]	Yes	—	No	Powder	Mix 400 mg daily dose w/ 4 oz. of apple sauce
Darunavir (DRV / Prezista)[3]	—	Yes	Yes	No	
Fosamprenavir (FPV / Lexiva)[1]	—	No data	Yes	No	
Indinavir (IDV / Crixivan)[1]	Yes	—	No	No	Mix with fruit puree
Lopinavir + Ritonavir (LPV/r / Kaletra)[2]	—	No	Yes	No	
Nelfinavir (NFV / Viracept)[1]	—	Yes	No	No	Add to small amount of water; Consume immediately
Ritonavir (RTV / Norvir)[2]	No	No	Yes	Powder	Powder does not contain propylene glycol or alcohol; May be administered via tube if mixed with water; Use within 2 hrs of mixing
Saquinavir (SQV / Invirase)[2]	Yes	No	No	No	
Tipranavir (TPV / Aptivus)[1]	No	—	Yes	No	
Integrase and Entry Inhibitors					
Dolutegravir (DTG / Tivicay)[1]	—	Yes	No	No	Add to small amount of semi-solid food or liquid; Consume immediately
Maraviroc (MVC / Selzentry)[1]	—	No	No	No	Tablets are film coated
Raltegravir (RAL / Isentress / Isentress HD)[4]	—	Yes (400 mg) No (600 mg)	No	Chewable tablet Powder	Chew tabs adult dose = 300 mg PO BID No adult dose for powder
Fixed-dose Combinations					
Atripla (EFV+FTC+TDF)[1]	—	No data	—	—	Not recommended; EFV insoluble in water
Biktarvy (BIC+FTC+TAF)	—	No data	—	—	Not recommended
Complera (RPV+FTC+TDF)[1]	—	No data	—	—	Not recommended; RPV insoluble in water
Delstrigo (DRN+FTC+TDF)[1]	—	No data	—	—	
Descovy (TAF+FTC)[1]	—	No data	—	—	Not recommended; Soluble in water
Dovato (DTG+3TC)[1]	—	Yes	—	—	Split tablet into halves or crush and add to a small amount of semi-solid food or liquid and consume immediately
Evotaz (ATV+COBI)[1]	—	No data	—	--	Not recommended
Genvoya (EVG+COBI+FTC+TAF)[1]	—	No data	—	—	Not recommended
Juluca (DTG+RPV)	—	Yes	—	—	Add to a small amount of semi-solid food or liquid; Consume immediately
Odefsey (RPV+FTC+TAF)[1]	—	No data	—	—	Not recommended
Prezcobix (DRV+COBI)[1]	—	Yes	—	—	Not extended release
Stribild (EVG+COBI+FTC+TDF)[1]	—	No data	—	—	Not recommended
Triumeq (DTG+ABC+3TC)[1]	—	Yes	—	—	Administer with a small amount of semi-solid food or liquid; Consume immediately
Symtuza (DRV+COBI+FTC+TAF)[1]	—	Split	—	—	Tablet may be split; crushing tablet may reduce TAF bioavailability (~20%)
Truvada (TAF+FTC)[1]	—	Yes	—	—	Crush at discretion of provider; Minor stirring/pressure required; Mix with water or grape/orange juice
Pharmacokinetic Enhancer					
Cobicistat (COBI / Tybost)[1]	—	No data	—	—	Not recommended; Insoluble in water

1. Data on file from manufacturer.
2. Nyberg CR, Patterson BY, Williams MM. When patients cannot take pills: antiretroviral drug formulations for managing adult HIV infection. Top Antivir Med 2011;19:126-31.
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tubing, therefore it is recommended for the powder formulation of RTV to be used when administration through polyurethane tubing is required.

While absorption of some antiretroviral drugs may decrease upon crushing, raltegravir (RAL) has been shown to have opposite results. Studies have demonstrated a difference between chewing and swallowing whole RAL tablets. Higher absorption and less interpatient variation was observed when patients chewed tablets dosed at 400 mg twice daily in comparison to swallowing whole tablets at the same dose.[11] Under acidic conditions, the dissolution of whole tablets in vitro was low and improved in neutral conditions (water and pH 6.8 buffer). When tested under similar neutral conditions, crushed tablets readily dissolved and demonstrated higher concentrations under acidic conditions. Crushing RAL tablets and administering via a gastrostomy tube demonstrated concentrations within therapeutic ranges when peak and trough concentrations were measured at steady-state concentrations. Due to a lack of data, the long-acting formulation of RAL (Isentress HD™) should not be crushed.

