

THE AMERICAN ACADEMY OF HIV MEDICINE ■ WINTER 2023

HIV

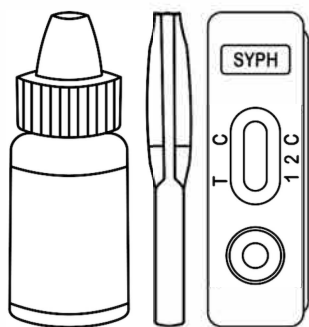
SPECIALIST

A group of healthcare professionals, including a woman in the foreground wearing a white lab coat and a stethoscope, and three men in the background, all looking directly at the camera. The setting appears to be a clinical or hospital environment.

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By BRUCE J. PACKETT II

Executive Director, AAHIVM

New Treatments, New Possibilities

THE COMPLEX LANDSCAPE OF HIV PREVENTION, treatment, and care through the history of the epidemic unfolds like chapters of a novel written in the hand of human resilience and ingenuity. The theme of our winter issue of the *HIV Specialist* centers on the latest horizons and recent developments in HIV prevention, treatment, and care. Having recently observed World AIDS Day this year, we recognize that the historical losses of the epidemic cast a foreboding shadow; but we also are seeing the present situation beckon with an exciting tapestry of clinical possibilities.

Here in this latest issue of *HIV Specialist* we are hoping to offer a cross-sectional glimpse of this transformation. The introduction of long-acting injectables (LAIs) onto the scene for both prevention and treatment, as one major point of reference, is another paradigm shift, forcing us to reconsider so much about a disease (and its treatment modalities) that we've known for so long.

In many of the articles that follow, we move across the horizon of LAIs, exploring their nuances and impact. Dr. Kathy Ton and Dr. Sorosh Kherghenpoug unravel the transformative journey of CAB/RPV LAI coming to market, while envisioning its broader implications. Dr. Julie Darnell lends her expertise to help guide clinics through the logistical complications of incorporating LAIs into practice and offering employable wisdom for those navigating this nascent treatment modality.

Dr. Alexander Nelson, in sharing experiences from his clinic, reinforces the necessity of a multidisciplinary approach to ensure the seamless integration of LAIs into the fabric of HIV treatment. Meanwhile, Dr. Britt Gayle pushes our attention to the realm of broadly neutralizing antibodies (bNAbs), a beacon of hope for those with extensive ART resistance, and sheds light on the outcomes of groundbreaking clinical trials.

In a compelling narrative, Dr. Hannah Zimmerman, Dr. Cara McAnaney, and Dr. Allison Vogl unravel the enigma of Long-Acting Early Viral Inhibition (LEVI)

syndrome, reminding us that, even in the wake of robust progress in the science, inevitably there will remain emerging concerns and complications.

Our CE-certified article, "Emerging Sexually Transmitted Infections: Considerations for the Care Team," by Dr. Ank Nijhawan and Dr. Helen King, invites us to delve into the complexities of current STIs, offering a panoramic view of prevention strategies and the ever-vigilant stance required in the face of emerging challenges.

Finally, our At the Forefront article confronts an uncomfortable truth: PrEP is still not reaching cisgender Black women, who bear a disproportionate burden in the HIV epidemic of today. A call to action resonates through these pages, urging us to center Black women in the broader narrative, to acknowledge their unique and specific challenges, and to weave a more inclusive and, ultimately, effective response to end the HIV epidemic.

The journey toward a world without HIV is ongoing and, in the ebb and flow of progress, we find the stories that propel us forward in our work. I hope that each of these articles offers some practical food-for-thought in the clinic in considering all of the important advancements in care, treatment, and prevention.

A stylized, handwritten signature in black ink, appearing to read "B. J. Packett II".

IN THE NEWS

Winner of the 2023 Cesar Augusto Caceres Award for Technology in HIV Practice Offers Creative Telehealth Program to Overcome Barriers to Care

THE AMERICAN ACADEMY OF HIV MEDICINE and the Institute for Technology in Health Care (ITHC) have awarded the 2023 Cesar Augusto Caceres Award for Technology in HIV Practice to Damien Cares in Indianapolis, Ind. The organization and its president and CEO, Alan Witchey, are being recognized for developing and implementing a creative telemedicine program that helps to expand needed services to individuals who typically face barriers to care. Damien Cares offers individuals in central Indiana access to infectious disease care, primary care, HIV/STI testing, HIV pre-exposure prophylaxis and post-exposure prophylaxis, and mental health and substance use services.

Damien's telehealth program helps to ensure that care is accessible to all clients, including those who may lack transportation, face housing instability, or are struggling with mental illness or substance use disorder. The program has provided patients, free of charge, with 100 tablets, each including an unlimited 4G data connection to allow them to connect with providers. Damien Cares focused on distributing the devices to those most in need: patients who are at the

highest risk of complications and those who are low-income. Early patient surveys conducted by the organization indicated that clients agreed that having a tablet makes it easier to access services at Damien (81%) and they agreed that having a tablet helped them stay in care at Damien (87%).

"Damien's telehealth devices are integral to patient care because they help us overcome a multitude of barriers faced by our most vulnerable clients, reaching patients who might otherwise not have access to telehealth activities," said Mr. Witchey. "I am honored to be recognized by the Academy and ITHC and am committed to continuing this essential program for our patients who are most in need."

Telehealth can improve continuity of care and health outcomes, but it is often inaccessible to many people because they do not have access to technology, such as a laptop or tablet, or connectivity to the internet. Damien Cares serves a large percentage of those patients facing the greatest barriers to access. A high percentage of Damien Cares patients are unstably housed or homeless, have experienced past incarceration, or are dealing with a mental illness and/or substance use disorder. The tablets ensure these patients can access care when and where they need it. In addition to direct contact with providers, the tablets offer clients access to educational videos, complete Google searches for medication and disease related sites, and connect to an online portal where patients can review their medical records, including viral load data and provider notes.

In its twelfth year, the Cesar Augusto Caceres Award for Technology in HIV Practice seeks to acknowledge those who have created, adapted, and/or used innovative technology in their HIV practice and to share that technological knowledge with others in the practice of HIV medicine to improve patient care. The award honors the legacy of Dr. Cesar Caceres, founder of the Institute for Technology in Health Care.

Mr. Witchey hosted an Academy webinar to share best practices and discuss the program outcomes. To watch the webinar, visit <https://aahivm.org/webinars/>.



IN THE NEWS

Latest Data from HRSA Ryan White HIV/AIDS Program Highlight Nine Out of Ten Clients with HIV Are Virally Suppressed

Program Continues to Improve HIV Health Outcomes and Make Progress to End the Epidemic in the U.S. Overall and for High Need Populations

ON DECEMBER 1, in commemoration of World AIDS Day, the U.S. Department of Health and Human Services (HHS), through the Health Resources and Services Administration (HRSA), released the latest Ryan White HIV/AIDS Program data, which show that nine out of 10 people with HIV receiving medical care through the program are virally suppressed. Viral suppression means people with HIV taking their medication cannot sexually transmit HIV and can live longer and healthier lives. The percentage of Black/African American clients, Hispanic/Latino clients, and youth and young adult clients receiving care through the program and achieving viral suppression all far exceed overall national viral suppression rates. This announcement highlights the Ryan White HIV/AIDS Program's vital role in expanding access to care for individuals with HIV, improving HIV health outcomes, and ending the HIV epidemic in the United States.

"The Biden-Harris Administration remains dedicated to supporting people with HIV by increasing HIV awareness, ending stigma, and reducing barriers to HIV prevention and treatment," said HHS Secretary Xavier Becerra. "We have the tools to end the HIV epidemic in the U.S. thanks to our ability to expand upon the vital work of our Ryan White HIV/AIDS Program and community health center program. But we need support to continue this critical fight."

The Ryan White HIV/AIDS Program provides care and treatment services to low-income people with HIV, with a strong focus on tailoring approaches to best meet the needs of high-need communities and addressing factors like access to housing and transportation that directly affect clients' ability to enter and stay in care. The federal Ending the HIV Epidemic in the U.S. (EHE) initiative expands upon the vital work of the Ryan White HIV/AIDS Program

to reach people newly diagnosed with HIV and people with HIV out of care by enhancing linkage to and engagement in care, decreasing disparities, and improving viral suppression. However, the Appropriations Committee in the House of Representatives recently proposed eliminating funding for this initiative.

"Our Ryan White HIV/AIDS Program has made incredible progress over the last 33 years toward making it possible for people with HIV to live long, healthy lives," said HRSA Administrator Carole Johnson. "Today's data highlights that achievement and underscores the importance of sustained investments in HIV care, prevention and treatment activities so that we can end the HIV epidemic in the U.S. once and for all."

New Ryan White HIV/AIDS Program data highlight:

- Nearly 560,000 people with HIV in the U.S. received life-saving care, medication, and essential support services through Ryan White HIV/AIDS Program recipients.
- Nine out of ten clients receiving HIV medical care were virally suppressed in 2022, which means they can live longer and healthier lives without fear of transmitting HIV. This is up from 70 percent of clients virally suppressed in 2010 and significantly higher than 66 percent virally suppressed nationally.
- More than 87 percent of Black/African American clients receiving HIV medical care were virally suppressed and over 91 percent of Hispanic/Latino clients were virally suppressed in 2022. This represents a significant increase from 63 percent (Black/African American clients) and 74 percent (Hispanic/Latino clients) in 2010.
- Among youth and young adult clients aged 13 to 24 years, nearly 84 percent receiving HIV medical care were virally suppressed in 2022, a



major increase from 47 percent in 2010.

The Ryan White HIV/AIDS Program supports recipients that address the epidemic in communities most severely affected by HIV, including cities and counties (Part A); states and territories (Part B); local community-based groups that provide ambulatory health services for people with HIV (Part C); local community-based groups that provide medical care for low-income women, infants, children, and youth with HIV (Part D); and for HIV workforce education and training, oral health care, improving access to HIV care and health outcomes for minorities, and other innovative models of HIV care and treatment (Part F).

To access the new 2022 Ryan White HIV/AIDS Program Client-Level Data Report, visit: <https://ryanwhite.hrsa.gov/sites/default/files/ryanwhite/data/rwhap-annual-client-level-data-report-2022.pdf> - PDF.

To learn more about HRSA's Ryan White HIV/AIDS Program, visit ryanwhite.hrsa.gov.

For more information about HRSA's role in the Ending the HIV Epidemic in the U.S. initiative, visit www.hrsa.gov/ending-hiv-epidemic.

U.S. Syphilis Cases in Newborns Continue to Increase

A 10-Times Increase Over a Decade

THE CDC is recommending concerted action to stop the increase of newborn syphilis cases and continues to sound the alarm about the consequences of a rapidly accelerating epidemic of sexually transmitted infections in the United States. Syphilis during pregnancy can cause tragic outcomes, like miscarriage, stillbirth, infant death, and lifelong medical issues. Newborn syphilis occurs when mothers do not receive timely testing and treatment during pregnancy.

New CDC data reveal that more than 3,700 babies were born with syphilis in 2022, which was more than 10 times the number in 2012. The increase in newborn syphilis follows rising syphilis cases among women of reproductive age combined with social and economic factors that create barriers to high-quality prenatal care and ongoing declines in the prevention infrastructure and resources.

“The congenital syphilis crisis in the United States has skyrocketed at a heartbreaking rate,” said CDC Chief Medical Officer Debra Houry, MD, MPH. “New actions are needed to prevent more family tragedies. We’re calling on health care providers, public health systems, and communities to take additional steps to connect mothers and babies with the care they need.”

Key findings

Almost nine in 10 cases of newborn syphilis in 2022 might have been prevented with timely testing and treatment during pregnancy.

- More than half were among people who tested positive for syphilis during pregnancy but did not receive adequate or timely treatment.
- Nearly 40 percent were among mothers who were not in prenatal care.

One of the biggest risk factors for syphilis for some people is where they live. According to previous CDC data, in 2021, more than 70 percent of the U.S. population lived in counties considered to have high rates of syphilis among reproductive-age women (above the Healthy People 2030 target).

Barriers to timely syphilis testing and treatment during pregnancy

Missed opportunities to prevent newborn syphilis during pregnancy are due to a combination of individual and system-level barriers to timely syphilis testing and treatment. Individual-level barriers may include lack of insurance and substance use disorder, while system-level barriers may include systemic racism and limited health care access.

Tailored prevention strategies are critical to addressing newborn syphilis disparities

People from racial and ethnic minority groups are experiencing the brunt of the newborn syphilis epidemic. While newborn syphilis cases are increasing overall, babies born to Black, Hispanic, or American Indian/Alaska Native mothers were up to eight

times more likely to have newborn syphilis in 2021 than babies born to White mothers. Such disparities stem from decades of deeply entrenched social determinants of health that create greater obstacles to quality health care services and result in health inequities such as higher rates of syphilis in some communities. Community health workers, including local patient navigators, case managers, and disease intervention specialists, are critical components to developing tailored strategies to reduce newborn syphilis in every community. They play one of the most powerful roles in addressing racial and ethnic disparities in congenital syphilis.

“The congenital syphilis epidemic is an unacceptable American crisis. All pregnant mothers—regardless of who they are or where they live—deserve access to care that protects them and their babies from preventable disease,” said Jonathan Mermin, MD, MPH, director of the CDC’s National Center for HIV, Viral Hepatitis, STD, and TB Prevention. “Our nation should be proactive and think beyond the OB/GYN’s office and bridge prevention gaps. Every encounter a health care provider has with a patient during pregnancy is an opportunity to prevent congenital syphilis.”

CDC is urgently encouraging public health leaders and any health care provider with pregnant or reproductive-age patients to:

- Consider starting syphilis treatment right away following a positive rapid syphilis test during pregnancy if the patient faces greater obstacles to ongoing care (and still send for full confirmatory syphilis testing for optimal patient follow-up).
- Use rapid syphilis testing and treatment during pregnancy in settings such as emergency departments, syringe service programs, prisons/jails, maternal and child health programs.
- Address syphilis before pregnancy in counties with high syphilis rates, by offering to screen sexually active women and their partners for syphilis, as well as people with other risk factors for syphilis.
- Work with local community health workers who can help to overcome additional barriers to syphilis testing and treatment during pregnancy.

Due to the increase in cases of syphilis and congenital syphilis in the United States, senior leadership at the U.S. Department of Health and Human Services established the National Syphilis and Congenital Syphilis Syndemic Federal Taskforce dedicated to spearheading a national syphilis and congenital syphilis public health response. The overarching mission of this task force is to address the syndemic of syphilis and congenital syphilis, reduce their rates, promote health equity, and share resources with impacted communities.

For more information about this report, go to www.cdc.gov/vitalsigns.



IN THE NEWS

SAMHSA Announces Nearly \$35M in Grant Awards for Comprehensive Behavioral Health Care and HIV Prevention and Care for Historically Underserved Populations

THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) through the Substance Abuse and Mental Health Services Administration (SAMHSA) awarded nearly \$35 million in grant funding [in October 2023] to bring essential behavioral health services and HIV prevention and care to historically underserved populations. Health equity remains a critical focus of the Biden-Harris Administration, and these funds represent the continued commitment by the administration to address and remedy inequity of care.

Addressing the mental health crisis and beating the opioid epidemic are two core pillars of President Biden's Unity Agenda for the nation. The grant awards facilitate ongoing efforts throughout the nation in treatment, recovery support, and harm reduction, advancing the Biden-Harris Administration's National Drug Control Strategy and supports the goals of the National HIV AIDS Strategy.

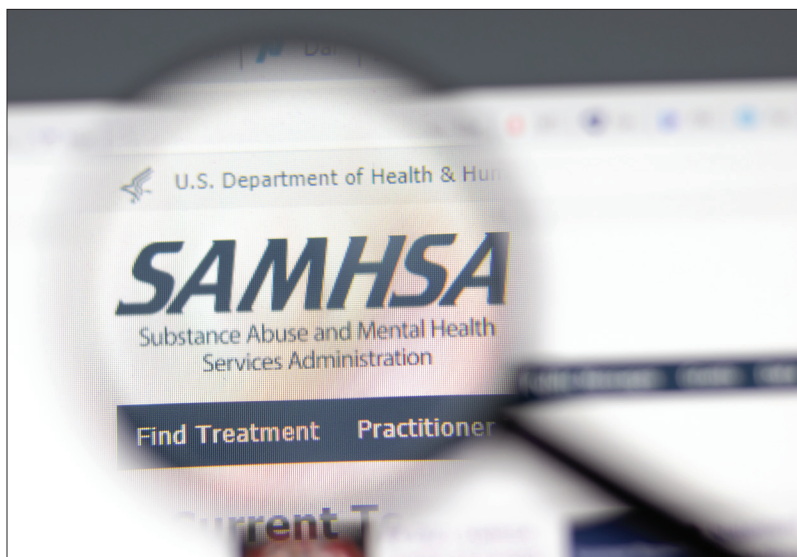
"The Administration remains deeply invested in ensuring those who need prevention services, treatment, and support receive the essential care they need," said HHS Secretary Xavier Becerra. "The dedicated work of these awardees

ensures our best efforts are thoughtfully and strategically implemented where they are most needed."

