THE AMERICAN ACADEMY OF HIV MEDICINE ■ DECEMBER 2020

HIV SPECIALIST

Metabolic Issues in HIV

Lipodystrophy in the Current Era of Antiretroviral Therapy

HIV-Associated Wasting

Managing Diabetes in People with HIV

Integrase Strand Transfer Inhibitors Update

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HIV SPECIALIST

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LETTER FROM THE

DIRECTOR

By BRUCE J. PACKETT II
Executive Director, AAHIVM

Managing Metabolics and More

I WOULD LIKE TO START BY WARMLY THANKING DR. DANIEL LEE, Academy member and HIV Specialist, for his work as guest editor for this issue of the *HIV Specialist* focused centrally on the issue of metabolics and HIV. Dr. Lee delivered a series of regional lectures on the topic (specifically looking at HIV-related weight gain and lipodystrophy) wherein his expertise in metabolics in the HIV clinic helped many HIV providers and learners over the course of the year gain a clearer perspective on the impacts of HIV on body fat distribution.

All of our members and credentialed specialists are managing so much more than just a virus, and so many HIV providers are now in a sense specializing not just in infectious disease but also in other organ systems, gerontology and primary care in order to care for the entirety of their patients with a chronic condition. The Academy has dedicated much of its resources to making sure that there are clinical trainings and other medical education programs in various general care arenas, including renal function, bone disease, diabetes, cardiovascular disease, neurocognitive issues and so on. You can find these activities, many with CE credits, in our online Provider Resource Center, including our newly released HIV Management in Primary Care module.

We also know that HIV is being managed by providers who specialize in these other, sometimes more generalized, clinical arenas, and we're very interested in seeing resources and trainings go in the other direction as well. We recently connected with the National AHEC Organization, which represents a network of more than 300 AHEC program offices and centers that serve over 85% of United States counties. Their mission is "to enhance access to quality health care, particularly primary and preventive care, by improving the supply and distribution of healthcare professionals via strategic partnerships with academic programs, communities, and professional organizations." We hope to partner with them in 2021 to advance HIV clinical knowledge in a more general healthcare population.

The New Year also brings an updated Board of Directors to the Academy, which is reflected in our *HIV Specialist* masthead. I'm pleased to welcome Dr. Jonathan Appelbaum as the incoming chair of the Academy's Board of Directors. Dr. Appelbaum has been a long-time Board member and has chaired our HIV and Aging initiative since its inception. To view a full list of our Board of Directors, please visit www.aahvim.org/board-of-directors.

Also in this issue, you'll find columns and information on long acting injectable prevention therapies in cisgendered women, the latest in HIV vaccine research, up-to-date information on the impacts of the election results on HIV providers and their patients, updates on the overlapping of epidemics and the racial disparities therein, and more. We hope that these topics as well as the central focus on metabolics, diabetes and lipodystrophy provides some unique clinical perspectives that you can incorporate into your medical practices to help improve the lives of your patients.

See you in what we hope is a better, healthier 2021!

IN THE NEWS

Teva Launches First Generic Versions of HIV-1 Treatments Truvada and Atripla Tablets in the US

A **U.S. AFFILIATE** of Israeli drugmaker Teva Pharmaceutical Industries Ltd. (NYSE: TEVA) (TASE: TEVA) has made available the first Food and Drug Administration-approved generic versions of Truvada and Atripla tablets, the company said. With 1.2 million people currently living with HIV-1 in the U.S., Teva is committed to increasing access to critical HIV therapies.

Despite significant advances in the treatment and prevention of HIV over the last two decades, there are still 12.6 million people globally who are unable to obtain treatment. With the introduction of these new generic HIV treatment options, Teva strives to further increase access to important therapies.

Emtricitabine and Tenofovir Disoproxil Fumarate tablets are expected to be available through retailers and wholesalers at a wholesale acquisition cost (WAC) of USD 48.51 per tablet.

Efavirenz, Emtricitabine and Tenofovir Disoproxil Fumarate Tablets are expected to be available through retailers and wholesalers at a WAC of USD 78.86 per tablet.

Actual costs to individual patients and providers are anticipated to be lower than WAC because WAC does not account for additional rebates and discounts that may apply. Savings on out-of-pocket costs may vary depending on the patient's insurance payer and eligibility for participation in the assistance program.

Severe acute exacerbations of Hepatitis B have been reported in HBV-infected individuals who have discontinued emtricitabine and tenofovir disoproxil fumarate tablets.

Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in individuals who are infected with HBV and discontinue emtricitabine and tenofovir disoproxil fumarate tablets. If appropriate, anti-hepatitis B therapy may be warranted.

Emtricitabine and tenofovir disoproxil fumarate tablets used for HIV-1 PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and at least every three months during use.

ViiV Healthcare announces once-monthly injectable HIV treatment implementation science study positive findings

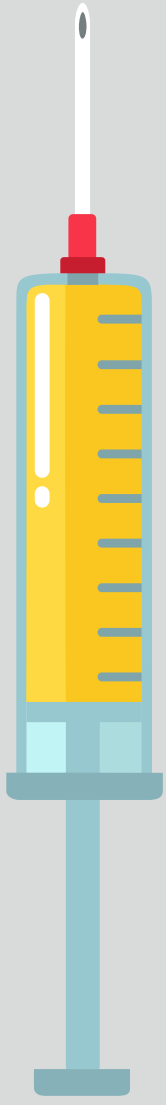
ViiV HEALTHCARE announced positive findings on Thursday from people living with HIV (PLHIV) who are participating in the CUSTOMIZE trial (Cabotegravir plus Rilpivirine in the U.S. to Optimize and Measure Implementation and Experience).