Pharmacokinetic studies do not demonstrate the ability to crush DRV tablets, however, several case reports have shown positive results when crushed DRV is administered.[12-14] One report detailed two patients who received crushed DRV, one via the oral route and one via a "permanent stomach tube."[13] Both patients were able to achieve plasma concentrations within therapeutic range. A patient undergoing continuous venovenous hemodiafiltration (CVVHD) was administered crushed DRV via a duodenal port of a double-lumen nasogastroduodenal tube.[14] The author concluded that absorption of DRV was adequate and dose adjustments were not recommended. Similarly, a patient newly diagnosed with HIV was administered crushed DRV dissolved in water through an orogastric tube due to the need for mechanical ventilation.[12] HIV-1 RNA data was obtained before and after mechanical ventilation with no clinically significant change observed. The DRV trough concentrations were found to be within the recommend range.

A study of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) tablets measured the bioequivalence between a whole tablet with food and a crushed/suspended tablet with either food or enteral nutrition.[15] Bioequivalence was shown with a crushed/suspended tablet and enteral nutrition and an intact tablet. Even though it was not considered clinically relevant, bioequivalence was not shown for C-max with a crushed/suspended tablet and food. Of note, area under the curve was considered bioequivalent.[15]

Sufficient pharmacologic and clinical data are lacking for many ART agents to support crushing or splitting tablets. Unfortunately, this also includes the majority of the commonly used single-tablet regimens. Due to the multifactorial issues that may arise when a PLWH cannot swallow tablets, bioavailability research should continue, and pharmacokinetic studies performed to determine specific dosing recommendations. **HIV**

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UPDATE

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FEATURED LITERATURE:

Huhn GD. Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in a Rapid Initiation Model of Care for HIV-1 Infection: Primary Analysis of the DIAMOND Study. *Clinical Infectious Diseases, https://doi.org/10.1093/cid/ciz1213. Published: December 27, 2019*

Current HIV Treatment guidelines recommend rapid initiation of ART for newly diagnosed patients. However, data looking at the implementation and results of this recommendation are limited. The DIAMOND study is a phase-3 trial evaluating the efficacy and safety of a single-tablet regimen (STR) containing darunavir/cobicistat/emtricitabine/tenofovir alafenamide in a rapid treatment initiation model of care. Inclusion criteria were adults aged ≥18 years who were ART-naïve and newly diagnosed with HIV-1 infection less than two weeks from the screening visit. The study enrolled 109 individuals of whom 87 percent were men with a median age of 28 years. The subjects were started on the four-drug STR at a median time of five days post-HIV diagnosis and one-third started treatment within 48 hours of their diagnosis. All started ART prior to the availability of laboratory results. Overall, 97 of the participants completed the study and 12 discontinued treatment before 48 weeks. None stopped treatment due to drug resistance mutations but mainly due to lab abnormalities. By observed analysis, 92 (96%) of participants achieved HIV-1 RNA < 50 copies/mL and four were < 200 copies m/L. There were no protocol-defined virologic failures and the incidence of both adverse events (AEs) or adverse drug reactions were low. None of the AEs were drug-related, and only one (<1%) participant discontinued due to study drug-related AE. At week 48, 98 percent of participants self-reported a high level of satisfaction with their treatment.

AUTHOR'S COMMENTARY: The most recent update in the DHHS guidelines recommends, "that ART be started immediately or as soon as possible after diagnosis to increase the uptake of ART, decrease time to linkage to care and virologic suppression, and reduce the risk of HIV transmission." For rapid initiation of treatment, recommended regimens include BIC/TAF/FTC, DTG plus (TAF or TDF) plus (3TC or FTC), or (DRV/r or DRV/c) plus (TAF or TDF) plus (3TC or FTC). Implementing rapid start ART at the clinic level presents some financial and logistical challenges but we now have several studies including DIAMOND and RAPID in the U.S. and CASCADE from sub-Saharan Africa showing the efficacy of this strategy.

FEATURED LITERATURE:

R. Stephenson, et al. Accuracy in self-report of viral suppression among HIV-positive men with HIV-negative male partners. *Journal of Acquired Immune Deficiency Syndromes. January 07, 2020 – published ahead of print. doi: 10.1097/QAI.0000000000002240*

The U=U campaign has promoted the science and clinical implications regarding viral suppression and non-transmissibility of HIV. However, there is little data regarding how this information is communicated from HIV-positive MSM to their partners. This study used data from "Stronger Together" which is an efficacy trial of adherence interventions with MSM living in Atlanta, Boston, and Chicago who are in serodiscordant relationships. The authors combined patient self-reporting and biomarker-confirmed measures to assess the accuracy of self-report of viral load suppression. Among this group only 73 percent of men could accurately report their viral load status. In addition, 20 percent reported that they were virally suppressed when they actually had no biomarker confirmed measure of their viral load. The authors note these results confirm the findings of other recent studies in which there was a great deal of inaccuracy among patients reporting viral suppression. They cite the need for collaborative interventions to help the infected partner in serodiscordant relations adhere to medical therapy and maintain an undetectable viral load, thus applying the strategy of U=U.