"These specific funds will help support programs that bring special emphasis to those who have historically not had equitable access to behavioral health care and infectious disease services," said Miriam E. Delphin-Rittmon, PhD, the HHS Assistant Secretary for Mental Health and Substance Use, and the leader of SAMHSA. "The HIV prevention and substance use services provided through this grant will help to improve overall health and wellness of individuals and communities across the country."

The awards include:

- \$21.9 million for the Minority AIDS Initiative: Substances Use Disorder Treatment for Racial/Ethnic Minority Populations at High Risk for HIV/AIDS. This program increases engagement in care for racial and ethnic medically underserved individuals with substance use disorders (SUDs) and/or co-occurring SUDs and mental health conditions (COD) who are at risk for or living with HIV. Award recipients will take a syndemic approach to SUD, HIV, and viral hepatitis.
- \$10.5 million for the Minority AIDS Initiative: Substance Use and Human Immunodeficiency Virus Prevention Navigator Program for Racial/Ethnic Minorities. This program provides substance use and HIV prevention services to racial and ethnic minority populations at high risk for SUDs and HIV infection. The program places emphasis on those who identify as Lesbian, Gay, Bisexual, Transgender, Queer/Questioning, and Intersex persons who are not in stable housing and/or reside in communities with high rates of HIV, viral hepatitis (including Hep A, B, and C), and/or sexually transmitted infections.
- \$1.9 million for the Minority HIV/AIDS Fund: Integrated Behavioral Health and HIV Care for Unsheltered Populations Pilot Project. This pilot program provides comprehensive health care for racial and ethnic medically underserved people experiencing unsheltered homelessness through the delivery of portable clinical care delivered outside that is focused on the integration of behavioral health and HIV treatment and prevention services.



HHS, SAMHSA Release 2022 National Survey on Drug Use and Health Data



ON NOVEMBER 13, the U.S. Department of Health and Human Services (HHS), through the Substance Abuse and Mental Health Services Administration (SAMHSA), released the results of the 2022 National Survey on Drug Use and Health (NSDUH). The report shows how people living in United States reported about their experience with mental health, substance use, and treatment related behaviors in 2022. The report is accompanied by a high-level brief that includes infographics.

"The National Survey on Drug Use and Health provides an annual snapshot of behavioral health nationwide," said HHS Secretary Xavier Becerra. "This data informs knowledge, policy, and action, and drives our shared commitment across government, health care, industry, and community to offer resources and services to those in need."

The NSDUH report provides nationally representative data on the self-reported use of tobacco, alcohol, and illicit drugs; substance use disorders; mental health conditions; suicidal thoughts and behaviors; and substance use and mental health treatment among the civilian, noninstitutionalized population aged 12 or older in the United States. The NSDUH estimates allow researchers, clinicians, policymakers, and the general public to better understand and improve the nation's behavioral health. Addressing the nation's mental health crisis and drug overdose epidemic is a top priority of the Biden-Harris Administration and a core pillar of the Administration's Unity Agenda.

"To tackle the behavioral health crisis in this nation, we need to fully understand the issues surrounding mental health and substance use, and the impact they have on people and communities," said Deputy Secretary Andrea Palm. "The Biden-Harris Administration is committed to meeting people where they are with information, resources, and support. The 2022 National Survey on Drug Use and Health allows us to follow an evidence-based path forward as we provide support for those struggling with substance use and work to build healthier futures."

"The data released today is crucial for informing our policies, protocols, and understanding of our nation's health," said HHS Assistant Secretary for Mental Health and Substance Use Miriam E. Delphin-Rittmon, PhD, the leader of SAMHSA. "This important work better situates policy makers, researchers, practitioners, and the general public to understand the collective behavioral health needs across the country and anticipate the needs of future generations."

The 2022 NSDUH report includes the following key findings:

- Among people aged 12 or older in 2022, 59.8 percent (or 168.7 million people) used tobacco products, vaped nicotine, used alcohol, or used an illicit drug in the past month (also defined as "current use"), including 48.7 percent (or 137.4 million people) who drank alcohol, 18.1 percent (or 50.9 million people) who used tobacco products, 8.3 percent (or 23.5 million people) who vaped nicotine, and 16.5 percent (or 46.6 million people) who used an illicit drug.
- In 2022, 70.3 million people aged 12 or older (or 24.9%) used illicit drugs in the past year. Marijuana was the most used illicit drug, with 22.0 percent of people aged 12 or older (or 61.9 million people) using it in the past year.

- In 2022, 48.7 million people aged 12 or older (or 17.3%) had a substance use disorder (SUD) in the past year, including 29.5 million who had an alcohol use disorder (AUD), 27.2 million who had a drug use disorder (DUD), and 8.0 million people who had both an AUD and a DUD.
- In 2022, almost one in four adults aged 18 or older had any mental illness (AMI) in the past year (59.3 million or 23.1%).
- Among adolescents aged 12 to 17 in 2022, 19.5 percent (or 4.8 million people) had a past year major depressive episode (MDE).
- One in 20 adults aged 18 or older had serious thoughts of suicide in the past year (13.2 million or 5.2%), 1.5 percent (or 3.8 million people) made a suicide plan, and 0.6 percent (or 1.6 million people) attempted suicide in the past year.
- Over one in eight adolescents aged 12 to 17 had serious thoughts of suicide in the past year (13.4% or 3.4 million adolescents), one in 15 made any suicide plans (6.5% or 1.7 million adolescents), and nearly one in 25 (3.7% or 953,000 adolescents) attempted suicide in the past year.



About the National Survey on Drug Use and Health

Conducted each year by the federal government since 1971, the NSDUH is a primary source of statistical information on self-reported substance use and mental health of the U.S. civilian, noninstitutionalized population 12 or older. The NSDUH measures include:

- Use of illegal drugs, prescription drugs, alcohol, and tobacco,
- Substance use disorder and substance use treatment,
- Major depressive episodes, suicidal thoughts and behaviors, and other symptoms of mental illness, mental health care, and
- Recovery from substance use and mental health disorders.

What We've Learned and What We Can Look Forward To

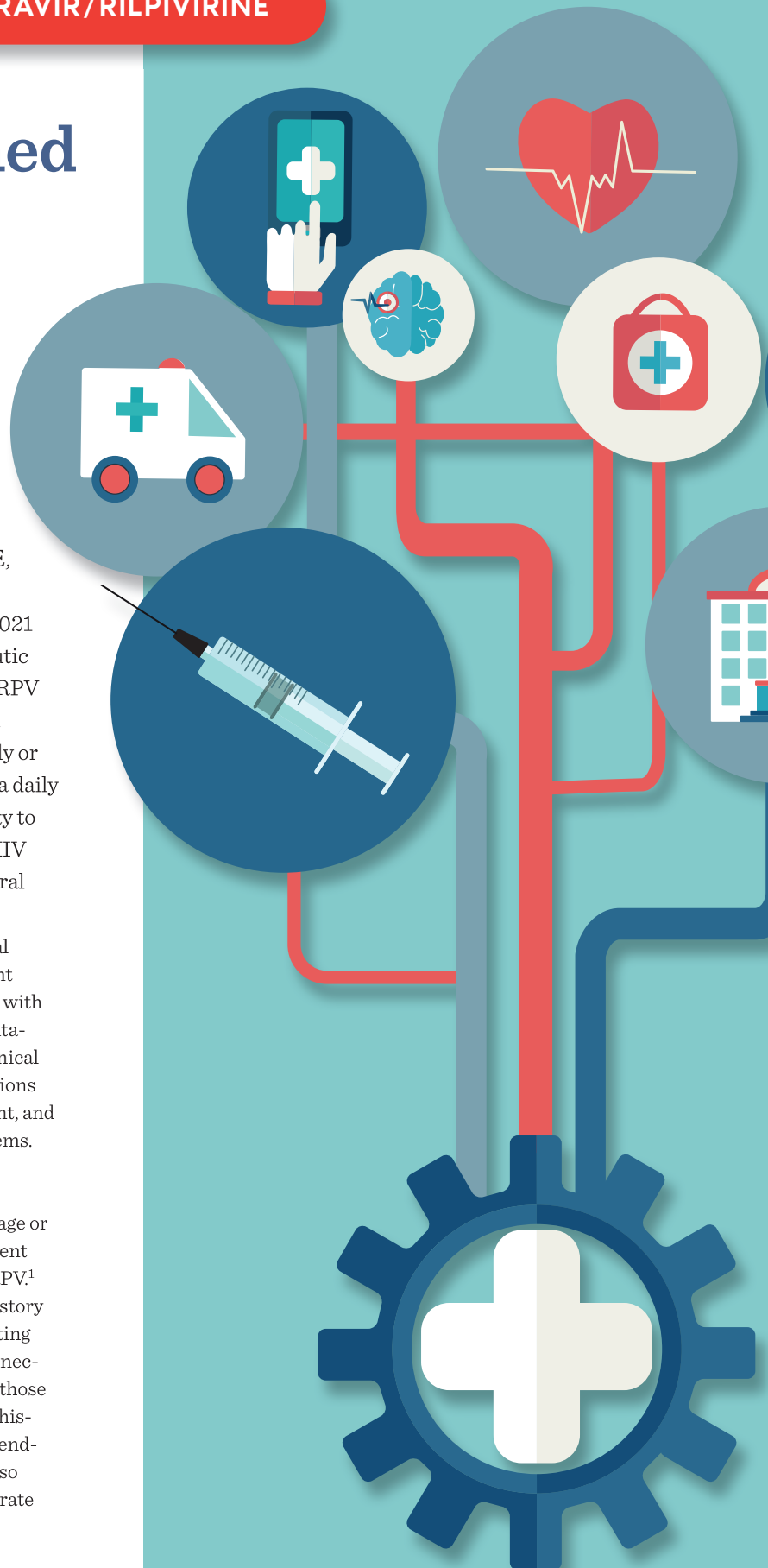
By Kathy Ton, PharmD, AAHIVP, and
Sorosh Kherghehpoush, PharmD, AAHIVP

IN ABSENCE OF A VACCINE OR A CURE, the approval of long-acting (LA) injectable cabotegravir/rilpivirine (CAB/RPV) in January 2021 has proven to be one of the most exciting therapeutic advancements in the HIV landscape. LA injectable CAB/RPV is the first and only intramuscular injection approved as a complete regimen for the treatment of HIV. These monthly or bimonthly injections have eliminated the requirement of a daily oral regimen for treatment and allowed for the opportunity to rid patients of an uncomfortable daily reminder of their HIV status, to reduce the worry surrounding missed doses of oral antiretroviral therapy (ART) and improve health privacy.

Despite the approval of CAB/RPV over two years ago, several studies have highlighted implementation barriers and important considerations when selecting this treatment option for people with HIV (PWH). Challenges seen in the first few years of implementation at our Federally Qualified Health Center and important clinical considerations are detailed here as lessons learned and suggestions on how to improve the process, as the direction of HIV treatment, and even prevention, shifts towards novel medication delivery systems.

Eligibility of Therapy

Individuals are candidates for CAB/RPV if they are 12 years of age or older, weigh at least 35 kilograms, are without history of treatment failure, and have no known or suspected resistance to CAB or RPV.¹ Extensive review of a person's health history, which includes history of viral resistance or treatment failure, is essential prior to starting someone on CAB/RPV. Review of an HIV genotyping history is necessary to ensure no risk of treatment failure with CAB/RPV. In those who are already virally suppressed with unclear or unavailable history, archived genotyping may be necessary. Use is not recommended for individuals who have active hepatitis B unless they are also receiving oral hepatitis B treatment. Individuals must demonstrate



appropriate adherence to their current, stable ART and be virally suppressed for at least six months prior to initiation of CAB/RPV, which is often more challenging for certain demographics, including those with housing instability, comorbid psychiatric conditions, substance use, or mistrust of the medical system.^{2,3,4,5}

Real-world data shows that there is a high prevalence of sub-optimal compliance to ART, suggesting that this treatment may only be an option for a subset of our PWH in the United States.⁶ Currently, no randomized controlled trials exist that have studied the use of CAB/RPV in those with detectable viral loads. Therefore, CAB/RPV is currently not recommended for use in this population. Though not specifically detailed in the labeling for CAB/RPV, clinicians and other members of the care team must consider all the social, structural, and behavioral barriers that may impact patient adherence to both medication and clinical care, which may not be addressed by a change from oral to LA therapies.

Cost and Coverage

Unlike traditional ART, it is not clear whether CAB/RPV can be accessed through pharmacy or medical benefits and it requires additional steps to investigate insurance coverage and out-of-pocket costs for the individual receiving therapy. The oral lead-in (OLI) portion of treatment must be acquired through the manufacturer rather than a local community pharmacy and is provided at no cost to the patient. Fortunately, as of March 2022, the OLI portion of treatment has become optional rather than a requirement based on the findings seen in the extension period of FLAIR, a phase 3 open-label trial.⁷ This trial showed that safety, tolerability, and efficacy of treatment remained the same in those transitioning directly from their current oral ART without OLI compared to those who transitioned to OLI prior to their injections of CAB/RPV.

Initiating patients on the OLI may enhance the risk of disrupting their adherence to therapy and create more pill burden. In addition to this, there are food requirements with oral RPV for appropriate absorption, which may be an additional barrier for those who experience food insecurity. Despite this change, OLI may still be offered or recommended on a case-by-case basis. The overall experience with obtaining the OLI is simple but can be time consuming when coordinating delivery for individuals experiencing homelessness. On the other hand, acquisition and administration of the injectable agents may not be as straight-forward. Government programs typically cover treatment through pharmacy benefits, which allows for our in-house pharmacy to dispense the medication to the medical staff directly for administration. Other clinics/insurance providers may require utilization of specialty pharmacies that require a higher level of coordination, which has proven to be time- and labor-intensive and, ultimately, has led to further delays in starting therapy. Commercial or private plans cover CAB/RPV under medical benefits that require authorization and approval prior to medication administration. Other commercial plans may exclude LA CAB/RPV altogether, which is an insuperable barrier.

Evaluation of payor mix, or the percentage of patients with federal health insurance compared to private insurance or self-pay, among the clinic population can help to determine what resources are necessary to improve access to CAB/RPV. Other cost considerations

include proper storage of treatment (ex. cold chain supply) as well as space for injection administrations that limit disruptions to current workflow.

Administration

CAB/RPV is only approved to be administered by a health care provider in a professional setting. CAB and RPV are not co-formulated into one single injection and must be given as two separate injections on opposite sides or on the same side at least two inches apart in a single visit. Though advertised as an intramuscular injection, the volume may be two to three milliliters per injection based on the dose being administered, meaning that these injections must be administered into a large muscle, such as the gluteal muscle, to reach the appropriate tissue layers. Utilizing the “z-track” method can help to ensure appropriate tissue penetration and the preferred site of administration is the ventrogluteal area, though dorsogluteal sites may also be utilized. Individuals with buttock implants or soft tissue fillers may not be good candidates for CAB/RPV due to inadequate concentrations of CAB and/or RPV. Furthermore, body mass index (BMI) greater than 30 kg/m² was seen as a potential risk factor for treatment failure with CAB/RPV.⁸ Use of a two-inch needle for injecting CAB/RPV is recommended for these patients, which is not available with the original product packaging.

CAB and RPV injections require refrigeration and injections must come to room temperature for a minimum of 15 minutes prior to administration, which requires careful timing. Once the injections have been prepared, they must be administered within two hours.¹ Those who live in rural areas may have difficulty finding qualified health care providers or qualified sites for administration that are geographically feasible for travel. Traveling to a separate clinic for injections that is not the office of the primary care provider may pose additional difficulties for some individuals with transportation barriers. Although frequent clinic visits are a barrier for some, monthly or bimonthly visits may also afford the time and opportunity for mental and physical health screenings, treatment updates, medication reconciliation, vaccination administration, and help to close care gaps.