CUSTOMIZE is the first-ever implementation science study that aims to identify successful methods of integrating the investigational once-monthly, long-acting regimen of cabotegravir and rilpivirine for the treatment of HIV-1 into clinical practices in the U.S. These findings build on recently presented healthcare provider and clinical staff survey perspectives and were presented on the announcement date at the 2020 Infectious Diseases Society of America (IDSA) IDWeek.

The CUSTOMIZE study was launched in July 2019 to find the most practical and efficient ways to implement a monthly injectable treatment regimen in the U.S. which, if approved, has the potential to create a paradigm shift in HIV treatment. Since the study began, a team from ViiV Healthcare has worked with healthcare providers, clinical staff, and patients across a range of medical practices, including federally qualified health centres, academic medical centres, and private physician offices.

As part of a survey given to patient participants after the first four months of the study, the majority (91%) said they continued to perceive the once-monthly injectable regimen as highly acceptable for treating their HIV and an appropriate treatment option for their life.

The full 12-month results from the CUSTOMIZE study will be presented at an upcoming medical meeting. The corresponding CARISEL study, which will examine the implementation of the long-acting regimen of cabotegravir and rilpivirine in certain European healthcare settings, started in September 2020 and initial results are expected in 2021.



SHUTTERSTOCK/ SHADE DESIGN

NIH Study Finds Long-Acting Injectable Drug Prevents HIV Acquisition in Cisgender Women

Long-Acting Regimen More Effective than Daily Oral Pill Among African Women

A PRE-EXPOSURE PROPHYLAXIS (PrEP) regimen containing an investigational long-acting form of the HIV drug cabotegravir injected once every eight weeks was safe and more effective than a daily oral PrEP regimen at preventing HIV acquisition among a group of cisgender women. The women, from southern and east Africa, are enrolled in a clinical trial sponsored by the National Institutes of Health (NIH). This finding, from a planned interim analysis of study data, marks the first time a large-scale clinical trial has shown a long-acting injectable form of HIV prevention to be highly effective for cisgender women.

Findings reported earlier this year from a companion study established that the long-acting injectable regimen was safe and more effective than a daily oral PrEP regimen at preventing HIV among cisgender men and transgender women who have sex with men. Both studies are sponsored by NIH's National Institute of Allergy and Infectious Diseases (NIAID) and conducted by the NIH-funded HIV Prevention Trials Network (HPTN). NIAID is co-funding the trial in cisgender women in a unique partnership with ViiV Healthcare and the Bill & Melinda Gates Foundation. ViiV Healthcare and Gilead Sciences, Inc. are providing study medications.

Currently, only one PrEP medication, a daily oral pill that contains the HIV drugs emtricitabine and tenofovir disoproxil fumarate (brand name Truvada), is approved by the U.S. Food and Drug Administration for individuals at risk of acquiring HIV from receptive vaginal sex. While Truvada is highly effective at preventing sexual acquisition of HIV when taken daily as prescribed, a safe and effective long-acting injectable form of PrEP would offer a new option for HIV prevention that may be easier and more desirable for some women.

Launched in late 2017, the Phase 3 trial, called HPTN 084, enrolled 3,223 HIV-negative, sexually active cisgender women at 20 clinical research sites in Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda and Zimbabwe. They range in age from 18 to 45 years, with an average age of 26 years. Participants were randomly assigned to receive either injections of cabotegravir every eight weeks and placebo daily oral tablets or placebo injections every eight weeks and daily oral Truvada. Neither the participants nor the study team knew who was receiving which medication.

In a planned interim review meeting on Nov. 5, 2020, the independent data and safety monitoring board (DSMB) for HPTN 084 found that the study data indicated that long-acting injectable cabotegravir had superior efficacy to Truvada at preventing HIV in the study population. Among the 38 women in the trial who acquired HIV, four were receiving long-acting cabotegravir and 34 were receiving daily oral Truvada. This translated to an HIV incidence rate of 0.21 percent (95% confidence interval [CI] 0.06%-0.54%) in the cabotegravir group and 1.79 percent (95% CI 1.24%-2.51%) in the Truvada group. While both PrEP methods were highly effective at preventing HIV acquisition, the protective effect of cabotegravir met the statistical criteria for superiority (hazard ratio, 0.11; 95% CI 0.04-0.32).

Both cabotegravir and Truvada were well-tolerated among women in the study, and the DSMB found no safety concerns. Some participants experienced pain or tenderness at the injection site; this was more common among women in the cabotegravir group compared to those in the Truvada group, who received placebo injections. Most women in the cabotegravir group received their injections as scheduled, and no participants discontinued injections due to side effects. Adherence to daily oral PrEP can be challenging for some people; 64 percent of a subset of 362 HPTN 084 participants who provided blood samples had detectable concentrations of tenofovir in their blood. Investigators are continuing to analyze and gather data to determine the role that adherence plays.

Based on their review, the DSMB recommended that NIAID stop the blinded phase of the trial, originally designed to continue until 2022, and share the results. NIAID agreed with the DSMB's recommendations and is releasing the results now in the interest of public health. The HPTN 084 investigators will report more detailed information about the study findings, including more comprehensive data, as soon as feasible.

HPTN 084 participants will be informed of the findings and told which medication they were receiving. They will be offered the opportunity to continue in the trial, initially remaining on the PrEP medication that they were assigned to at the beginning of the study. Participants taking Truvada who wish to switch to long-acting cabotegravir will be able to do so as soon as it can be made available. Investigators will continue following participants to gather data about the long-term safety of injectable cabotegravir for HIV prevention among cisgender women.