AUTHOR'S COMMENTARY: The authors note in their conclusion that this study highlights the need to regularly provide patients with information regarding their viral loads. Continuous access to medical care including ART along with periodic lab monitoring are key components of keeping patients undetectable and untransmittable. However, promotion of condom use and PrEP may still have a role in serodiscordant relationships and are important educational issues. Engaging the HIV-negative partner, as is being done with the "Stronger Together" trial, may be possible as a model of care in some clinics.

FEATURED LITERATURE:

Ryom, L et al. Use of Contemporary Protease Inhibitors and Risk of Incident Chronic Kidney Disease in Persons with HIV: The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study. *J Infect Dis 2019; 220:1629-34.*

Data from HIV observational cohorts including D:A:D have found an association between the incidence of chronic kidney disease (CKD) and cumulative exposure to protease inhibitors (PIs) including indinavir, ritonavir-boosted lopinavir, and ritonavir-boosted atazanavir (ATV/r). Suggested mechanisms of renal insult include crystalluria, urolithiasis, and interstitial nephritis. The link of CKD with ritonavir-boosted darunavir (DRV/r) has generally been limited to case reports. This paper from the D:A:D cohort which includes patients from the U.S., Europe, and Australia looked at the association of CKD (eGFR <60 mL/min) and the use of ATV/r and DRV/r in patients followed from 2009 to 2016. The authors adjusted for age, sex, presence of renal risk factors (diabetes, HTN), CD4 count, hepatitis co-infection and other antiretrovirals that can affect renal function including tenofovir disoproxil fumarate. After excluding persons with CKD at baseline, there were 27,675 patients included in the analysis. The median baseline age was 44 years and 74 percent were male. Kidney disease developed in 1642 persons (6%) during a median follow-up of almost seven years. After adjusting for confounding factors, cumulative exposure to ATV/r but not DRV/r remained significantly associated with an increased risk of CKD.

AUTHOR'S COMMENTARY: This study provides some good safety data regarding the long-term use of DRV/ritonavir – and likely DRV/cobicistat, although this latter combination was not specifically addressed in this study. The use of ATV has significantly declined in recent years which is good, as in this D:A:D cohort ATV was associated with a 40% increase in CKD incidence after 4 years of use. Collectively, fewer patients are taking PIs although most patients with multi-class resistance still have a PI as part of their ART regimen and would be expected to stay on these agents long-term until newer salvage agents are available.

FEATURED LITERATURE:

Beer L, et al. Nonadherence to Any Prescribed Medication Due to Costs among Adults with HIV Infection — United States, 2016–2017. *MMWR Morb Mortal Wkly Rep 2019; 68:1129–1133. DOI:http://dx.doi.org/10.15585/mmwr.mm6849a1*

The U.S. spends more per capita on prescription drugs than other high-income countries, and in 2017 patients paid 14 percent of their drug cost out of pocket. It is known that drug costs limit access to medications and thus results in non-adherence by patients. This study from the CDC used data from their Medical Monitoring Project (MMP) and included 3,948 patients with HIV who were taking prescription medications including, but not limited to, antiretrovirals. Persons interviewed at clinical sites participating in the MMP were queried regarding their use of six cost-saving strategies over the past year: 1) asking their doctor for a less expensive medication, 2) skipping doses, 3) taking less medicine, 4) delaying getting a drug refilled due to cost, 5) purchasing their drug from another country, or 6) using alternative therapies. During 2016–2017, 14 percent of these individuals reported using a cost-saving strategy for their prescription medications and 7 percent had cost saving–related nonadherence. Three factors were identified as being associated with drug costs and subsequent nonadherence. These included having an unmet need for medications from ADAP programs, not having Medicaid coverage, and being covered by a private insurance plan. Patients who were non-adherent due to drug costs were more likely to NOT be virally suppressed, more likely to have required a visit to the emergency department and more likely to have been hospitalized. Reducing barriers to ADAP and Medicaid coverage, in addition to reducing medication costs for persons with private insurance, might help decrease nonadherence due to cost concerns. This could also help improve viral suppression rates and other health outcomes among persons with HIV disease.

AUTHOR'S COMMENTARY: In this study, nonadherence to any prescription medication (due to costs) was associated with lack of engagement in care as well as lack of both recent and sustained HIV viral suppression. Addressing financial barriers at every office visit is extremely important if we are to keep our patients virally suppressed and decrease HIV transmission risk. I believe most providers do a good job with adherence counseling, but all members of the patient care team should discuss drug access issues at every visit. I would encourage readers to link to the issue of MMWR cited above, read the full report and share this information with colleagues including nursing, pharmacy and case management staff.

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