Adherence to Clinic Visits

Currently, CAB/RPV is recommended to be administered as two separated intramuscular injections every one or two months. Strict adherence to injection appointments is necessary for optimal treatment and maintenance of viral suppression. Patients are educated to pick one day of the month, known as their target date, for their injections. The dosing window allows an individual to receive their injections seven days before or seven days after their target date as a grace period without needing to re-initiate therapy. Real-life challenges to keeping injection appointments include acute illness, mental illness, inconsistent transportation, forgetfulness, work schedules, competing life priorities, and side effects to CAB/RPV.⁹

Health care facilities should also provide individuals with the tools necessary to adhere to injection schedules. Booking appointments ahead of time can help to reduce chances of missed injections and gaps in treatment, and frequently assessing for planned missed doses allows for facilitation of oral ART to bridge a patient to their next injection dose. Clinicians and other care team members must assess these barriers and can work with clinic leadership to adjust hours of operation to accommodate injection visits for those with work schedules during standard operating hours. A sustainable reminder system for injection appointments should also be considered, and confirmation of appropriate means of communication between clinic staff and patients is vital in ensuring long-term success on CAB/RPV therapy.

Additional Resources

Evidence from studies such as CUSTOMIZE highlighted that teamwork and precise planning were important keys to successful implementation of CAB/RPV services.¹⁰ Investment of financial resources and staffing changes may be necessary for sustained success. These monthly and bimonthly injections may be new procedures for both clinics and patients. Clinics may need to increase staffing to support the service with administering medication, addressing scheduling concerns,

and providing reminder calls to patients. Close monitoring and tracking of all patients and injection appointments may be necessary to ensure adequate dosing periods and to determine the need to facilitate oral bridging.

It is pertinent that all staff involved are adequately trained in the importance of timing for this service. Patients on CAB/RPV therapy will need to adjust their personal schedules and communicate anticipated missed visits with the clinic in advance to avoid gaps in therapy. Prescribers may benefit from working closely with case managers to help retain patients in care, as support staff members of the care team may have a closer relationship or more frequent touchpoints with patients.^{11,12} These team members can also be crucial in helping to determine eligibility of LA CAB/RPV based on social barriers that may be present for a patient. Case managers can help improve engagement in care and support a clinician's decision to change an individual's oral therapy to LA injectable treatment.

Other Considerations

There are slight clinical differences between monthly and bimonthly injections and these key differences may guide treatment for specific patients. In the phase 3 study comparing monthly versus every-two-months injections, individuals administered CAB/RPV every two months were seen to have a higher rate of resistance to CAB and RPV, resulting in treatment failure.¹³ Data presented at the Conference on Retroviruses and Opportunistic Infections (CROI) 2023 showed that high BMI and absence of OLI may be factors that increase risk of subtherapeutic drug levels of CAB/RPV and suggest that OLI may need to be considered for these specific individuals to maintain adequate drug concentrations.¹⁴

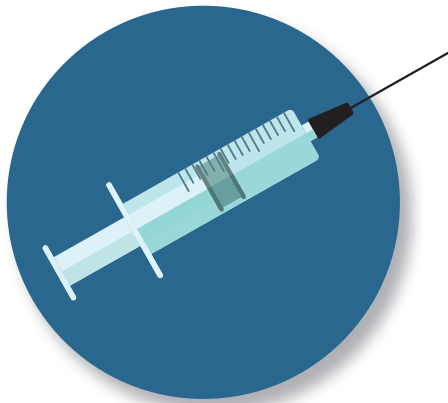
LA formulations afford the opportunity for less frequent administration of medications, but they are not without risk. One of the key pharmacokinetic attributes of drugs that make for a suitable LA formulation is a long half-life. The half-life of LA CAB and RPV has been reported to be 20 to 65 days

and 30 to 90 days, respectively, with concentrations of both drugs being detected for up to one year after last injection.^{15,16} The half-lives of these drugs allowed for the efficacy and approval of bimonthly dosing that is an advantage in those with adherence challenges. However, this also poses a potential risk of developing virologic resistance in that after abrupt discontinuation of therapy, individuals are exposed to increasingly lower concentrations of CAB and RPV over time, leading to subtherapeutic drug levels that are insufficient to maintain viral suppression.¹⁶ For individuals engaged in care, this can be overcome by continuing or resuming oral ART. It is important to provide comprehensive counseling to patients regarding these risks to minimize impact on future therapy options.

Future Considerations

Phase 3 clinical trials involving CAB/RPV showed high rates of adherence, but practical questions surrounding efficacy outside of a clinical trial setting still exist. Currently, CAB/RPV is only available for individuals who are virally suppressed, but limiting this treatment option to this portion of the population does not help to expand access to our hard-to-reach populations who have difficulty achieving viral suppression. One unique study that looked at a safety-net population of PWH in San Francisco reported that 12 of 15 individuals with detectable viremia prior to CAB/RPV achieved and maintained viral suppression or had a two-log decline in viral load within one month of their first injection. Two of these patients had long histories of HIV infection (greater than 10 years) and had never been virally suppressed in the past.¹⁷ Although this study had a small sample size and short duration, the data is promising for individuals who may have identified barriers to adhering to oral ART due to substance use, severe mental illness, or being unhoused.

There is some literature also exploring CAB/RPV as an option for those who are unable to achieve viral suppression on traditional regimens, those with advanced disease, and those with multiple



Currently, CAB/RPV is only available for individuals who are virally suppressed, but limiting this treatment option to this portion of the population does not help to expand access to our hard-to-reach populations who have difficulty achieving viral suppression.

complex comorbidities.¹⁸ Reviewing new and available data frequently will allow clinicians the opportunity to prescribe and use this therapy for broader populations. With additional research and clinician advocacy, LA CAB/RPV use may expand beyond only those with suppressed viral loads.

Conclusion

Many barriers exist with CAB/RPV implementation that may be easily managed while others are more difficult to overcome. Intense collaboration among members of the care team, use of external support, and excellent communication will be necessary for successful implementation in the short term, and for future expansion of use in individuals with viremia. Lessons learned from LA CAB/RPV injections, from clinic and patient perspectives, can improve access to care, help to increase rates of viral suppression, and contribute to ending the HIV epidemic. **HIV**



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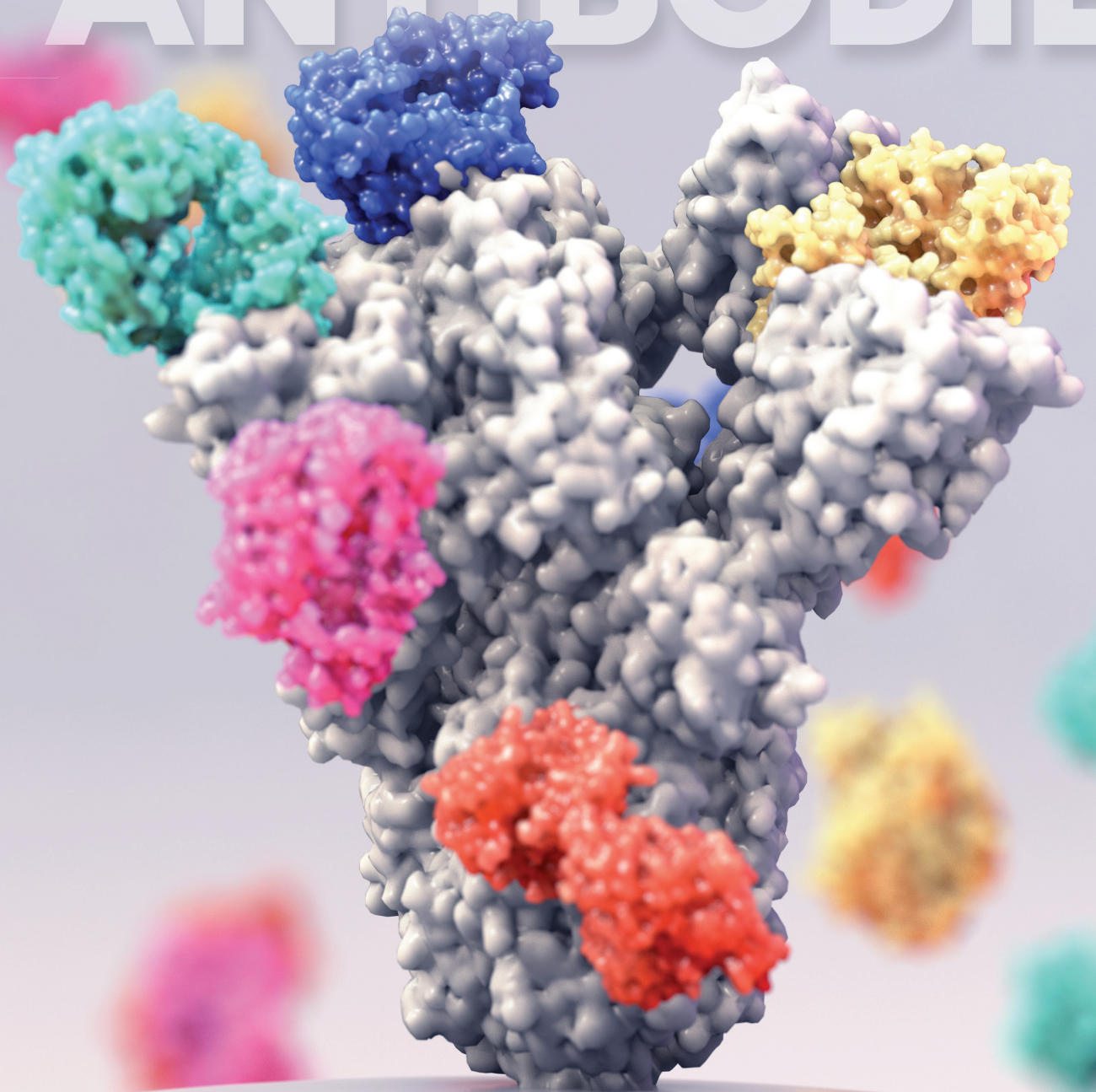


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BROADLY NEUTRALIZING ANTIBODIES



Exploring the Potential for the Prevention and Management of HIV Among Adults

By Britt Gayle, MD, MPH, AAHIVS

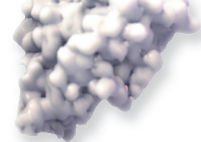
SOME PEOPLE WITH HIV (PWH) struggle maintaining sufficient adherence to oral antiretroviral therapy (ART) and therefore do not attain viral suppression. While long-acting antiretrovirals (ARVs) are available and remain a priority, most of them rely upon established mechanisms of action and have minimal impact upon the viral reservoir. Furthermore, the risk of side effects predominantly associated with long-term use of ARVs remains a present, though significantly reduced, concern.

Licensed immunoglobulins are available for anthrax, respiratory syncytial virus, rabies, and most recently SARS-CoV-2. Ibalizumab, a humanized IgG4 monoclonal antibody that targets CD4, is approved for use among people with extensive ART resistance and immunoglobulin combinations with broader coverage are being evaluated for efficacy in treating and preventing HIV infection.

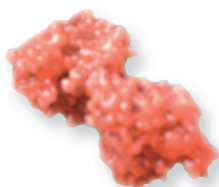
Broadly Neutralizing Antibody Development for HIV Treatment

Approximately 10 to 30 percent of individuals with HIV develop broadly neutralizing antibodies (bNAbs) that bind conserved, less variable regions of the HIV-1 envelope that are transiently exposed during the cell attachment process. BNabs typically develop after two to three years of infection, of which less than one percent exhibit elite neutralizing activity.^{1,2} Most bNAbs are isolated from elite neutralizers, slow progressors or non-progressors with consistent low-to-moderate viremia and preserved CD4 counts.

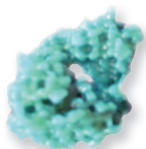
Attempts at using anti-HIV-1 antibodies as therapeutic agents started in the 1980s with use of inactivated hyperimmune plasma from PWH. In 1994 a CD4 binding site directed antibody, b12, was the first HIV-bNAb isolated from an asymptomatic individual.³ Subsequent studies observed that the administration of antibodies to the HIV core antigen (anti-p24) resulted in clearance of the p24 antigen for up to 11 weeks.



The bNAbs currently under investigation target epitopes on the HIV-1 envelope spike (Env), such as the CD4 binding site, V1/V2 loop, V3 loop, gp41 membrane proximal external region, gp120/gp41 interface, fusion peptide, and the silent face of gp120 (Table 1).¹ Two sets of mutations, the M428L/N434S (LS) and the M252Y/S352T and T256E mutations (YTE) in the Fc domains extend the half-life of the parental monoclonal antibodies, allowing for q6 month administration.⁴ The “J” mutation is inserted between the complementarity-determining regions to improve stability and manufacturability.⁵



Approximately 10 to 30 percent of individuals with HIV develop broadly neutralizing antibodies (bNAbs) that bind conserved, less variable regions of the HIV-1 envelope that are transiently exposed during the cell attachment process.



Due to the complexity and diversity of the HIV-1 envelope as well as HIV's mutation rate, bNAb monotherapy can transiently suppress virus sensitive to the particular bNAb but lacks the neutralization breadth to cover rebound competent viruses in the viral reservoir and prevent resistance emergence, resulting in the loss of suppression. The most recent phase of bNAb research is therefore focusing on combination therapy, more specifically multibody, bispecific, and trispecific bNAbs that combine antigen binding fragments (Fabs) from different antibodies. There are also early data suggesting that more recent samples of HIV-1, particularly clade B and C viruses have demonstrated more frequent and broader resistance to some of the bNAbs, most of which were isolated several years ago.

Combination Broadly Neutralizing Antibody Regimens

One well-studied bNAb combination is 3BNC117 and 10-1074, which targets nonoverlapping HIV-1 Env sites. One notable trial recruited participants who were virally suppressed on ART for a median of 8.5 years, provided up to seven doses of 3BNC117 and 10-1074 over 20 weeks, and assigned them to one of two groups without any prescreening for antibody resistance; ART discontinuation two days after bNAb infusion (group 1) and ART discontinuation 26 weeks after bNAb infusion (group 2). Among 17 group one participants, 13 maintained virologic suppression for at least 20 weeks with a median time to rebound of 28.5 weeks.³ A statistically significant decline in the size of the HIV reservoirs was also observed. Another study examining the impact of the same regimen among participants who started ART during acute/early HIV found that five out of seven participants maintained viral suppression for over 28 weeks, with a median time to rebound of 33 weeks (seven to 43 weeks).

Another trial examined the efficacy of a combination of three bNAbs in reducing viral load: PGDM1400, PGT121, and VRC-07-523LS. Despite a significant decline in viral load within 10 days of bNAb infusion, virological rebound occurred approximately 20 days later, indicating the continued need for optimization of bNAb combinations to overcome antibody resistance.⁶

Additional trials are examining bispecific and trispecific bNAbs, such as VRC01/10E8v4-PGDM1400-LS (SAR441236), VRC01/PGDM1400/10E8, and PGDM1400LS + VRC07-523LS/PGT121.414. LS. The bNAb 10E8.4/iMab has demonstrated exquisite breadth and potency in vitro and is currently in clinical trials.⁷ Some HIV-1 clades appear to be neutralized by more diverse combinations of bNAbs than others. For example, clade A/E viruses are poorly neutralized by V3 loop bNAbs, clade B viruses appear to be better targeted by MPER/V3/CD4bs combinations, and clade C viruses appear to be better targeted by V2/V3/CD4bs combinations.⁸

Non-neutralizing Functions

Antigen specific antibodies have two key functional components, the Fab and the fragment crystallizable region (Fc). In addition to their antigen binding and viral neutralization properties, bNAbs have a variety of non-neutralizing antibody immunomodulatory functions that are still under investigation that may facilitate the elimination of virus-infected cells. The Fc portion of the antibody interacts with the Fc receptors on effector cells, such as natural killer cells or phagocytes for antibody-dependent cellular cytotoxicity.