More information about HPTN 084 and the companion study in men and transgender women who have sex with men, called HPTN 083, is available on ClinicalTrials.gov using identifiers NCT03164564 and NCT02720094, respectively. Three other NIH institutes also collaborate on these trials: the National Institute of Mental Health, the National Institute on Drug Abuse, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

IN THE NEWS

New Cause of Inflammation in People with HIV Identified

WHILE CURRENT antiretroviral treatments for HIV are highly effective, data has shown that people living with HIV appear to experience accelerated aging and have shorter lifespans—by up to five to 10 years—compared to people without HIV. These outcomes have been associated with chronic inflammation, which could lead to the earlier onset of age-associated diseases, such as atherosclerosis, cancers, or neurocognitive decline. A new study led by researchers at Boston Medical Center examined what factors could be contributing to this inflammation, and they identified the inability to control HIV RNA production from existing HIV DNA as a potential key driver of inflammation. Published in *The Journal of Infectious Diseases*, the results underscore the need to develop new treatments targeting the persistent inflammation in people living with HIV in order to improve outcomes.

After infection, HIV becomes a part of an infected person's DNA forever, and in most cases, infected cells are silent and do not replicate the virus. Occasionally, however, RNA is produced from this HIV DNA, which is a first step towards virus replication. Antiretroviral treatments help prevent HIV and AIDS-related complications, but they do not prevent the chronic inflammation that is common among people with HIV and is associated with mortality.

"Our study set out to identify a possible association between HIV latently infected cells with chronic inflammation in people with HIV who have suppressed viral loads," said Nina Lin, MD, a physician scientist at Boston Medical Center (BMC) and Boston University School of Medicine (BUSM).

For this study, researchers had a cohort of 57 individuals with HIV who were treated with antiretroviral therapy. They compared inflammation in the blood and various virus measurements among younger (age less than 35 years) and older (age greater than 50 years) people living with HIV. They also compared the ability of the inflammation present in the blood to activate HIV production from the silent cells with the HIV genome. Their results suggest that an inability to control HIV RNA production even with antiretroviral drugs correlates with inflammation.

"Our findings suggest that novel treatments are needed to target the inflammation persistent in people living with HIV," said Manish Sagar, MD, an infectious diseases physician and researcher at BMC and the study's corresponding author. 'Current antiretroviral drugs prevent new infection, but they do not prevent HIV RNA production, which our results point as a potential key factor driving inflammation in people living with HIV."

According to the Centers for Disease Control and Prevention, it is estimated that 1.2 million Americans are living with HIV; however, approximately 14 percent of these individuals are not aware that they are infected. Another CDC reporter found that of those diagnosed and undiagnosed with HIV in 2018, 76 percent had received some form of HIV care; 58 percent were retained in care; and 65 percent had undetectable or suppressed HIV viral loads. Antiretroviral therapy prevents HIV progression and puts the risk of transmission almost to zero.

The authors note that these results need to be replicated in larger cohorts. "We hope that our study results will serve as a springboard for examining drugs that stop HIV RNA production as a way to reduce inflammation," added Sagar, also an associate professor of medicine and microbiology at BUSM.

This study was supported in part by the National Institutes of Health (grant award numbers AG060890 and AI145661, the Boston University Genomic Science Institute and was facilitated by the Providence/Boston Center for AIDS Research.

SHUTTERSTOCK/ LIGHTSPRING

Death Rate Decreases in People with HIV

ACCORDING TO A *VITAL SIGNS* REPORT published in the Nov. 20 issue of the U.S. Centers for Disease Control and Prevention *Morbidity and Mortality Weekly Report*, there was a 36.6 percent decrease in the rate of death among persons with diagnosed HIV from 2010 to 2018.

The researchers found that death rates decreased by 36.6 percent overall during 2010 to 2018 (from 19.4 to 12.3 per 1,000 PWDH). HIV-related death rates decreased 48.4 percent during 2010 to 2017 (from 9.1 to 4.7), while there was an 8.6 percent decrease in non-HIV-related deaths (from 9.3 to 8.5). During 2017, the rates of HIV-related deaths were highest by race/ethnicity among persons of multiple races and Black/African American persons (7.0 and 5.6, respectively), followed by Whites and Hispanic/Latinos (3.9 and 3.9, respectively). The highest and lowest HIV-related death rates were seen in the South and Northeast (6.0 and 3.2, respectively).

The report concludes "early diagnosis, prompt treatment, and maintaining access to high-quality care and treatment have been successful in reducing HIV-related deaths and remain necessary for continuing reductions in HIV-related deaths."

Engineered immune cells elicit broad response to HIV in mice, offering hope for vaccine or functional cure

SCIENTISTS developed an approach that successfully generates antibodies against numerous strains of the fast-evolving human immunodeficiency virus.

Unlike so many other deadly viruses, HIV still lacks a vaccine. The virus—which continues to infect millions around the world—has proven especially tricky to prevent with conventional antibodies, in part because it evolves so rapidly in the body. Any solution would require coaxing the body into producing a special type of antibody that can act broadly to defeat multiple strains of the virus at once.

This week, scientists at Scripps Research moved closer to attaining that holy grail of HIV research with a new vaccine approach that would rely on genetically engineered immune cells from the patient's body.

In experiments involving mice, the approach successfully induced broadly neutralizing antibodies—also called bnabs—that can prevent HIV infection, says principal investigator James Voss, PhD, of Scripps Research. The study appears in *Nature Communications.*

Voss and his team showed in 2019 that it was possible to reprogram the antibody genes of the immune system's B cells using CRISPR so the cells would produce the same broadly neutralizing HIV antibodies that have been found in rare HIV patients.

The new study shows that such engineered B cells, after being reintroduced to the body, can multiply in response to a vaccination—and mature into memory cells and plasma cells that produce high levels of protective antibodies for long periods of time in the body. The team also demonstrated that the engineered genes can be improved to make antibodies that are even more effective against the virus, using a process that normally occurs in B cells that are responding to immunization.

"This is the first time it has been shown that modified B cells can create a durable engineered antibody response in a relevant animal model," Voss explains.

He hopes that his vaccine approach may someday prevent new HIV infections and possibly offer a functional cure to those who already have HIV/AIDS. The virus is still prevalent throughout the world, with an estimated 38 million people with the disease in 2019.

Voss notes that in humans, the starting cells to create the vaccine could be obtained easily from a simple blood draw, then engineered in the lab before being reintroduced to the patient. He and his team—including first author Deli Huang, PhD, Jenny Tran, PhD, Alex Olson, PhD, and graduate student Mary Tenuta—are now exploring ways to improve the technology so that it would be accessible to the greatest number of people. Because the approach relies on delivering genes to a patient's own immune cells, this could be a significant challenge.

"People think of cell therapies as being very expensive," Voss says. "We're doing a lot of work towards trying to make the technology affordable as a preventative HIV vaccine or functional cure that would replace daily antiviral therapy."

The study, "Vaccine elicitation of HIV broadly neutralizing antibodies from engineered B cells," was authored by Deli Huang, Jenny Tuyet Tran, Alex Olson, Thomas Vollbrecht, Mary Tenuta, Mariia Guryleva, Roberta Fuller, Torben Schiffner, Justin Abadejos, Lauren Couvrette, Tanya Blane, Karen Saye, Wenjuan Li, Elise Landais, Alicia Gonzalez-Martin, William Schief, Ben Murrell, Dennis Burton, David Nemazee and James Voss.

SPOTLIGHT

BY AARON AUSTIN, MEMBERSHIP DIRECTOR

Milena Murray, PharmD, MSc, BCIDP, AAHIVP
Chicago, Illinois

MILENA MURRAY went to the Philadelphia College of Pharmacy in Philadelphia, Pennsylvania before moving to Brooklyn, New York to complete a PGY-1 Pharmacy Residency at Maimonides Medical Center. As a resident, she staffed the emergency room. "I later found that I loved this environment because of all the antibiotic use," reflects Dr. Murray. Immediately following residency, she completed an ID fellowship at Northwestern Memorial Hospital through Midwestern University in Chicago/Downers Grove, Illinois. That was about seven years ago and, since then, Dr. Murray has been engaged in the care of people living with HIV.

"I practice at a large clinic with over 1,000 patients in Chicago, Illinois. We have nurses, social workers, advanced practice providers, and physicians. We also train ID fellows. I am one of two pharmacists for the clinic." Dr. Murray and her team have a wide variety of patient types. The clinic sees 60 to 70 patients a day for a variety of reasons. Most of her patient population is living with HIV and her team also has transplant ID, follow-up ID, and a special clinic half-day for pregnant patients living with HIV. They see patients of all socioeconomic statuses and types of insurance. Many of their patients have been followed for 20+ years with a large population of aging patients.

With these patients, it is important to try to understand reasons for adherence or non-adherence. "You have to develop a relationship with the patient to find out this information," says Dr. Murray, "Once the true barrier is known, you can help the patient overcome it. For those who are adherent, the reason that drives adherence can be a helpful reminder when a patient is experiencing pill fatigue."

One successful practice that Dr. Murray would share with others is having pharmacy students that are pharmacist extenders in the clinic, enabling reach to so many more patients. Reflecting on unique opportunities she has had in her career; she remembers the experience of counseling a patient with vision impairment about his new therapy. "It was a most humbling moment to tell the patient about the medications and have him touch each tablet/capsule."

"...In pharmacy school, I had a clinical rotation at an outpatient ID clinic and I loved the role of a pharmacist in this setting..."

Asked about what motivated her to pursue specializing in HIV care, Dr. Murray recalls, "I have always had a fascination with HIV. In the third grade, our gym teacher taught us about blood-borne illness and HIV piqued my interest. In pharmacy school, I had a clinical rotation at an outpatient ID clinic and I loved the role of a pharmacist in this setting. During residency, I found my true love in ID and pursued fellowship training. When it came time to find a job, I felt like the luckiest person in the world to be placed in an outpatient ID clinic with such a large patient base living with HIV."

Dr. Murray is a teacher at heart and loves educating patients, other providers, and answering all of the "hard" questions about antiretrovirals. She enjoys facilitating medication access for patients and solving clinical issues such as Dr.ug-Dr.ug interactions. Says Dr. Murray, "My greatest obstacle is insurance companies limiting treatment for life-saving medications. I never give up and appeal as many times as necessary!" Looking to the future, Murray envisions "Injectable everything! We will be seeing patients less frequently unless we are also providing primary care."

Dr Murray counsels on medication regimens (*above*), pictured (*top right*) with her pharmacy school advisor, Dr Daniel Hussar, and preparing for an annual continuing education program at Midwestern University (bottom right).

Beyond her professional life, Murray loves to bake, especially in fun-shaped bundt pans such as castles. "A word of warning though, they are 'too pretty' to eat, so I cut out a piece before serving so everyone thinks that someone already took the first piece! During COVID, I have started cultivating plants and find taking care of them to be very therapeutic."