Complement dependent cytotoxicity activated by bNAbs appears to be specific to some epitopes, namely the CD4 binding site and the V3 loop. Recent evidence also indicates that bNAbs tether virions at the surface of infected cells, trapping them in membrane-associated immune complexes and enhancing antigen presentation.⁹ However, enhanced immune responses are not consistently observed and the clinical significance of the enhanced magnitude and breadth of the immune response when observed is unclear.^{2,10}

Table 1. Summary of bNAb class characteristics^{1,5,7}

Epitope	Antibody	Serum Half-life	Median IC80	Breadth at IC80<10ug/ml(%)	Additional comments
V1/V2 loop	PGDM1400	ND	0.033	72	CAP256-VRC26.25 is considered the most potent, especially against clade C isolates
	CAP256V2L2	ND	0.004	48	
V3 loop	PGT121	23.5	0.098	55	Highly potent against clade B & C viruses but poorly neutralize CRF 01_AE strains.
	PGT1212.BJ414LS	ND	0.051	50	
	Elipovimab	26	0.18	60	
	10-1074	24	0.126	59	
	10-1074LS	ND			
	10-1074LS-J	ND			
CD4 binding site	VRC01	15	0.966	85	Take longer to develop in natural infection. N6 has demonstrated the ability to potentially neutralize 80% of HIV-1 strains that were resistant to VRC01
	VRC01-LS	71			
	VRC07-523LS	38	0.24	94	
	N6LS	44	0.238	96	
	3BNC117	17	0.298	78	
	3BNC117LS	ND			
	3BNC117LS-J	ND			
Bispecific	10E8v2.0/iMab	ND	0.008	97.5	
Trispecific	SAR441236 (VRC01-LS/PGDM1400/10E8v4)	ND	0.095	96	
			IC50 range (ug/mL)		
Silent face			3.u714	53–62	
Gp120/41			0.023–1.115	56–72	
Fusion peptide			0.359	73%	
Membrane Proximal External Region Epitope (MPER)			0.299–6.06	58–99%	Broadest overall global viral coverage. 10E8 and DH511 are among the most potent molecules

Routes of Administration

Most clinical trials have investigated intravenous infusion, with evidence of systematic distribution with the exception of the central nervous system. However, intramuscular and subcutaneous delivery is also being investigated, with many subcutaneous formulations containing hyaluronidase to modify the

subcutaneous space and permit administration of larger volumes.

While the majority of studies examining subcutaneous delivery have demonstrated safety and pharmacokinetics similar to intravenously administered bNAbs, a phase 1 study evaluating the subcutaneous administration of 10E8VLS alone or in combination with

VRC07-523LS was suspended due to safety concerns regarding local reactogenicity, with seven out of eight participants who received 10E8VLS at 5mg/kg subcutaneously developing erythema and induration within 24 hours. A biopsy from one participant with induration was significant for a nonspecific injection site reaction and panniculitis.¹¹

The CAPRISA 012A study, a randomized, double-blinded, placebo-controlled dose-escalation phase 1 trial observed adverse event outcomes among 45 HIV negative women randomized to one of nine groups assigned to receive VRC07-523LS and/or PGT121 subcutaneously. Participants were monitored for adverse events for 24 weeks. All reported reactogenicity events were mild and resolved within three days, and the most common events were injection site tenderness and headache, despite participants receiving higher doses than the 3-5mg/kg subcutaneous doses administered in previous trials. The neutralizing activity of VRC07-523LS and PGT121 was not reduced by subcutaneous delivery.¹²

The CAPRISA 012B study was a dose-escalation phase 1 trial that evaluated the safety, pharmacokinetics, and neutralization activity of CAP256V2LS alone and in combination with VRC07-523LS in women in Durban, South Africa, and included a subcutaneous delivery arm. No serious adverse events or dose-limiting toxicities were observed.

The CAPRISA 012C study is an ongoing double-blinded, randomized, placebo-controlled phase 2 trial conducting an extended safety and pharmacokinetic evaluation of subcutaneously delivered CAP256V2LS and VRC07-523LS among HIV negative women in South Africa and Zambia. The trial will also look for a prevention efficacy signal.

Broadly Neutralizing Antibodies and Antiretroviral Therapy Regimens

Clinical evaluation of these combination regimens is still in its early stages, however a phase 1a clinical trial involving the combination of lenacapavir, teropavimab, and znlirvimab (with randomization between two doses) found that 18 of 20 participants maintained virologic suppression for over 26 weeks. One participant experienced viral rebound at week 16 but resuppressed after resuming his baseline ART regimen. Inclusion criteria included virologic suppression on ART for at least two years and susceptibility to both bNABs, with only 45 percent of those screened meeting the second criterion.⁴ A pilot study examining the safety and efficacy of monthly cabotegravir and bimonthly VRC07-523LS is fully enrolled.^{4,13}

While second generation integrase inhibitors are well known for their relatively high barrier to resistance, the emergence of cabotegravir resistance in the setting of PrEP failure and lenacapavir resistance in the setting of treatment failure serve as reminders of the risk of resistance in the setting of a bNAb plus ARV combination that would result in ARV monotherapy.

Broadly Neutralizing Antibody Development for HIV prevention

The first bNAb evaluated for prevention in an efficacy trial was VRC01 among men who have sex with men in the Americas and heterosexual women in sub-Saharan Africa (the Antibody Mediated Prevention (AMP) studies). While VRC01 failed to prevent overall HIV-1 infection more effectively than placebo, a pre-specified analysis by VRC01 sensitivity identified a higher prevention efficacy (75.4%;

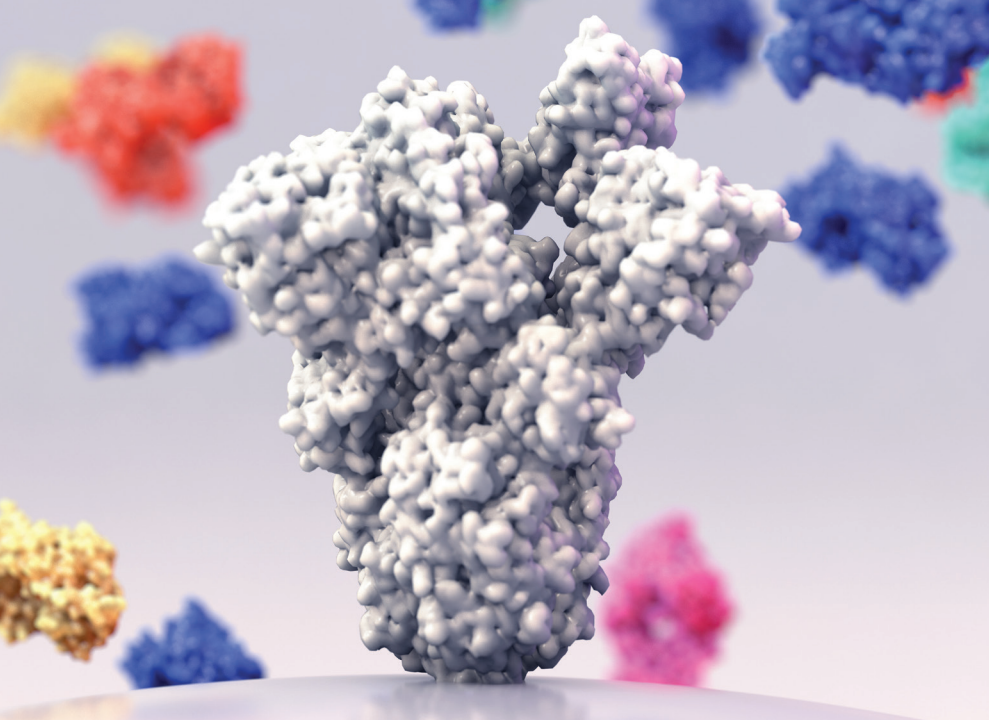
95% CI 45.4 – 88.9) for viruses with an 80 percent inhibitory concentration <1ug/mL, demonstrating for the first time that bNABs could prevent HIV acquisition from bNAB sensitive viruses. However, only 30 percent of the isolates were sensitive to VRC01.^{10,14}

Role of Sensitivity/Resistance Testing

Clinical trial data continue to demonstrate that baseline resistance remains a critical barrier to the efficacy of bNABs and use of a screening resistance assay will likely be an essential step preceding bNAB administration in future clinical contexts. However, screening resistance assays are currently subject to multiple limitations. Neutralization thresholds still require refinement, complete sampling of the reservoir is currently impossible, and the predictive value of current screening methods is limited and may differ between viremic individuals and individuals with virologic suppression, with the greatest predictive value likely to be among those with early HIV and relatively homogenous reservoirs. The tests are also currently labor and cost-intensive and require large volumes of cells.^{15,16}

Currently the only clinical laboratory improvement amendments (CLIA) certified phenotypic assay for bNAB screening is Monogram Biosciences' PhenoSense HIV Neutralizing Antibody Assay, which is based on the Trofile assay system. It was validated for clinical bNAB use in a collaboration between Monogram and the AIDS Clinical Trials Group (ACTG), and in a demonstration study successfully generated a resistance measure for 88 percent of the samples, with values that were similar between plasma and peripheral blood mononuclear cells (PBMC).

Post hoc use of the PhenoSense assay on samples from a subset of participants of a study of VRC01 on analytic treatment interruption (ATI) the pretrial PhenoSense neutralization measures tightly correlated with the published results. However, the PhenoSense neutralization measures did not tightly correlate with time to rebound. Baseline PhenoSense neutralization measures



did not tightly correlate with time to rebound when used in two additional ATI studies involving the use of 3BNC117 and 10-1074. Baseline PhenoSense neutralization measures in a study of multiple doses of 3BNC117 and 10-1074 also did not correlate with durable viral suppression. In summary, while the PhenoSense assay is a commercially available tool whose results are closely correlated with those from research assays, it remains unable to predict the ability of bNAbs to maintain viral suppression.^{15,16} The challenge of HIV's continual evolution will also require the updating of virus panels and sequence information used for sensitivity testing.⁸

Conclusion

Modern ART retains the advantages of broad effectiveness and multiple ARVs with high genetic barriers that permit rapid initiation prior to the receipt of resistance test results. The arrival of long-acting ART further reduces adherence barriers. However, bNAbs may offer a long-acting treatment option with unique mechanisms of action, resistance pathways that are distinct from conventional ARVs, and potential immunologic benefits.

There is currently a broader selection of bNAbs with half-lives that exceed those of long-acting ARVs apart from lenacapavir. As well, several clinical studies have demonstrated that multiple bNAbs are well tolerated, can transiently decrease viral load, and prevent infection with sensitive virus. However, there are multiple barriers to the incorporation of bNAbs into standard clinical care.

There is insufficient evidence supporting the use of bNAbs as a viable first-line treatment option to maintain virologic suppression, and the number and/or combination of epitopes targeted to attain and maintain virologic suppression remains unclear.

Prescreening for antibody resistance will likely be a requirement for bNAb use, though resistance testing options are currently subject to technical, logistical, and financial limitations. Production and dissemination of bNAbs is also subject to significant manufacturing costs and cold-chain storage and transport, and the discovery and isolation of novel bNAbs will have to be accelerated in response to HIV's continual evolution. Similar to ART, an effective bNAb regimen for HIV treatment will be a bi- or trispecific molecule, potentially in combination with a long-acting ARV and possess a sufficiently high barrier to resistance that's durable. Preliminary data suggests that bNAbs may also offer the immunologic benefit of a "vaccinal effect" and elicit host HIV-specific immunity. **HIV**



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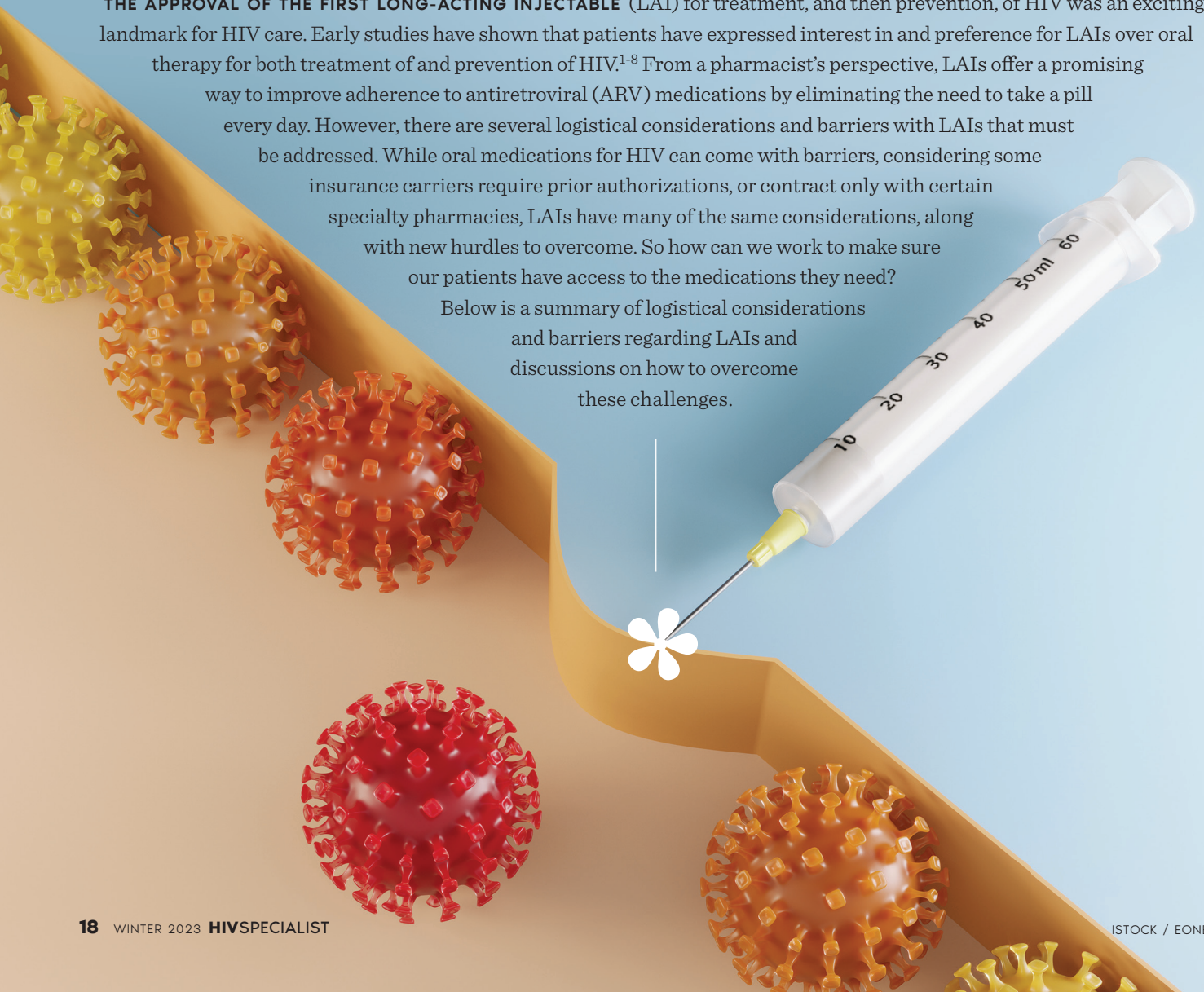
Long-Acting Injectable Therapy

LOGISTICS AND BARRIERS

By Julie Darnell, PharmD, BCACP, AAHIVP

THE APPROVAL OF THE FIRST LONG-ACTING INJECTABLE (LAI) for treatment, and then prevention, of HIV was an exciting landmark for HIV care. Early studies have shown that patients have expressed interest in and preference for LAIs over oral therapy for both treatment of and prevention of HIV.¹⁻⁸ From a pharmacist's perspective, LAIs offer a promising way to improve adherence to antiretroviral (ARV) medications by eliminating the need to take a pill every day. However, there are several logistical considerations and barriers with LAIs that must be addressed. While oral medications for HIV can come with barriers, considering some insurance carriers require prior authorizations, or contract only with certain specialty pharmacies, LAIs have many of the same considerations, along with new hurdles to overcome. So how can we work to make sure our patients have access to the medications they need?

Below is a summary of logistical considerations and barriers regarding LAIs and discussions on how to overcome these challenges.



Assessing Clinic Readiness

Before starting to offer LAIs, a clinic needs to assess if they have the necessary resources and procedures in place. The following questions can help a clinic with this process, several of which are discussed in detail through this commentary:

- What is the anticipated number of patients that will be offered LAIs?
- Will additional staff be needed to support the expected volume of LAI appointments?
- Who will determine if a patient is eligible for an LAI?
- Who will be in charge of determining LAI coverage?
- How will LAIs be procured?
- Is there a place to properly store the medication?
- Who will be in charge of LAI inventory management?
- How will patient injections be scheduled?
- Is there adequate clinic space to accommodate injection appointments?
- What staff will be trained to administer LAIs?
- Who will be responsible for billing for LAIs and associated costs?
- How will patient injections be tracked to ensure on-time dosing?
- What is the procedure for planned and unplanned doses?

Determining Eligibility for LAIs

For patients interested in an LAI, the first step is to determine clinical eligibility. While many patients may be excited about LAIs, certain clinical considerations may preclude a patient from LAI therapy. Table 1 features a summary of clinical considerations to assess when determining medical eligibility.