Asked why she joined AAHIVM as an Academy Member, she says, "This will sound crazy. I saw 'AAHIVP' at the end of a colleague's credentials and I didn't know what it was. So I asked her and then decided credentialing would be a good idea if I were going to practice in the HIV arena. I joined the Academy and earned my AAHIVP credential. Fast forwarding to today, I am on the Executive Committee of the Academy's National Board of Directors! I have really enjoyed my involvement with the Academy and all of the wonderful staff." **HIV**

ABOUT THE AUTHOR: AAHIVM Membership Director **AARON AUSTIN** organizes, engages and leads the Academy's global membership of frontline HIV care providers around initiatives of advocacy, education and professional development. He is currently completing coursework for his MPH at The George Washington University Milken Institute School of Public Health.

The 2020 Election Results May Impact Ending the HIV Epidemic

BY WILLIAM McCOLL, McCOLL STRATEGIES

IN A NAIL BITER OF AN ELECTION and after four days of waiting for final results, the Associated Press and most other press organizations called the Presidential election in favor of Joseph R. Biden becoming the President-Elect. With legal challenges from President Donald Trump falling by the wayside, all states are likely to certify the election results before December 8th, Mr. Biden will take office becoming the 46th President of the United States at 12:00 noon Eastern on January 20th. The American Academy of HIV Medicine has been following the election closely and continues to review House and Senate seats as they are being counted.

The Senate is currently 48 Democrats to 50 Republicans, with two seats in Georgia headed to a January 5th runoff. If Democrats win both of those races, the Senate would be split 50/50 and deciding votes would go to the new Vice President-Elect Kamala Harris (D-CA). Senator-Elect Mark Kelly, a Democrat from Arizona, will be seated as early as the end of the month.

As of this writing in mid-November there are now at least 218 Democratic seats enough for House Democrats to retain their majority although they will lose seats. Nancy Pelosi (D-CA) is expected to remain as Majority Leader. Three seats flipped from Republican to Democratic and at least 11 seats have flipped from Democratic to Republican. A particular loss for the HIV community is the expertise of Rep. Diana Shalala, a former Secretary of Health and Human Services who lost her Miami area seat to Maria Elvira Salazar who is a former television journalist and campaigned strongly on retaining sanctions against Cuba. It is expected that there will be approximately 55 new members of Congress. The Academy plans to research the backgrounds of all members and to reach out especially to new members who are doctors, along with those strongly committed to public health and ending the HIV epidemic.

Following the announcement of his presumed win, President-Elect Biden announced the formation of a transition team that would focus on four key issue areas, COVID-19, Economic Recovery, Racial Equity and Climate Change. The Academy is focusing on several key members of the transition team who have healthcare experience including Representative Cedric Richmond (D-LA), New Mexico governor Michelle Lujan Grisham (a former member of Congress), Vivek Murthy the former Surgeon General of the United States under President Obama and Gautam Raghavan, who is a former chief of staff to Representative Pramila Jayapal (D-WA) and was previously an associate director of public engagement for LGBTQ and Asian-American Pacific Islander issues under President Obama.

The transition team also announced a new COVID task force that has already begun working and President-Elect Biden has called for Americans to join together to wear masks and bring the epidemic under control. The COVID task force includes:

- David Kessler, M.D., co-chair, former FDA commissioner
- Marcella Nunez-Smith, M.D., co-chair, Yale associate dean for health equity research
- Vivek Murthy, M.D., co-chair, former surgeon general
- Luciana Borio, M.D., former assistant FDA commissioner
- Rick Bright, Ph.D., former BARDA director
- Zeke Emanuel, M.D., former Obama administration health policy adviser
- Atul Gawande, M.D., Brigham and Women's hospital professor of surgery
- Celine Gounder, M.D., NYU Grossman School of Medicine assistant professor
- Dr. Julie Morita, M.D., former Chicago public health commissioner
- Michael Osterholm, Ph.D., director of the Center for Infectious Disease Research and Policy at the University of Minnesota
- Loyce Pace, MPH, executive director of the Global Health Council
- Dr. Robert Rodriguez, M.D., UCSF emergency medicine professor
- Eric Goosby, M.D., former Ryan White Care Act director

Notably, doctors Gawande, Goosby, Murthy and Osterholm all have significant expertise in HIV issues.

Reprinted from The Academy Voice, a bi-weekly policy e-newsletter distributed to AAHIVM members. You can find past copies of The Academy Voice under the Advocacy section of the Academy website.

Attention has also turned to who is likely to become a cabinet secretary in various positions. The Secretary of Health and Human Services has particular impact on HIV policy with many notable names said to be in contention. Some of the names that the Academy has been hearing include: Dr. Mandy Cohen (the current North Carolina Secretary of Health), Dr. Emanuel, Governor Lujan Grisham, Dr. Murthy, and Andy Slavitt (a former Acting Administrator of the Centers for Medicare and Medicaid Service under President Obama). The Secretary of Housing and Urban Development is also important in the HIV response due to the Housing Opportunities for People With AIDS (HOPWA) program. Rep. Karen Bass (D-CA), Mayor Keisha Lance Bottoms of Atlanta, GA, Mayor Alvin Brown of Jackson, MS; National Low Income Housing Coalition, and Diane Yentel, President & CEO of the National Low Income Housing Coalition have all been rumored as potential picks.

There is additional speculation that an upcoming Biden administration would restore the position of the Director of Office of National AIDS Policy (ONAP), a position that has not been filled by the Trump Administration. It is not clear what will happen with the Trump Administration's Ending the HIV Epidemic plan. President-Elect Biden has said that he would support ending the epidemic by 2025 which may include absorbing the plan into a new Biden Administration effort. The Academy strongly supports both restoring ONAP and Ending the HIV Epidemic.

In the meantime, during the final months of the year Congress is expected to move forward on both new emergency funding to combat COVID-19 and appropriations funding for fiscal year (FY) 2021. Both Democrats and Republicans are well positioned to try to make something happen at the end of what is now a lame duck session of Congress. Senator Richard Shelby (R-AL) released the FY '21 appropriations bills on November 10th. The current continuing resolution funding the federal government runs out on December 11th creating a deadline for passage of the appropriations bills. Given the time constraints, advocates are expecting that both appropriations and a COVID package could move forward together.

One concern is whether enough funding for HIV will be provided in a COVID package and the Academy is expecting to fight hard along key allies to ensure that appropriate levels of funding in both will be included. Contentious parts of the COVID package legislation include ensuring adequate funding for state and local jurisdictions that have had their budgets depleted by the need to respond to COVID, extending liability protections to businesses from lawsuits related to COVID and extending funding from the CARES Act extend through December of 2022.

Although it is unclear how well the transition will operate as President Trump continues to contest the election, the Academy is currently working with Congress to pass the COVID package and appropriations funding and stands ready to move forward on priorities seeking an end to HIV, COVID and related epidemics. **HIV**

WILLIAM D. MCCOLL, ESQ., is currently the owner of McColl Strategies a private unincorporated firm providing consulting, strategy and planning for federal and state level public health, criminal justice and harm reduction policy issues. He is a long-time advocate on behalf of criminal justice reform, healthcare policy, and HIV/AIDS and alcohol and other drug treatment and reform issues. An expert in Congressional appropriations and advocacy, he is currently consulting with organizations regarding the response to COVID-19, criminal justice sentencing alternatives, HIV/AIDS issues and overdose prevention. He has long worked to enact and implement healthcare reform, effectively advocated for ending the ban on federal funding for syringe exchange, multiple successful reauthorizations including SAMHSA and the Ryan White CARE Act, treatment instead of incarceration, almost all facets of HIV national policy, ending HIV-specific criminal prosecutions throughout the U.S. and other state level advocacy.

SHUTTERSTOCK/ MATT GUSH

Introduction to the Metabolic Package

Dear Readers,

I started my journey working in HIV care as an Internist who chose to specialize in HIV medicine. As part of my HIV Fellowship training at UC San Diego Medical Center in 1998, I was tasked with performing a research project. This was a unique time in HIV care, soon after the initiation of highly active antiretroviral therapy (HAART) starting in 1995. The severely ill patients I was seeing at that time were starting to do much better on triple therapy with mainly a protease inhibitor-based regimen.

However, what was clear to see was the onset of multiple metabolic issues, including primarily dyslipidemias and body composition changes. My research project as an HIV fellow was in evaluating how common these metabolic pertubations were happening at the Owen Clinic, UCSD's HIV clinic.

After finishing my HIV Fellowship, I was encouraged by my mentor, Dr. Christopher W. Mathews, to start a metabolic clinic focused on the clinical management of these metabolic problems. Thus, the Owen Lipid/Lipodystrophy Clinic began in 1999 and this subspecialty clinic still exists 20+ years later. We remain focused on managing the broad variety of metabolic issues in HIV care, including dyslipidemia, insulin resistance/diabetes, lipodystrophy, wasting, weight gain/obesity, and osteopenia/osteoporosis.

The following invited articles, while mostly supported by basic science and clinical research, are also based on my own interpretation of the data and my clinical observations from seeing patients with these metabolic conditions over the past 20+ years. I feel that the addition of clinical observations to these invited articles are important, as not everything that we do as clinicians is necessary supported by research, but still has clinical relevance and applicability to patient care. I will do my best to note when I am stating my opinions versus presenting published data, which will be cited.