Another important consideration for eligibility is a patient's ability to attend injection appointments. Historical information regarding if the patient has a history of missed appointments may be used to predict if the patient will be able to keep injection appointments. However, a patient with missed clinic appointments should not be

automatically excluded from LAI therapy without first assessing barriers to attending appointments.

If barriers are identified, the clinic should work to provide resources that can help the patient keep scheduled appointments, including education on importance of attending injection appointments, assistance with transportation, appointment reminders, flexible scheduling, and any additional resources an individual clinic might be able to offer the patient. If after addressing barriers to attending appointments there is still concern with the patient's ability to consistently make appointments, then LAI therapy might not be appropriate.

Discussing the Oral Lead-In

For patients eligible for LAIs, the provider should use shared decision-making with the patient regarding if they would like to complete an optional oral lead-in or go straight to injections. Patients may find oral lead-ins reassuring to test tolerability of the medications. While lack of side effects with oral therapy cannot guarantee lack of side effects with injection therapy, it is one way to help patients feel confident in their decision to continue with injections.

If the patient chooses to complete the oral lead-in, oral cabotegravir is ordered directly through the manufacturer and is provided at no cost to the patient.

Table 1: Clinical Consideration for Determining LAI Eligibility

	Cabotegravir ⁹	Cabotegravir/Rilpivirine ¹⁰
FDA approved indication	HIV prevention in adults and adolescents at risk of HIV through sexual contact.	Treatment of HIV in adults and adolescents 12 and older who are virally suppressed on a stable ARV regimen with no history of treatment failure and no known or suspected resistance to cabotegravir or rilpivirine.
Contraindications	Unknown or positive HIV status; Previous hypersensitivity to cabotegravir.	Previous hypersensitivity to cabotegravir or rilpivirine.
Contraindicated concurrent medications	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin, rifapentine.	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin, rifapentine, systemic dexamethasone, St. John's Wort.
Use in pregnancy and lactation	Due to lack of data in the population, use is not advised.	Due to lack of data in the population, use is not advised.

Determining LAI Coverage

Next, the patient’s medical and pharmacy benefits should be confirmed, and benefits queried to ensure LAI coverage. Depending on the type of insurance a patient has, the LAI may be covered as a medical or pharmacy benefit. The type of benefit will determine how the medication will be billed and how the medication can be procured. Costs associated with administering the medication are billed separately from the medication itself. Even if an LAI is covered, a prior authorization may be required for the medication to be approved. Since the coverage determination may take time, coverage of LAIs should be confirmed before a patient starts oral therapy, if oral lead-ins are used, to prevent a gap between oral and injectable therapy.

When determining eligibility, it is important to identify who in the clinic will be responsible for determining coverage. If a clinic has in-house billing support, this might be the easiest route to pursue. Alternately, prescribers and their medical team can enroll patients through ViivConnect, which can help to streamline the medication eligibility process.¹¹

Assessing Patient Cost of Medications

Affordability of LAIs may be a concern for patients who are uninsured or underinsured. Even in patients with medication coverage, cost of medication copays or deductible payments may still prevent access to LAIs. Several programs exist to help patients with affording LAIs that are summarized in Table 2.

Procuring LAIs

Once coverage and cost savings have been assessed, the clinic needs to procure the medication. There are two main methods of procuring LAIs: 1) Use of a contracted specialty pharmacy or 2) ordering from a distributor.¹⁵ Using a specialty pharmacy is most common when the medication is covered as a pharmacy benefit. The prescription is sent to a contracted specialty pharmacy, and billing is handled by the

pharmacy. The pharmacy will procure the medication and will send it directly to the clinic for administration. This process is also referred to as “white bagging.”

With white bagging, the clinic will receive medication that is labeled for the individual patient for which it was prescribed. Also, with white bagging, the clinic does not take on a financial risk since the specialty pharmacy handles the procurement and billing. The copay is also more transparent to patients, since pharmacies can adjudicate the claim and let the patient know the cost before the LAI is ordered or injected. One con of white bagging is that it does not allow for the clinic to have a backup stock of medication since each medication obtained is labeled for a specific patient.

If the medication is covered as a medical benefit, the clinic will need to order the product from a distributor, and will bill the medication after it is administered. This is referred to as “buy and bill.” Buy and bill allows the clinic the option to directly buy a clinic supply of medication from a specialty distributor without going through a pharmacy. This is the main method of procuring LAIs for patients whose insurance deems the medication to be a medical benefit.

As the name suggests the clinic must pay for the product upfront and submit for reimbursement after the LAI is administered. This may not be a viable option for a clinic with limited financial resources, and

Table 2: Cost Assistance Programs for LAIs

Program	Eligibility	Income Restriction	Maximum Benefit
Manufacturer Savings Program ¹²	Patient has commercial insurance that covers the prescribed medication.	None	\$13,000/year for cabotegravir/rilpivirine; \$7,850*/year for cabotegravir.
Manufacturer Patient Assistance Program ¹²	Uninsured patients not eligible for state Medicaid and not enrolled in an Alternate Funding Program. ^{**}	≤ 500% of the FPL ^{****}	No max benefit specified. Medication will be provided at no cost to patients who qualify.
Good Days ^{13***}	Patients with Medicare or military insurance.	≤ 500% of the FPL	\$10,000/year for medication, administration fees, and medical fees.
Patient Advocate Foundation ^{14***}	Patients with any insurance type. ≤ 400% of the FPL		\$7,500/year for medication, administration fees, and medical fees.

*Benefit is further broken down to \$7,500 in assistance with drug copays or deductibles, plus up to \$50 in assistance in administration fees per injection, up to seven injections a year.
** Patients can also qualify if they have Medicare Part B, Part D, or Medicare Advantage and have at least \$600 in out-of-pocket costs in the current calendar year.
*** Programs for treatment and prevention of HIV currently open at time of writing this article. Enrollment is subject to availability and may close if funds are no longer available.
**** Federal Poverty Level



When determining eligibility, it is important to identify who in the clinic will be responsible for determining coverage. If a clinic has in-house billing support, this might be the easiest route to pursue.

Figure 1:
Dosing Schedule
for LAIs^{9,10}



may lead to questions of how much the clinic will actually be reimbursed. There is also less transparency with what the patient's out-of-pocket cost will be since the insurance can only be billed after the procurement and administration of the medication.

Storage and Inventory of LAIs

For either method of procuring the drugs, a clinic should ensure proper space for medication storage. Cabotegravir alone can be stored at room temperature, while cabotegravir/rilpivirine needs to be refrigerated, so the clinic should ensure there is an appropriate temperature-controlled storage space for the medication.^{9,10}

Procurement through either channel (white bagging or buy and bill) will require diligent inventory management to ensure there is sufficient product for scheduled appointments. Clinics that utilize white bagging should work closely with the specialty pharmacy to ensure maintenance doses arrive in time for all scheduled patient appointments. LAIs procured through white bagging will be dispensed for a specific patient, and should be labeled as such by the dispensing pharmacy. Therefore, it is important that the clinic keeps a log of all injections received via this method, including information such as patient name, date dispensed, date of injection, etc. Clinics

that utilize buy and bill should ensure they order enough product to cover all appointments for the given timeframe for which they will be ordering, and may want to consider keeping additional doses on hand for any new starts or unexpected dosage issues.

Administration

LAIs must be administered by a trained medical professional in a clinical setting, often the medical clinic that is prescribing the medication.^{9,10} Outside of an approved medical clinic, there are a number of alternative sites for administration (ASAs) that can offer injections.¹⁶ These ASAs are often infusion centers that also offer injection therapies and handle acquisition, administration, and billing of the LAIs.

For patients who use the clinic for administration, the clinic should determine who will be responsible for administering the injection. The clinic should ensure that there is always a trained individual available to give LAIs on days that patients are scheduled for injections. Staff should be trained on proper administration of the LAIs, including the following points:

- For cabotegravir/rilpivirine, remove the product from refrigeration and allow it to sit at room temperature for at least 15 minutes before injection.

- Once removed from the refrigerator, the product must be used within six hours, and should be discarded if not used within this timeframe.
- The vial should be shaken vigorously for 10 seconds before drawing into the syringe.
- Each LAI package will come with its own 1.5 inch needle(s). In patients with a BMI of 30 or greater, it is recommended to use a longer needle length, which is not provided.
- Injections should be administered in the gluteal muscle, preferably the ventrogluteal site.
- For cabotegravir/rilpivirine, two separate injections will be given and the injections should be given on opposite sides, at least two centimeters apart from each other.
- The "z track" injection technique should be used to prevent medication leakage.

Continuing Injections

Once a patient starts LAI therapy, the clinic needs to decide how continued injections will be managed. The first two doses of either LAI cabotegravir or cabotegravir/rilpivirine must be given one month apart. After the initiation doses are complete, patients can move to every two-month dosing (See Figure 1.). Cabotegravir/rilpivirine also has the option for every one-month dosing; however, with the approval of every two-month dosing, this dosing

schedule is unlikely to be preferred by most patients and providers.

It will be important to identify who will maintain the patient schedule for LAI appointments to ensure patients are able to continue to receive doses on time. Schedules for LAIs should be available to whomever is in charge of procuring medications to allow for optimal inventory management. This ensures patients will have medication available on the date of their injection.

Missed Doses

A planned missed dose could occur if a patient will be traveling or otherwise unable to receive their injection within seven days of the target date and knows this ahead of time. In this case, the manufacturer recommends bridging with oral medication for up to two months until the next injection can be administered.^{9,10}

An unplanned dose could occur for a variety of reasons, including loss or change in insurance coverage, difficulties getting to the clinic, unexpected illness, etc. The patient can receive the late dose and resume every two-month dosing if given within one month after the target injection date. If the next dose is to be given more than one month after the target injection date, the initial dosing series (two injections given one month apart) will need to be reinitiated before

every-two-month dosing can occur.^{9,10}

In patients with unplanned missed doses, it is important to address any barriers that led to the missed injection, to provide education on the importance of getting injections on time, and to discuss if continuing injection therapy is appropriate, or if switching back to oral therapy is recommended to reduce risk of treatment failure and viral resistance.

Summary

LAI therapy is an exciting new way for people with HIV to receive treatment that eliminates the need to take a daily pill. While many patients and clinics are eager to explore LAI therapy, there are several clinical and logistic factors that must be considered that are unique to LAI therapy. With adequate planning and protocols, clinics can anticipate and overcome common barriers associated with LAIs. **HIV**



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An HIV Clinic's Experiences with Long-Acting Injectables

Insights for Practitioners

By Alexander Nelson, PharmD, AAHIVP

HIV THERAPY has changed substantially in the past few years with the introduction of long-acting injectables (LAIs). Until 2018, enfuvirtide was the only non-oral option available for the treatment of HIV. For practitioners, the barrier to prescribing LAIs is not likely a lack of drug information, but instead concerns around implementation. In this article, I hope to highlight some of the challenges and opportunities that come along with each of the options now available to us.

For background, I am a clinical specialty pharmacist at MetroHealth in Cleveland, Ohio. Our outpatient HIV clinic provides care for roughly 1,700 people with HIV. We have approximately 200 patients currently on cabotegravir/rilpivirine (CAB/RPV) injections, 10 patients on lenacapavir (LEN), and two patients on ibalizumab-uiyk (IBA). MetroHealth's specialty pharmacy handles most of the logistical concerns with the medication start-up at the direction of the clinic.

The process is multidisciplinary and requires collaboration from multiple parties, including the patient, prescriber, nursing staff, prior authorization specialists, retail pharmacy, and infusion pharmacy. We are fortunate to have all of these departments connected through our health system, and I mention this to highlight that independent clinics or specialty pharmacies may experience additional challenges with these medications. And these medications have plenty of challenges on their own!



Many times, patients bring up the idea of being on an LAI and they explicitly state that they have a problem with tablets.

Challenges and Opportunities: Medications

Each LAI comes with its own challenges and opportunities that clinicians need to factor into clinic and treatment protocols when considering LAIs for their patients.

Cabotegravir/Rilpivirine

CAB/RPV was the first FDA approved standalone LAI regimen for the treatment of HIV.¹ It consists of two gluteal injections: an integrase strand transfer inhibitor (INSTI) and a non-nucleoside reverse transcriptase inhibitor (NNRTI). It can be given monthly or bimonthly. Our clinic's LAI workflow evolved from this medication. It represents the bulk of our clinic's experience with LAIs and exemplifies many of the challenges inherent in the LAI process.

When the medication was first approved, the oral lead-in was mandatory. Unfortunately, access to oral cabotegravir was limited to a single specialty pharmacy. Our experience with them has been excellent, but any external parties represent opportunities for miscommunication. Patients with unstable housing, for example, required additional coordination to pick up the oral lead-in at the clinic and, in many of those instances, transportation would have to be arranged as well. Fortunately, data existed early on indicating that the oral lead-in could be optional, and the FDA label was updated to reflect this in March of 2022.²⁻³

Another challenge is that long acting RPV must be refrigerated.⁴ This is an unfortunate aspect when a clinic experiences no-show appointments. To ensure no medication is wasted, our procedure requires the patient to physically be in the clinic before pulling the medication from refrigeration, which means that the 15-minute wait for the medication to reach room temperature necessarily extends the length of the patient's time in clinic.

Finally, the insurance approval process for this medication can be tricky. The FDA labeling of CAB/RPV indicates that it is "a complete

regimen for the treatment of HIV-1 infection in adults and adolescents 12 years of age and older and weighing at least 35 kg to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine."⁴ This can leave the clinic in the difficult position of arguing that the patient has never had any problems maintaining viral suppression, but nevertheless requires a change in therapy. Our clinic often overcame this by accepting that the real process starts after the prior authorization denial. We still made our strongest case in hopes of approval, but denials provide specific information that we then can address directly. Our course of action and strategies for approval then evolve based on the information from the denial and past experience with the plan.

Practitioners are also prescribing CAB/RPV outside of these parameters. For example, there are reports describing the use of this regimen in patients who have detectable viral loads.⁵⁻⁷ In our clinic, many patients on CAB/RPV struggled with adherence to oral antiretroviral therapy (ART) and started this regimen with detectable viral loads. This subgroup stands to benefit significantly from an alternative means of ART administration. The approval process for these patients is not any more difficult, because the lack of viral suppression is offset by the clear need for change of therapy.

Lenacapavir

LEN contrasts with CAB/RPV in many ways. It is a novel drug class (capsid inhibitor), requires additional medications for a complete regimen, and is indicated for multi-drug resistant HIV. Its oral lead-in is commercially available and required for pharmacokinetic reasons. The injection does not require refrigeration, is given subcutaneously, and dosed every six months.⁸ At the time of this writing, LEN has been FDA approved for less than a year. As a result of that, we do not have any patients who have received more than two doses.

LEN was FDA approved in December of 2022.⁹ It interferes with the viral lifecycle at several steps around both capsid disassembly and reassembly. There is no cross-resistance with other classes due to this unique mechanism of action.⁸

There are two different options for the oral lead-in with LEN. The first option is a five-tablet lead-in that consists of two 300 milligram tablets on day one, two tablets on day two, one tablet on day eight, and then two injections on day 15. The second option is a simplified four-tablet lead-in that is given as two 300 milligram tablets on the day of the first injections and then two tablets the following day. The injections are given as 927 milligrams split into two 1.5 milliliter subcutaneous injections into the abdomen.⁸

Our clinic's low patient volume for LEN, limited time since initiation of therapy, and confounding factors with heavily treatment-experienced patients make it difficult to make any general claims about our patients' experience with the medication. But so far, the main complaint from our patients is some injection site pain, especially for those without much subcutaneous fat in the abdomen.

Approval and acquisition of LEN has not been a challenge for us so far. There was one instance where a patient's plan approved the injection but refused to approve the oral tablets. The biggest issue with LEN, and with salvage regimens up to this point, is what to pair it with.

Typically, LEN would be paired with an oral medication, maybe an entry inhibitor like maraviroc or fostemsavir. I have an operating assumption that if a patient has gotten to the point where salvage regimens are being considered, then pill burden and adherence

to oral regimens is likely a large factor. This makes adding something like maraviroc or fostemsavir problematic, since they both are dosed twice daily.

Many times, patients bring up the idea of being on an LAI and they explicitly state that they have a problem with tablets. In this scenario, is it reasonable for a clinician to exclude adding injectable CAB/RPV to LEN from consideration? Our clinic does not believe so. If a clinical determination is made that at least one of the agents will retain full activity, we will consider CAB/RPV as the background regimen for LEN. This is off-label use of CAB/RPV, since it is only approved for virally suppressed patients without a history of regimen failure, but in a patient with multi-drug resistant HIV, we are going to consider every weapon in our arsenal.

Ibalizumab-uiyk

IBA was the first long-acting antiretroviral approved, and many of the drawbacks listed above with LEN are also a challenge with prescribing this drug. Other challenges with IBA are shorter dosing intervals and windows, difficulty of acquisition and administration, and difficulty assessing activity.

This monoclonal antibody (MAB) was approved in 2018.¹⁰ It works by binding to a secondary domain of the CD4 receptor.¹¹ It allows the virion to bind to the CD4 receptor, but prevents it from binding to the secondary receptor, thus preventing entry of it into the cell.

There are many advantages to this medication. It has a novel mechanism of action, being the only MAB approved for the treatment of HIV. As a MAB, there are no drug-drug interactions listed and pharmacokinetics are not expected to be impacted by renal or hepatic impairment.¹¹ It has a novel dosage form, given as an intravenous (IV) infusion every two weeks, and maintenance doses were approved for administration via IV push in October of 2022, avoiding the need for dilution and speeding up the process of administering for the patient.¹²

These advantages are offset by numerous practical hurdles, though. For one, the medication shows some decreased efficacy in patients with absolute CD4 counts under 50 cells per cubic millimeter.¹³

This drug also suffers from the issues highlighted above with LEN in that it requires an optimized background regimen that would typically necessitate adherence to at least one oral tablet. The dosing window is incredibly tight as well. If the maintenance dose (four vials) is missed by three days or longer, the patient must receive the loading dose (10 vials) again to resume therapy.¹¹

From our experience, the manufacturer's support team has been incredibly helpful and involved in the process of coordinating care for the patient. They have attempted to overcome these dosing issues by partnering with specialty pharmacies who offer home infusion, but working with external pharmacies created confusion and a lack of documentation in the electronic health record (EHR) at our clinic. Initially, the social worker was the best option to coordinate with the patient and external pharmacy. They eventually discovered, though, that rather than providing home infusions, the pharmacies were sending the patients via rideshare services to affiliated infusion centers across town.

This was almost certainly due to nursing staff shortages in the midst of the pandemic, but was not communicated to the care team. It was only after this issue was brought to the manufacturer that purchasing access was granted to our internal pharmacy to allow for in-house administration and billing through the patient's medical benefit. From our perspective, it appeared that the company restricted access to the drug for quality control, but in our case, it hindered patient care.

Finally, there is no commercial resistance testing available if failure is suspected of the regimen.

Challenges and Opportunities: LAI Implementation

Whether it's approval, clinic access to medication, or patient coordination, there are many other hurdles to address before the LAIs get to the patients.

Approval

Understanding the prior authorization process for insurance is crucial with all of these medications. Our guiding principle is "believe half of what you see and none of what you hear." To illustrate with an example,

AN HIV CLINIC'S EXPERIENCES WITH LONG-ACTING INJECTABLES

we tried to go through the manufacturer's assistance program for one of the first CAB/RPV referrals we had. They returned information stating that the patient's insurance required them to use an external pharmacy to be billed through the patient's medical benefit. Nevertheless, we obtained approval through the patient's pharmacy benefits and the plan allowed us to fill the prescription internally. I do not doubt that the information from the manufacturer was obtained directly from the plan, but both pieces of information—needing to go through an external pharmacy and use medical benefits—were incorrect.

Plan information does not transfer perfectly to the pharmacy benefits manager and vice-versa. We believe the medication is covered by the plan when we see a successful claim with no copay for the patient. This is why we opt to pursue authorization through pharmacy benefits first, and medical benefits only when that option has been exhausted; claims through pharmacy benefits are adjudicated prior to administration, whereas claims through medical benefits are reviewed after the fact. Pharmacy billing also allows for test claims, so information about copays can be given up front and taken care of proactively. Through medical benefit, this information can vary based on factors such as the patient's remaining deductible. We have heard instances where an external specialty pharmacy provides the medication and then sends a bill after, though, so be aware of this risk.

Access to Medication

Clinics can experience difficulty accessing the medications they need for their patients because of insurance complications. Since plans may opt to have injectable medications go through either pharmacy or medical benefits, the challenge becomes how to coordinate those two workflows. Because our clinic's access is completely internal, the specialty pharmacy is in charge of coordinating fills with the involved parties. Through pharmacy benefit, the prescription is scheduled to be filled through a retail pharmacy based on the patient's upcoming appointment and brought up to clinic ahead of time.

If a patient's plan requires fills through medical benefit, the infusion pharmacy and clinic nursing staff are informed and the

medication is filled once the patient arrives for the appointment. An additional advantage of this process is it creates a small amount of redundancy in inventory, so if retail or infusion pharmacies happen to be out of stock, inventory can be quickly transferred to ensure that the patient does not leave without getting the injection.

Patient Coordination

Just as with patients on oral regimens, it is a team effort to keep patients on LAIs linked to care. We have a part-time nurse coordinator dedicated to our LAIs. Also, social workers are needed to coordinate transportation and provide outreach when patients miss appointments. We have even had pharmacists coordinate injections to be given when patients were hospitalized at other health systems.

We have multiple reports with nursing and pharmacy staff to create some overlap to make sure patients do not slip through the cracks if appointments are missed. One report within the EHR inclusive of all current recipients of LAI in our clinic has follow-up injection visits highlighted yellow and red based on medication administration windows, and this report is monitored at least weekly by an LAI coordinator.

Issues still arise, though. Missed visits do occur, although not at the frequency we feared. Patients have, on occasion, electronically rescheduled their appointments too early for the dosing window. Some patients have shown up a day or two after their scheduled appointment. We always try to accommodate when we can. Lessons learned in adaptability and timely communication from our Rapid Start protocol have been immensely helpful in these instances.

Future Considerations

LAIs have already created a paradigm shift in the treatment of HIV. Each new drug that is approved shifts the therapeutic utility of the ones that have come before. Niche clinical problems may be examined through the lens of the new medications and new clinical problems may present themselves.

One such problem is the lack of LAI options for patients with a history of NNRTI resistance. The 2021 WHO HIV Drug Resistance Report highlighted a high

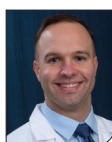


prevalence of NNRTI resistance worldwide.¹⁴ Notably, they have not recommended CAB/RPV for worldwide use. Within our clinic, we have several patients who have indicated a desire to be on an LAI regimen, but for whom CAB/RPV was not an option due to history of NNRTI or INSTI mutations. A small subset of these patients have been deemed appropriate candidates for LEN+CAB with or without RPV. These patients have responded well to therapy, and this LAI regimen warrants further investigation. It could be an option to provide LAI ART for low and middle income countries with high prevalence of NNRTI resistance.

Another problem that is presenting itself is how to approach LAIs in patients with viremia. Dr. Paul Sax stated in a recent blog post about CAB/RPV in the setting of viremia, "If the alternative is untreated and progressive HIV disease, and the patient has advanced immunosuppression, we should stop discouraging use of this potentially life-saving therapy."¹⁵ However, if starting a viremic patient on CAB/RPV, what level of viremia is acceptable? Prior treatment history with NNRTIs may complicate this decision. When there is concern with time



Just as with patients on oral regimens, it is a team effort to keep patients on LAIs linked to care.



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to viral suppression leading to potential resistance mutations, in rare instances we have augmented CAB/RPV with IBA. While the logistical concerns with IBA make it a poor long-term option, it may have a place in helping to quickly suppress patients and maintain activity of the main LAI regimen, with the intent to remove it once the patient achieves viral suppression. This too requires further investigation.

For our clinic in particular, we plan to expand access to LAI ART to our satellites. We have begun to provide LAI CAB for pre-exposure prophylaxis at one of our PRIDE clinics. Once workflow for multi-site coordination is determined, we hope to continue rollout with additional sites and medications. We also believe pharmacist-administered CAB/RPV could help to improve patient access and hope to explore that with our retail sites.

LAIs hold the promise of viral suppression in patients where this was not previously possible by providing an alternate route of administration as well as novel drug classes. The challenges of implementation are surmountable in multidisciplinary teams where a priority has been placed on access to these medications for patients. **HIV**

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Long-Acting Early
Viral Inhibition

(LEVI)



SYNDROME

A Subtle Presentation of New HIV Infection Seen with Use of Cabotegravir PrEP

By Hannah Zimmerman, MD, AAHIVS;
Cara McAnaney, MD, AAHIVS; and Allison Vogl, MD, AAHIVS

THE APPROVAL of long-acting cabotegravir injections (CAB-LA) for pre-exposure prophylaxis (PrEP) for the prevention of HIV in December 2021 has revolutionized the PrEP landscape. It has also led to new diagnostic challenges for clinicians, with the recognition of the long-acting early viral inhibition (LEVI) syndrome. When HIV is acquired while on CAB-LA PrEP, there may be minimal symptoms and atypical serology conversions. Delays in diagnosis due to atypical serologies increase the risk of drug resistance, as patients are exposed to an incomplete single-drug regimen for extended periods of time. Cabotegravir is an integrase inhibitor (INSTI), the potent class of medications used in first-line treatment regimens.¹ Resistance to this class greatly limits treatment options.

Acute HIV infection is the earliest stage of HIV infection. Classic acute HIV infection is characterized by high viral loads and symptoms of viral illness, including fever, chills, night sweats, lymphadenopathy, fatigue, rash, and sore throat. This phase of illness typically lasts for one to two weeks. Due to high levels of viremia, there is great risk for transmission.¹ During this period, HIV nucleic acid or HIV p24 antigen (Ag) is present, but HIV antibodies (Ab) have not yet formed. Current fourth- and fifth-generation HIV tests, also called Ag/Ab assays, can detect acute HIV as early as 18 days after exposure.² If there is a high index of suspicion for acute HIV—for instance, someone presenting with fevers, lymphadenopathy, and a new sexual partner in the past one to two weeks—an HIV-1 RNA test can detect acute infection just 10 days after the exposure.² We typically use quantitative tests in practice; however to be diagnostic, the qualitative RNA test must be used. Notably, the eclipse period is the first 10 days after HIV acquisition when no test can detect HIV infection.³

LEVI syndrome manifests in stark contrast to typical acute HIV presentation. LEVI syndrome is characterized by minimal to no symptoms of viral illness and inconclusive testing. In a presentation at the Conference on Retroviruses and Opportunistic Infections (CROI) in 2023, Dr. Susan Eshleman at Johns Hopkins University School of Medicine described LEVI syndrome viral replication as “smoldering” to explain how viremia during LEVI syndrome transmission of HIV is low, and thus is unlikely.¹ Point-of-care tests (most FDA-approved point-of-care tests are antibody-only tests with a longer window period.) and Ag/Ab assays are not as accurate at detecting HIV infection in the setting of cabotegravir use, when compared to RNA testing.⁴ This leads to delays in detection, and potentially development of INSTI resistance.¹



Delays in detection of HIV and INSTI resistance were seen in HIV Prevention Trials Network clinical trial 083 (HPTN 083). This study compared the safety and efficacy of CAB-LA to tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) in cisgender men and transgender women who have sex with men. This study had over 4,500 participants, split evenly between the CAB-LA and TDF and FTC groups. CAB-LA as PrEP proved to be extremely effective; use of CAB-LA reduced the risk of acquiring HIV by 66 percent compared to TDF/FTC. HPTN 084 studied use of CAB-LA compared to TDF/FTC in women, and the study found that CAB-LA reduced risk of HIV acquisition by about 90 percent compared to TDF/FTC.⁵

While HPTN 083 and HPTN 084 had very low rates of HIV in participants in the cabotegravir group, both studies noted that detection of incident infections were delayed. The study designs for HPTN 083 and HPTN 084 were similar. Participants were randomized to receive either active cabotegravir with placebo pills, or placebo injections with active oral PrEP pills and the studies were double-blinded. Participants were required to have a negative HIV-1 RNA test within 14 days of study enrollment. In both studies, participants received an oral lead-in phase, followed by injections at weeks five and nine, then every two months. Participants were followed for at least three years, after which injections were discontinued and all participants received active oral PrEP with TDF/FTC for one year.^{5,6} Study visits included an FDA-approved rapid HIV test and a lab-based Ag/Ab assay. Study visits did not routinely include HIV-1 RNA testing.

During HPTN 083, there were 12 cases of HIV acquisition in the cabotegravir arm, out of 4,566 participants. Of these 12 infections, four were deemed to be true breakthrough infections, occurring during the phase of intramuscular (IM) medication administration, despite on-time administration of the injections and expected levels of cabotegravir in the plasma. (The other infections in the cabotegravir arm were determined to be infections occurring prior to study enrollment that escaped detection on screening labs, infections occurring in the setting of poor adherence to the oral tablet lead-in phase, and infections that occurred

after IM cabotegravir had been discontinued.) In all four breakthrough infections, detection of HIV was delayed. Assay reversion, where a patient with a positive HIV Ag/Ab test had a subsequent negative HIV Ag/Ab test, was documented in four participants who received CAB-LA. In two participants, INSTI resistance developed due to exposure to cabotegravir and delayed infection detection.⁷

Delays in detection for these four cases ranged from 45 days (one study visit) to 117 days (five study visits). Once these study participants had a reactive or indeterminate HIV Ag/Ab assay, a confirmatory antibody test was run; if that was positive, the patient was considered HIV positive. If the confirmatory Ab test was negative or indeterminate, a qualitative RNA test was run; if that was positive, the patient was considered HIV positive. Once HIV acquisition was confirmed, test samples obtained at prior study visits from the same patient were tested retrospectively at the HPTN Network Laboratory with a qualitative HIV-1 RNA test until a negative result was obtained.⁷

Concentrations of cabotegravir were also calculated to determine if there were appropriate levels to provide protection. The cabotegravir concentration needed to ensure viral inhibition was calculated using data from animal studies in macaques. The in vitro concentration of cabotegravir needed for 90 percent inhibition of HIV is called PA-IC90. Animal studies showed that in rectal tissues, cabotegravir concentrations three times the PA-IC90 provided 100 percent protection; in vaginal tissues, cabotegravir concentrations four times the PA-IC90 conferred 87 percent protection from HIV. The four HIV acquisitions in HPTN 083 that were considered true breakthrough infections were found to have a cabotegravir concentration of four times PA-IC90 at 95 percent of study visits.⁷

HPTN 084 enrolled 3,224 participants, and 1,614 were randomized to the CAB-LA

LEVI syndrome manifests in stark contrast to typical acute HIV presentation. LEVI syndrome is characterized by minimal to no symptoms of viral illness and inconclusive testing.

group. Use of CAB-LA reduced the risk of HIV infection by 91 percent compared to the oral PrEP group. No incident infections occurred in HPTN 084 in the setting of adequate cabotegravir levels.^{6,8}

While breakthrough HIV infections with use of CAB-LA are rare, they unfortunately are starting to be seen outside of the study protocols. Recently, a case report was published on the first real-world incident of HIV-1 infection on cabotegravir PrEP.⁹ This person had a positive HIV-1 RNA test on day 91, after receipt of their third CAB injection. This case was confounded by a few factors: the patient experienced a SARS-CoV-2 infection and was prescribed nirmatrelvir with ritonavir prior to the HIV diagnosis. The authors speculated that PrEP may be less effective with SARS-CoV-2 infection, or that there may be a drug-drug interaction between cabotegravir and nirmatrelvir with ritonavir.

High inoculum effect, where the efficacy of a medication decreases in response to high exposure, may also be a contributing factor. The patient described in the case report endorsed 20-30 partners monthly, in addition to a primary partner who was known to have HIV with resistance-associated mutations, including resistance to nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and INSTIs. Other factors that have been speculated to contribute to the increase in risk of HIV acquisition include tissue injury and ulcerative sexually transmitted infections.⁹

Notably, it remains unknown how long it takes cabotegravir to become protective against HIV. A period of increased susceptibility to HIV infection may occur between the first and second cabotegravir injections.¹ Counseling people who use PrEP on this period of vulnerability may lead them to take extra steps to protect themselves, such as consistently using barrier protection.

Both oral and intramuscular PrEP options are effective at preventing HIV. While the risk

of HIV acquisition on PrEP remains low, the threat of acquired INSTI resistance is unsettling and of great clinical significance. INSTI resistance impacts many first-line treatment options for HIV, including bictegravir/emtricitabine/tenofovir alafenamide, abacavir/dolutegravir/lamivudine, and dolutegravir/lamivudine. When HIV is detected early after acquisition on cabotegravir, and fully suppressive antiretroviral therapy (ART) is initiated, development of INSTI resistance might be prevented.