By Daniel Lee, MD, AAHIVS

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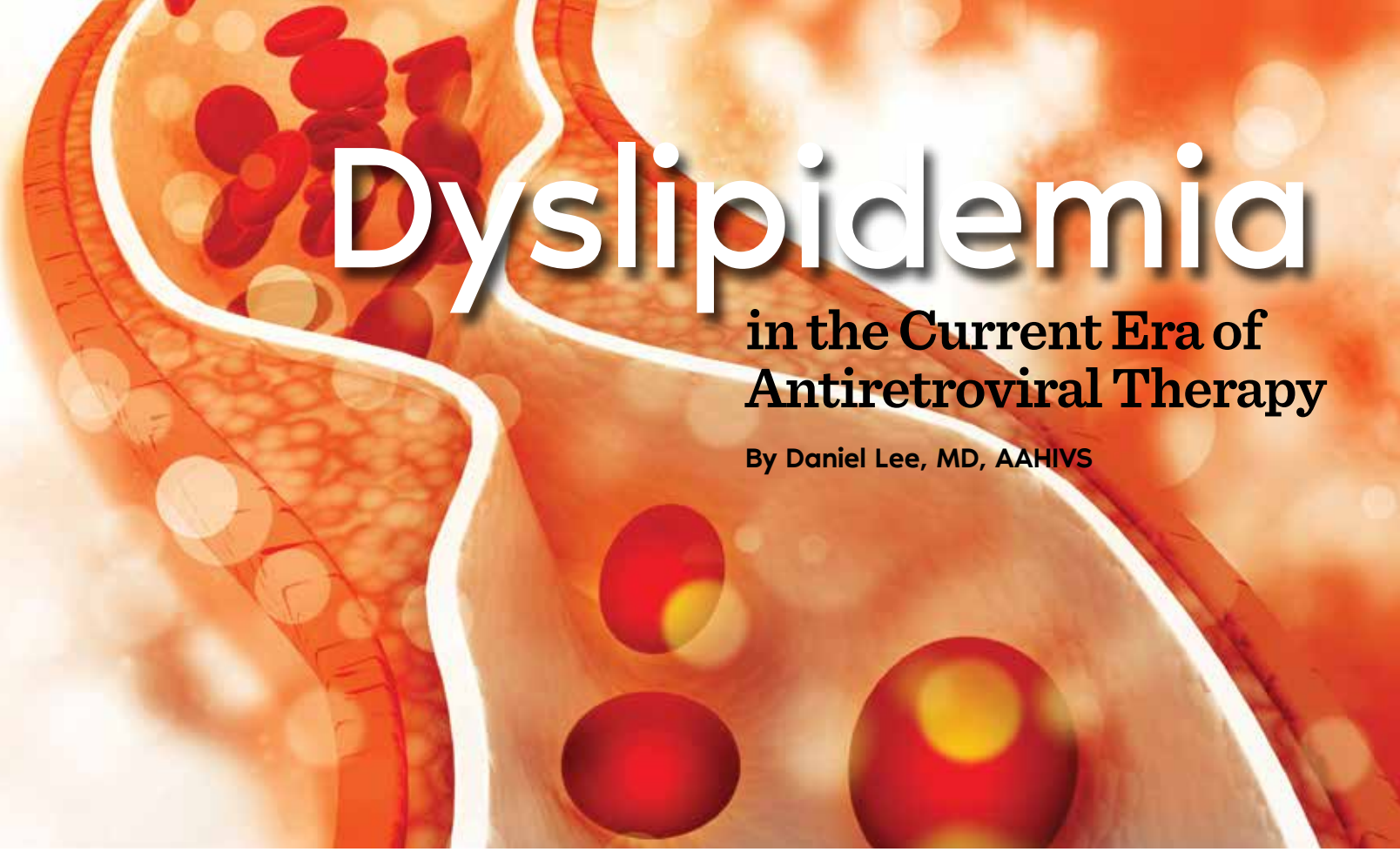


Dyslipidemia in the Current Era of Antiretroviral Therapy

By Daniel Lee, MD, AAHIVS

LET'S BEGIN WITH A CLINICAL CASE SCENARIO. Imagine that you have three patients, each which has the exact same lipid profile: Total cholesterol of 180 mg/dL, Triglycerides of 285 mg/dL, HDL-cholesterol of 30 mg/dL, and LDL-cholesterol of 93 mg/dL. Assuming that an antiretroviral (ARV) regimen will be started, can you predict who will develop dyslipidemia, and if so, how? Which of the following three patients will also likely have the worst lipid profile after starting on any ARVs? Which patient will likely have the worst lipid profile? Which patient will likely have the best lipid profile?

Dyslipidemia in the HIV population has evolved over time. In the era before highly active antiretroviral therapy (HAART) with monotherapy and dual therapy nucleoside reverse transcriptase inhibitors (NRTIs), the most common presentation of dyslipidemia was hypertriglyceridemia. This was mainly caused by uncontrolled and/or suboptimal control of HIV viremia, leading to increased cytokine activity and subsequent dysregulation of metabolic processes.[1-3] The result was increased free fatty acids and decreased clearance of triglycerides.[2]

In the early HAART era with the use of a protease inhibitor (PI) with two NRTIs, the main presentation of dyslipidemia was still hypertriglyceridemia, but mainly was driven by PT therapy.[4] Many of the older PIs directly caused hypertriglyceridemia (e.g. Ritonavir) and increased the risk of insulin resistance (e.g. Indinavir), which in turn may have also indirectly lead to hypertriglyceridemia. Furthermore, some of the older NRTIs (e.g. stavudine) caused mitochondrial toxicity, which led to lipoatrophy and the subsequent release of additional triglycerides into the bloodstream.[5]

In the current antiretroviral therapy (ART) era, which began with the introduction of integrase strand transfer inhibitors (INSTIs), these drugs appear to have fewer side effects compared to regimens used in the early years.[6] With this said, the main presentation of dyslipidemia is more likely to be hypercholesterolemia. This is less driven by ART as most current regimens are fairly lipid-neutral. However, this is more likely a result of weight gain in people with HIV (PWH) and perhaps impacted by the aging process (whether accelerated and/or accentuated aging exists in HIV is still to be debated), a general slowing of metabolism, living in an environment, and/or development of other comorbidities (e.g. diabetes or hypothyroidism).

To better understand the development of dyslipidemia in PWH, it is important to consider the natural evolution of lipids before and after HIV infection. The best natural evolution study of lipids is the MACS Cohort, which evaluated people without HIV and followed them before HIV infection and after HIV infection.[3] This study suggested that

SHUTTERSTOCK/ HYWARDS

CASE SCENARIO #1

PATIENT #1

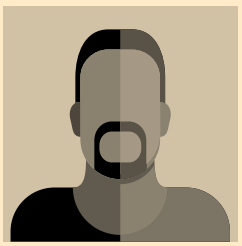
34 year old Caucasian male with HIV for 5 years

CD4 = 280 cells, VL = 145,000 copies/mL

PATIENT #2

56 year old Latina female with HIV for 1 year

CD4 = 365 cells, VL = 28,000 copies/mL



PATIENT #3

42 year old African-American male w/PCP pneumonia and recent diagnosis of HIV last week

CD4 = 25 cells, VL > 750,000 copies/mL

- Let us assume that each patient has the same lipid profile: TC = 180 mg/dL, TG = 285 mg/dL, HDL = 30 mg/dL, LDL = 93 mg/dL
- Assuming a HAART regimen will be started, can you predict who will develop dyslipidemia? If so,how?
- Which patient do you think may have the worst lipid profile after starting on any antiretroviral regimen? And what order from worst to best?