New HIV treatment guidelines recommend alternative initial ART regimens for people who acquired HIV with cabotegravir exposure, favoring a boosted protease inhibitor containing regimen over an INSTI-based regimen.¹¹ While boosted protease inhibitors are highly effective, they are usually second-line after INSTIs due to the greater potential for drug-drug interactions, harsher side effect profile, larger pill size/burden, and metabolic effects.

The person who acquired HIV on CAB-LA in the aforementioned case report (outside of a clinical trial) was initiated on an ART regimen of once-daily dolutegravir with darunavir/cobicistat. Subsequent labs showed that not only did this person achieve viral suppression with undetectable HIV-1 RNA, but they also had undetectable HIV DNA and nonreactive plasma HIV-1 and 2 Ag/Ab tests.⁹

Cabotegravir remains a highly effective tool for preventing transmission of HIV. While the risk of acquiring HIV on CAB-LA is extremely low, the possibility of developing INSTI resistance due to delayed diagnosis is concerning. This should not prevent us from using CAB-LA but should inform the discussions we hold with people who use PrEP and ensure education is provided on appropriate monitoring.

It is imperative that we keep in mind the difficulty in detecting HIV infection when someone has been exposed to CAB-LA. The new PrEP Guidelines from the CDC advise checking HIV-1 RNA every two months for all patients on CAB-LA.¹² Given HIV-1 RNA tests could detect new HIV infection several months prior to HIV Ag/Ab tests in HPTN 083, it is imperative to adhere to the guidelines. When the decision is made to discontinue CAB-LA as PrEP, we should offer oral PrEP for 12 months and we should stress the

importance of maintaining follow-up visits with HIV testing every three months. **HIV**



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PrEP, a Key HIV Prevention Tool, Isn't Reaching Black Women

By SAM WHITEHEAD

ALEXIS PERKINS THOUGHT her OB-GYN's office in Atlanta would be just the place to get a prescription for the type of drug that reduces a person's risk of contracting HIV.

But during a recent visit, the medical assistant who greeted her had not heard of the medicines known as pre-exposure prophylaxis, or PrEP, and she seemed uncomfortable discussing it, Perkins said. Her provider had heard of it but didn't feel confident prescribing it.

"She was at least honest enough to say that she was interested in it, but she didn't really know that much about it," said Perkins, a 25-year-old nurse, who decided to get on PrEP after participating in a sexual health education class and thinking more about her own risk. She's still trying to find a provider to write her a prescription.

"If I wasn't really confident in myself, this could have been a very discouraging experience," Perkins said.

PrEP is a crucial tool in the fight against the ongoing HIV epidemic and, when taken as prescribed, is highly effective at preventing infection from sexual contact or injection drug use.

But more than a decade after the first PrEP drug was approved for the U.S. market, one of the groups that would benefit most from the medications isn't taking them: Black women, such as Perkins, whose gender identity align with their sex assigned at birth.

Doctors, public health researchers, and those who provide HIV treatment and prevention services say long-standing, systemic factors, such as stigma and racism, are major barriers to PrEP uptake among cisgender Black women. Transgender Black

women face obstacles to PrEP uptake as well, especially discrimination related to their gender identity.

But many researchers focus on cisgender Black women, who, they say, are often overlooked by the health care system and face obstacles like: noninclusive marketing leading to a lack of awareness about who would benefit, fewer treatment options for women than for men, and medical professionals wary to prescribe it. These challenges are even more apparent across the South, which has the highest rates of new HIV diagnoses in the country.

Women had about a fifth of new HIV infections in 2021, according to recent data from the Centers for Disease Control and Prevention. And cisgender Black women made up an outsize share.

"If we don't figure out how we can change the system, we're just going to continue to keep failing Black women," said Tiara Willie, an assistant professor of mental health at the Johns Hopkins Bloomberg School of Public Health.

The FDA has approved three drugs for use as PrEP: the pills Descovy and Truvada, which also has a generic version, and the injectable Apretude. Descovy is newer and comes in a smaller tablet than Truvada, which can make it more desirable. It was approved for men and transgender women who have sex with men, but wasn't tested on people assigned female at birth.

That decision frustrated HIV researchers and advocates, including Rochelle Walensky, who worked at the Harvard University Center for AIDS Research before later leading the CDC.

In a 2019 editorial, Walensky and her colleague Robert H. Goldstein criticized this "two-tier system," in which men can get the medication knowing it's safe for them and with insurance approval, but women can't.

Gilead Sciences, the company that makes Descovy, later announced it would conduct a trial focused on the drug's use among cisgender women. The company said that study is ongoing, with data expected in late 2024. The CDC, for its part, earlier this year announced an \$8 million grant to fund studies on strategies to increase PrEP uptake among Black cisgender women.

Black women face the same obstacles as other populations when it comes to PrEP, researchers said, but many do so with fewer resources. Recent data from the U.S. Census Bureau shows Black Americans disproportionately live in poverty and women are more likely than men to live in poverty.

Taking PrEP requires regular testing and doctor visits to check for



HIV infection, which can present a “tremendous barrier” to access because of cost and logistics, said Michael Fordham, a program manager at the University of Alabama at Birmingham’s 1917 Clinic, the largest HIV care facility in the state.

“We’re actually seeing PrEP patients more frequently than we see our patients living with HIV that are stable,” he said.

The CDC updated its PrEP guidelines in 2021 to reflect the latest science and drug approvals, but the agency has heard complaints from providers that they’re still too onerous, said Robyn Neblett Fanfair, acting director of the agency’s Division of HIV Prevention. She added the CDC is “moving toward” guidelines that are more “timely and nimble.”

Fanfair said her division is also focused on reducing the costs associated with taking PrEP, which can be significant. Just starting on PrEP can cost more than \$2,000.

For now, the federal government mandates that private insurance plans cover PrEP, even as that rule faces a legal challenge. Still, in a recent study, CDC scientists found some 50,000 people had uncovered PrEP costs in 2018.

“Policies that increase access to health insurance, such as Medicaid expansion, can improve access to PrEP,” the study said. “This may be especially impactful for the southern U.S.,” where many states have yet to expand the state-federal insurance program for low-income people under the Affordable Care Act.

But paying for PrEP isn’t the only barrier to access, especially in the South.

HIV and other sexually transmitted infections can still be uncomfortable for physicians and nurse practitioners to talk about in the “Bible Belt,” despite their prevalence, said Anitra Walker, the vice president of operations at Mercy Care, an Atlanta-area health clinic that gets federal funding.

Social stigma not only can prevent Black women from talking about PrEP with their friends, neighbors, and doctors, but it can seep into their domestic relationships, said Mauda Monger, an assistant professor at the School of Population Health at the University of Mississippi Medical Center.

“If their partner is the person providing their housing, their food, and resources for their children, saying ‘I’m on PrEP’ openly may actually put her livelihood in jeopardy,” said

Monger, noting further that broaching the subject can put women at risk of physical harm.

Increasing PrEP uptake requires expanding access to good jobs, affordable health care, and stable housing, Monger said, to allow Black women to feel more empowered to take control of their health.

Researchers also said messaging about PrEP and how it’s marketed needs to change.

Willie, from Johns Hopkins, conducted focus groups in 2019 in Jackson, Mississippi, with Black cisgender women, who said they felt their experiences weren’t reflected in advertising campaigns for PrEP.

If “it wasn’t just gay men or transgender people who are in the ads,” one participant said, “then it would make everybody feel like... it’s not just for specific people.”

Researchers have to “work upstream” to undo those perceptions once they take hold, said Jessica Sales, an associate professor at Emory University’s Rollins School of Public Health.

Sales is partnering with Atlanta sexual health nonprofit SisterLove to train a small fleet of “influencers” to host informal conversations with community members and study their effectiveness in increasing PrEP knowledge, interest, and uptake among cisgender women. Perkins, the nurse who was unable to get a PrEP prescription from her OB-GYN, is part of the cohort.

SisterLove’s Healthy Love curriculum, backed by the CDC, gives Black women and their social groups the “freedom to hold conversations differently” than they would with medical providers, said the group’s founder, Dázon Dixon Diallo.

Failing to ensure cisgender Black women have access to—and are actually interested in taking—PrEP will undermine the fight to bring the HIV epidemic under control, Diallo warned.

There’s “damage that has to be undone,” she said. “If we’re not centering Black women in this epidemic, we are getting nowhere to the end.” **HIV**

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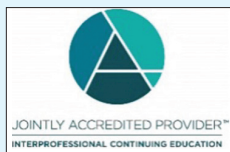
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DESCRIPTION/LEARNING OBJECTIVES

The presentation on which this article is based was selected by ACTHIV® 2023 conference attendees and the conference planning committee as being among the best sessions of the conference. The goal of this article is to help members of the frontline HIV care team to be better able to:

- Review the evidence behind Doxy-PEP.
- Describe the epidemiology of emerging sexually transmitted infections (STIs) including *M. genitalium*, MDR Gonorrhea, LGV, and mpox.
- Educate your team about the clinical syndromes related to these emerging STIs and how to diagnose them.
- Describe first-line treatments for emerging STIs.

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Emerging Sexually Transmitted Infections

Considerations for the Care Team

By ANK E. NIJHAWAN, MD, MPH, MSCS, and HELEN L. KING, MD

THE PREVENTION, DIAGNOSIS, AND MANAGEMENT of sexually transmitted infections (STIs) continue to be an important component of comprehensive HIV care and prevention. In this article, we will address three topics relevant to emerging STIs: prevention (specifically doxycycline post-exposure prophylaxis), complex management (e.g. *Mycoplasma genitalium*, multidrug-resistant *Neisseria gonorrhoeae*, lymphogranuloma venereum), and a novel outbreak (mpox) impacting people with or at risk for HIV.

STI Prevention and Doxycycline Post-Exposure Prophylaxis

Doxycycline post-exposure prophylaxis (doxy-PEP) is the use of doxycycline 200 mg orally within 24 to 72 hours after condomless sex to prevent certain bacterial STIs. A recent randomized controlled trial, the Doxy PEP trial, assessed the efficacy of doxy-PEP at preventing chlamydia, gonorrhea, and syphilis in men who have sex with men (MSM) and transgender women with HIV or who were on HIV pre-exposure prophylaxis (PrEP) in the United States. Participants who received doxy-PEP had over 65 percent reduction in quarterly STI rates, including chlamydia, gonorrhea, and syphilis, compared to those who did not. The reduction in chlamydia rates were the greatest (88% for participants on PrEP and 74% for those with HIV). The reduction of gonorrhea was lower at 55 percent.¹ Similar reductions in chlamydia and syphilis among MSM and transgender women were seen in the iPrEX and DOXYVAC trials conducted in France; however, the iPrEX trial did not see reductions in gonorrhea rates among participants.^{2,3} The baseline resistance rates of gonorrhea to doxycycline are higher than chlamydia and syphilis and vary geographically, which likely explains the differences in trial findings.

Doxycycline was well-tolerated overall with no serious adverse events in the Doxy PEP trial and only two percent of participants discontinued doxycycline for either side effects or patient preference.¹ When taken routinely, people taking doxycycline may develop phototoxicity, esophagitis, or esophageal ulcerations.⁴ The long-term impacts on antimicrobial resistance of STI and non-STI organisms, the microbiome, changes in sexual behavior, and interpretation of STI testing (e.g., syphilis serologies) will require more longitudinal

follow-up of patients who are receiving doxy-PEP.

Doxy-PEP has been shown to significantly reduce bacterial STIs in MSM and transgender women. MSM and transgender women who have high baseline STI rates can be offered doxy-PEP using shared decision making to discuss the potential benefits, adverse effects, and unknown impacts. More research is needed to determine whether doxy-PEP is effective in other populations.

Complex Management

Mycoplasma genitalium

Mycoplasma genitalium was first isolated in 1981 from two men with non-gonococcal urethritis and has since been identified as an emerging sexually transmitted pathogen causing urethritis in men and is associated with cervicitis, pelvic inflammatory disease (PID), infertility, and preterm delivery in women.⁵⁻⁸ *M. genitalium* is estimated to cause 15 to 20 percent of non-gonococcal urethritis and 40 percent of persistent or recurrent urethritis.⁶ *M. genitalium* has also been associated with increased risk of HIV acquisition.⁶ The clinical significance of asymptomatic infection or colonization is unclear, thus routine screening is not currently recommended.⁶

Until recently, diagnostic testing for *M. genitalium* was limited, which contributed to under-recognition of this pathogen. Culturing *M. genitalium* is difficult and can take up to six months.⁶ *M. genitalium* nucleic acid amplification tests (NAAT) are now FDA-approved for vaginal, endocervical, urethral, penile meatal, and urine samples and provide a more rapid and sensitive diagnostic tool. Incorporation of molecular testing to detect macrolide resistance genes is being developed but is

not yet commercially available in the U.S. While routine screening is not recommended, Centers for Disease Control and Prevention (CDC) recommends testing with *M. genitalium* NAAT in men with recurrent urethritis and in women with recurrent cervicitis.⁶

M. genitalium macrolide resistance has increased over time with resistance rates as high as 40 to 90 percent.^{6,9} Thus macrolides, e.g., azithromycin, are no longer recommended for treatment of *M. genitalium* without access to resistance testing. Fluoroquinolone resistance has been observed, but the rates are much lower and stable over time compared to macrolides.⁹ *M. genitalium* lacks a cell wall and thus is inherently resistant to beta-lactam antibiotics.⁶

The 2021 CDC STI treatment guidelines recommend a two-staged approach to treatment of *M. genitalium*.⁶ When resistance testing is unavailable or macrolide resistance mutations are identified on molecular testing, treatment should include doxycycline 100 mg orally twice a day for seven days followed by moxifloxacin 400 mg orally once a day for seven days. If resistance testing is available and no macrolide resistance mutations are detected, treatment should include doxycycline 100 mg orally twice a day for seven days, followed by azithromycin 1 g orally followed by azithromycin 500 mg orally daily for an additional three days.

Multidrug-Resistant Gonorrhea

While gonorrhea is a common sexually transmitted infection worldwide, multidrug-resistant gonorrhea infections are emerging and pose a huge threat to public health. Multidrug resistance is defined as decreased susceptibility/resistance to one currently recommended therapy plus resistance to at least two other antimicrobials. In 2013, the CDC identified drug-resistant *Neisseria gonorrhoeae* as one of three urgent antibiotic resistant public health threats that require immediate and aggressive action due to global identification of resistance to antibiotics commonly used to treat gonorrhea infections, including ceftriaxone, the mainstay of treatment.¹⁰

Since the introduction of sulfonamide antibiotics for the treatment of gonorrhea in the 1930s, *N. gonorrhoeae* has successfully

Emerging Sexually Transmitted Infections: Considerations for the Care Team

POST-ASSESSMENT QUESTIONS

Question 1
A 32-year-old MSM with HIV presents to clinic for routine follow-up. His CD4 count is 532 and his HIV viral load <20 copies/mL. He has been treated two times in the past six months for STIs (once for syphilis, once for chlamydia). He continues to be sexually active and is currently asymptomatic. You renew his antiretroviral medications, offer free condoms, and counsel the patient on safer sex practices. What else would you do at this time?

- A. Repeat STI testing (GC/CT at exposed sites, syphilis testing).
- B. Discuss option of doxycycline post-exposure prophylaxis.
- C. Offer the mpox vaccine if he has not had it yet.
- D. All of the above.

Question 2
Multidrug-resistant gonorrhea is not a concern in the United States.

- A. True
- B. False

Question 3
Which of the following is NOT correct about mpox?

- A. During the 2022 outbreak, mpox disproportionately affected gay men, bisexual men, and other men who have sex with men.
- B. Mpox vaccine should be offered to all adults.
- C. Treatment may be indicated for individuals with severe mpox manifestations or risk factors for development of severe disease.
- D. The diagnosis of mpox is an indication to test for HIV and STIs.

developed antimicrobial resistance to each antibiotic introduced as recommended treatment, including penicillin, tetracycline, spectinomycin, ciprofloxacin, and azithromycin.¹¹ The Gonococcal Isolate Surveillance Project (GISP), the main surveillance system monitoring trends of gonococcal resistance in the U.S., is a collaboration between the CDC, state and local health departments, select STI clinics, and regional laboratories. In 2020, the GISP estimated that the proportion of gonococcal isolates resistant to ciprofloxacin (minimal inhibitory concentration [MIC] ≥ 1.0 $\mu\text{g/ml}$) had increased to 35.4 percent and that 5.8 percent had reduced susceptibility (MIC ≥ 2.0 $\mu\text{g/ml}$) to azithromycin.¹² Increases in azithromycin MICs demonstrated by the GISP led to the removal of azithromycin as part of the first-line treatment combination regimen for gonorrhea in the 2021 CDC STI treatment guidelines. Ceftriaxone was left

as a monotherapy, and due to the threat of cephalosporin-resistant gonorrhea globally, the recommended ceftriaxone dose for all gonorrheal infections was increased to 500 mg intramuscularly once or 1000 mg intramuscularly for those weighing over 150 kg.⁶

While there are no reported cases of gonorrhea treatment failure in the U.S. using cephalosporins, such as ceftriaxone or cefixime, there have been cases of multidrug-resistant and extensively drug-resistant (defined as decreased susceptibility/resistance to two currently recommended therapies plus resistance to at least two others) gonorrhea internationally.^{13,14} Globally, there have been cases of failure to cure gonorrhea with ceftriaxone alone or in combination with azithromycin, including cases in the United Kingdom (U.K.), Australia, Japan, Sweden, and Slovenia.¹⁴ Most cases of treatment failure have been

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pharyngeal gonococcal infections, likely due to decreased antimicrobial penetration and possible cross-resistance with commensal *Neisseria* species colonization of the pharynx.¹⁴ Additionally, in January 2023, there were two locally acquired cases of gonorrhea reported from Massachusetts with isolates found to have decreased susceptibility to ceftriaxone, cefixime, and azithromycin and resistance to ciprofloxacin, tetracycline, and penicillin.¹⁵ A mutation in the *penA60* allele was determined to be the cause of reduced susceptibility to ceftriaxone, which was also found in nine of 10 individuals with ceftriaxone-resistant gonorrhea in the U.K.

All cases of suspected gonorrhea resistance or treatment failure where re-infection has been ruled out should be reported to the CDC by completion of the Suspected Gonorrhea Treatment Failure Consultation Form.¹³

Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is a sexually transmitted infection caused by *Chlamydia trachomatis* serovars L1, L2, and L3.⁶ It was previously relatively rare and is generally classified as an ulcerative disease, however outbreaks of colitis and proctocolitis among MSM, especially MSM with HIV, have been increasingly reported in the U.S. and Europe.¹⁶ This more recent and now more common clinical presentation can mimic inflammatory bowel disease, including rectal pain, mucoid and/or bloody discharge, and tenesmus. LGV can also present with painful inguinal lymphadenopathy.

The laboratory diagnosis of LGV is made by LGV-specific molecular testing, however these tests are not widely available. For this reason, LGV is typically diagnosed based on the clinical presentation, epidemiologic data, and a positive *C. trachomatis* NAAT test at the anatomic site of involvement.⁶ NAAT for *C. trachomatis* does not distinguish between non-LGV and LGV strains, and serologic testing has not been validated and is not recommended for LGV diagnosis. Therefore, a patient with a clinical presentation consistent with LGV should be treated empirically (doxycycline 100mg twice daily for 21 days), as recommended by the CDC.⁶ This 21-day course, though not rigorously studied in

clinical trials, has a high cure rate for LGV.¹⁷ Shorter courses of treatment (e.g. seven to 14 days) may be effective in less severe disease, but prospective trials are needed.¹⁸

Mpox Outbreak

Mpox, formerly known as monkeypox, is an orthopox virus that was previously most commonly seen as a zoonosis in west and central Africa. However, in May 2022, a global outbreak of mpox occurred and on May 17, 2022, the first case of mpox was confirmed in the U.S.¹⁹ In the first year of the outbreak, which peaked in August 2022, over 30,000 cases were detected, with 42 deaths.¹⁹ Though technically not an STI, mpox is associated with close, skin-to-skin physical contact and many cases were detected among gay, bisexual, and other MSM. Of people diagnosed with mpox, over 60 percent were noted to have either HIV or an STI in the preceding year.²⁰ Racial and ethnic disparities were noted in prevalence of disease, with 33 percent of cases occurring among non-Hispanic Black and 31 percent among Hispanic individuals.¹⁹ Differences in mortality were also noted, with 87 percent of deaths occurring among non-Hispanic Black individuals, and of those who died who had information available, 94 percent were immunocompromised due to HIV infection.²¹

The clinical presentation of mpox is variable, but is often characterized by a rash, which may have vesicles or pustules, occurring on the palms, feet, chest, mouth and oral mucosa, genitals, and/or perirectal areas. Skin lesions may be localized or more diffuse, the latter being more common in immunocompromised individuals. Other symptoms include fever, chills, myalgias, fatigue and

headaches, with these usually occurring within three weeks of exposure.²² Mpox is diagnosed through detection of orthopox virus DNA by a polymerase chain reaction (PCR) test, sent on specimens collected directly from skin lesions.

Most patients with mpox can be managed with supportive care and pain control. However, treatment should be considered in individuals with severe disease, immunocompromising conditions such as HIV and malignancy, or with a high risk of developing severe disease, such as pregnant persons, children, and people with pre-existing skin conditions. Severe disease may include numerous confluent lesions, necrotic lesions, severe obstructing lymphadenopathy (such as in the airway), or multi-organ involvement (including myocarditis, pulmonary or ocular lesions).²³

Tecovirimat is FDA-approved for the treatment of human smallpox disease, and though not approved for the treatment of mpox, has been used for this indication through the CDC's investigational new drug protocol. A current ongoing trial, called the Study of Tecovirimat for Human Monkeypox Virus (STOMP), will assess safety and effectiveness of this therapy.²³ Other treatments that have been added for severe cases include brincidofovir or cidofovir, vaccinia immune globulin IV as well as topical trifluridine for ocular involvement. The CDC has published interim guidance on mpox treatment, including an algorithm for treatment of patients with or at risk for severe disease. It should be noted that for each of these treatments there is a limited evidence base for treatment in mpox and safety, efficacy, and dosing should be carefully considered prior to administration.²³

The 2022 mpox outbreak serves as an important reminder to focus on prevention. The JYNNEOS vaccine has been authorized for use in prevention of mpox and should be considered for individuals who are at increased risk for mpox, including individuals who have had close contact with someone who has mpox, gay and bisexual men with a recent STI and one or more sexual partners, or other individuals who anticipate a potential mpox exposure.²⁴ Furthermore, a diagnosis of mpox is an indication to test for HIV and STIs, and to consider PrEP.²⁰ Though the 2022 mpox outbreak has generally subsided, mpox cases continue to occur in 2023 and care teams should remain vigilant to both identify new cases and offer mpox vaccination for those at risk.

Conclusion

We highlight several key issues related to the prevention, management, and recognition of emerging STIs that are relevant to comprehensive sexual health care for people with or at risk for HIV. Key takeaways from this overview include:

- Doxy PEP is an emerging intervention for the prevention of bacterial STIs and may be appropriate for patients with recurrent STIs, though long-term data about resistance is pending.
- *M. genitalium* should be suspected in cases of recurrent urethritis without new exposures, and treatment should be directed by resistance testing if it is available.
- Resistance to *N. gonorrhoeae* is a long-standing and evolving issue with increasing resistance to cephalosporins internationally. Contact the CDC if resistant gonorrhea is suspected.
- LGV is seen commonly among MSM with HIV, typically presenting as proctitis or proctocolitis.
- Mpox spread rapidly in the U.S., especially among MSM with HIV. Populations at risk should be vaccinated and screened for STIs and HIV. **HIV**



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UPDATE

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FEATURED LITERATURE:

Podzamczar D, Imaz A, Lopez-Lirola A, et al. Switching to bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) plus darunavir/cobicistat in heavily antiretroviral-experienced, virologically suppressed HIV-infected adults receiving complex regimens. *J Antimicrob Chemother.* 2023; dkad285. doi: 10.1093/jac/dkad285. PMID: 37725999

Sixty-three participants were enrolled in this single-arm, open-label multi-center pilot evaluating efficacy and safety of BIC/F/TAF + DRV/cobicistat as a switch regimen. Prior to switch, participants had been taking combinations involving three or more ARV classes and three or more pills/day. People with known or suspected INSTI resistance were excluded, as well as people with a darunavir resistance mutation score of ≥ 15 per the Stanford HIV Drug Resistance Database. Median time on ART was 24.3 years, with a current median of four pills daily (some took as many as 10 pills/day). Ten people switched from a regimen which included twice-daily boosted darunavir. Proviral DNA from 39 (62%) participants revealed that 85 percent had resistance associated mutations at baseline; calculated GSS using DNA genotype results indicated that 95 percent of participants had two or more sensitive ARVs. After 48 weeks, 95 percent maintained an undetectable VL. Three people discontinued therapy due to adverse events including rash, headache, and mood symptoms (anxiety), and grade two eGFR decrease. The participant who experienced eGFR decrease had a history of low eGFR attributed to prior TDF use. Pre-dose bicittegravir concentrations increased by 11 to 31 percent compared with reference Cmin values and were 24 percent higher than reference Cmax. Both treatment satisfaction and perception of adherence increased.

AUTHOR'S COMMENTARY:

Although this was a single-arm study involving a fairly uniform patient demographic (95% were assigned male at birth and all sites were in Spain), all participants were switching from complex regimens involving multiple pills. No virologic failures were observed over 48 weeks of follow-up and the new combination appeared to be highly acceptable among participants, with few discontinuations. Given various drug interaction concerns about the co-use of bicittegravir, TAF, and cobicistat, the inclusion of bicittegravir levels in this analysis is informative (N.B. TAF levels were not measured). Due to the high prevalence of kidney disease and TDF exposure among many older PWH, as well as the known interaction between bicittegravir and cobicistat and certain renal transporters, further investigation (including potential use of additional biomarkers) into the safety of this switch regimen are needed. Nevertheless, results of this pilot help support the consideration of additional, larger studies examining this combination.

FEATURED LITERATURE:

Frangé P, Veber F, Burgard M, Blanche S, Avettand-Fenoel V. Bicittegravir/emtricitabine/tenofovir alafenamide in pediatrics: real-life experience from a French cohort (2018-2023). *HIV Med.* 2023. doi: 10.1111/hiv.13562. PMID: 37807595

This retrospective study of the French Necker cohort evaluated safety and efficacy of co-formulated bicittegravir/emtricitabine/tenofovir alafenamide (BIC/F/T) among 74 children and adolescents weighing ≥ 25 kg between January 2019 and July 2023. Of the participants, 93.2 percent were ART experienced and median duration of prior ART use was 7.2 years. As well, 85.1 percent had previous INSTI exposure (mostly dolutegravir). Prior to BIC/F/T initiation, 67.6 percent were suppressed, 25.7 percent had VL ≥ 50 on baseline ART, and 6.8 percent were ART-naïve.

Among individuals with baseline/historical genotype information, 0/59 (0%) had mutations associated with BIC resistance, 15/69 (21.7%) had FTC-associated mutations, and 3/69 (4.3%) had TAF-associated mutations. Overall, one patient discontinued BIC/F/T due to adverse events (suspected gastrointestinal and psychiatric toxicity) and one changed to a two-drug regimen. Over a median follow-up of 40 months, 97.3 percent remained on BIC/F/T and virologic failure occurred in 28/74 (37.8%). With reinforced adherence support and no change in ART, 16/28 (57.1%) patients with virologic failure re-suppressed by the last visit. Emergent T69D/N was identified in one patient and no emergent INSTI mutations were identified.

AUTHOR'S COMMENTARY:

Overall, higher rates of virologic failure were observed in this retrospective pediatric cohort study compared to clinical trials and real-world studies involving adults on BIC/F/TAF. Nevertheless, over half who experienced failure were able to re-suppress with tailored adherence interventions. Perhaps unsurprisingly, BIC/F/T initiation resulted in high rates of virologic suppression among patients who were already suppressed or ART-naïve at baseline. Virologic failure was significantly more common in patients who were viremic prior to BIC/F/TAF. Additionally, given pre-treatment genotypic susceptibility scores in this population, findings of this study may not be generalizable to heavily treatment experienced children/youth with extensive HIV drug resistance. Additionally, the observed association between presence of archived M184V/I and virologic failure bears further investigation.

FEATURED LITERATURE:

Haidar L, Crane HM, Nance RM, et al. Weight loss associated with semaglutide treatment among people with HIV. *AIDS*. 2023. doi: 10.1097/QAD.0000000000003791. PMID: 37976053

Investigators from the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort conducted an observational, longitudinal examination of adult PWH to describe weight changes after semaglutide initiation. There were 222 new semaglutide users at eight academically affiliated study sites across the U.S. (study period 2018–2022) who contributed data. Outcomes of interest were within-person bodyweight change, percentage bodyweight change, and hemoglobin A1c percent change at one year. Almost three-quarters of patients were male, with mean baseline age of 53 years. Average baseline weight was 108 kg (mean BMI: 35.5 kg/m²). Mean HbA1c was 7.7 percent and 77 percent had diabetes at baseline. Of the participants, 89 percent had VL < 50 copies/mL at baseline, with 97 percent on ART (82% were receiving an INSTI-based regimen). Eighty-seven out of 125 received low-dose and 24/125 received high-dose injectable semaglutide, and 14/125 received oral doses. Multivariate modeling indicated that semaglutide treatment was associated with significant bodyweight and percent bodyweight loss at one year (6.47 kg and 5.72%, respectively). Body weight changes among PWH on INSTIs were -6.49 kg vs. -6.38 for people not on INSTIs, with no significant difference between these two subgroups. Semaglutide was also associated with significant A1c reduction at one year: 1.07 percent.

AUTHOR'S COMMENTARY:

This brief report, one of the first describing short-term clinical outcomes among PWH initiating semaglutide, affirms it is an effective pharmacologic intervention for weight loss and diabetes management among PWH. Body weight changes observed among this cohort were comparable to results from trials involving people without HIV. Although limitations include lack of information on semaglutide adherence, ARV adjustments during the observation period, and/or intensive lifestyle modifications adopted by participants, findings indicate that semaglutide at various doses leads to weight loss and A1c reduction. Larger studies including longer follow-up time and incorporation of additional data points such as other clinical outcomes of interest (e.g., CVD and CKD) will help further establish the role of semaglutide in HIV care.

FEATURED LITERATURE:

Zino L, Wit F, Rokx C, et al. Outcomes of bariatric surgery in people with Human Immunodeficiency Virus: a retrospective analysis from the ATHENA Cohort. *Clin Infect Dis*. 2023; 77(11):1561–8. doi: 10.1093/cid/ciad404. PMID: 37392435

This study examined 51 patients who underwent bariatric surgery between 2004 and 2022 in the Netherlands. Median age at surgery was 46 years and 55 percent were women; 76 percent underwent gastric bypass and 24 percent had sleeve gastrectomy. Median weight and BMI pre-procedure were 121kg and 39.8kg/m². Forty-three out of 51 people (84%) had VL < 40 at baseline. Forty-nine percent were on a INSTI + 2 NRTI combination, with 29 percent using DTG as their anchor. Of these 43 people, only one person (who was receiving a three-class regimen) developed virologic failure eight months post-surgery; this was attributed to non-adherence. Three people with undetectable VL at baseline developed blips after six to seven months. The three people on dual therapy remained suppressed over the 18-month follow-up period. Of the participants, 89 percent achieved >20 percent loss of baseline weight, and lipid profiles improved significantly. There were 24 ART modifications among 21 patients, mostly for routine reasons (e.g., desire for treatment simplification, pregnancy, other). One person modified therapy due to persistent low-level viremia. Twelve people stopped all their non-HIV medications and approximately half stopped their antihypertensive or antihyperlipidemic medications; 75 percent stopped their antidiabetic medications. Plasma concentration testing found adequate/therapeutic exposure for elvitegravir, dolutegravir, emtricitabine, and tenofovir (TDF and TAF); darunavir/ritonavir results were mixed. There was no significant difference in weight reduction among people who continuously took INSTI without TAF, or INSTI plus TAF vs. non-INSTI/non-TAF regimens.

AUTHOR'S COMMENTARY:

This retrospective analysis provides reassuring medium-term clinical outcome data across HIV and metabolic-related parameters. Although gastric bypass and other weight-loss surgeries will be considered for only a subset of patients, obesity is likely to remain a priority health concern for HIV providers in the years ahead. As highlighted in a 2018 review, it is critical to understand how these procedures will impact medication absorption, other pharmacologic considerations, and ART efficacy. Additionally, with widespread use of second-generation INSTIs and TAF, more data on post-operative weight changes and hyperlipidemia/other metabolic-related outcomes among people on these specific ARVs are needed. Finally, the medication profile changes highlighted in this study are notable and highly relevant given increasing polypharmacy concerns for aging PWH. **HIV**

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