Questions to your HIV patients when evaluating dyslipidemia

- Do you know what your fasting lipids were prior to HIV infection?
- How long do you think that you have been HIV-infected?
- What is the lowest CD4 or highest viral load that you have had in the past?
- Has anyone else in your family had high cholesterol or triglycerides?

after seroconversion to HIV, total cholesterol (TC), LDL-cholesterol (LDL), and HDL-cholesterol (HDL) declined over time. However, with the initiation of HAART, there is a subsequent "return to health" phenomenon with a rise of TC, LDL, and HDL (much less so) back to baseline levels.[3] This is a key concept to keep in mind when evaluating lipids in someone with HIV.

There are many other factors to consider when a rise in lipids is seen. It is possible that the patient may have had dyslipidemia prior to HIV infection. There are also both direct and indirect effects of HIV and ART on lipid metabolism (PI effect on lipid and glucose metabolism and NRTI effect on mitochondrial toxicity as per above).[4,5] Other factors include weight gain due to poor diet and a lack of exercise are associated with subsequent dyslipidemia.

It has been observed, that prior to initiation of ART, people with untreated HIV may have been compensating for weight loss with increased caloric intake. In addition, those with untreated HIV may have medical conditions and/or opportunistic infections which affect their motivation or ability to exercise, such as foot pain from peripheral neuropathy, HIV-related wasting, chronic fatigue, or depression. The development of glucose abnormalities (impaired glucose tolerance, insulin resistance, or diabetes mellitus) and/or fat abnormalities (lipodystrophy) can also contribute to lipid elevations. Lastly, elevations in serum lipid levels are seen as PWH age and some of these individuals may have a familial hyperlipidemia.

Case Study Conclusion

Assuming that each patient noted in the case vignette above has the same lipid profile and will start ART, can you predict who might develop dyslipidemia? The answer is yes. In my experience, one can predict who will develop dyslipidemia based on how long that person has been likely HIV-infected. The longer that someone has been HIV-infected, the lower their lipids likely are prior to starting ART, which means that they are more likely to have a greater "return to health" rise in their lipids. Based on this understanding, Patient #3 is likely to have had HIV longer than the other two patients based on a lower CD4 count and higher HIV viral load. This is followed by Patient #1 and then Patient #2, who likely has been HIV-infected for the least amount of time.

Factors which can help to predict dyslipidemia in patients starting HAART include the "actual" date of HIV infection versus the date of HIV diagnosis. Although Patient #3's date of HIV diagnosis was last week, his "actual" date of HIV infection was likely be eight to 10 years prior. A second factor that may help to predict dyslipidemia is the nadir CD4 count and highest HIV viral load.[3] The lower the CD4 count and higher the viral load, the higher the likelihood that the person has been HIV-infected longer. Lastly, the choice of ART regimen can also predict dyslipidemia,[4] though in our current era, the majority of regimens are fairly lipid-neutral and less likely to cause dyslipidemia.[6]

Management of Dyslipidemia in People with HIV

The management of dyslipidemia in HIV is not that different than in people without HIV. However, there are several caveats.[4,7,8] Adult HIV guidelines recommend screening for dyslipidemia at baseline, prior to initiating HAART, within one to three months after starting a new regimen, and every six to 12 months thereafter.[4] Determination of the cause(s) of dyslipidemia, evaluation of cardiovascular disease risk factors, and standard risk reduction measures, such as smoking cessation, improving diet, and increasing exercise, should be implemented.

If a patient's current ART regimen is contributing to dyslipidemia, it is recommended switching to alternative medications provided this can be done without compromising virologic control. The indications for treatment of dyslipidemia is the same in people with HIV as with people without HIV,

SHUTTERSTOCK/ ETRAVELER

and is based on the 10-year Atherosclerotic Cardiovascular Disease (ASCVD) Risk Score.

The treatment options for dyslipidemia in individuals with HIV include behavior modification, modification/substitution of ART, and/or initiation of pharmacologic therapies. Behavior modification strategies include reduction of dietary cholesterol and triglycerides. General recommendations include eating fewer red meats, eggs (specifically egg yolks), cheese, and processed foods. Some experts recommend the "Mediterranean diet" (more nuts, olive oil, fresh fruits and vegetables). In regards to exercise, the American Heart Association recommends 150 minutes/week of moderate intensity or 75 minutes/week of vigorous intensity aerobic physical activity.[9] Alcohol cessation is recommended to reduce triglycerides and smoking cessation is recommended to reduce cardiovascular risk.

Modification or substitution of ART is a viable strategy if the etiology of dyslipidemia is deemed to be related to ART. This is especially true for patients at high-risk for cardiovascular disease (CVD). An example would be switching a patient from a PI boosted-regimen containing ritonavir to a non-boosted drug or a medication from a different class. This is based on clinical studies showing an elevation in lipids with boosted versus unboosted regimens.[10] If a person with HIV is still receiving an older ART regimen that is known to cause dyslipidemia, it may be ideal to switch out the offending agent to more lipid-neutral medication. Lipid-neutral non-nucleoside reverse transcriptase inhibitors (NNRTIs) include Rilpivirine, Doravirine, and Etravirine. Lipid-neutral PIs include unboosted Atazanavir. Lipid-neutral NRTIs include Abacavir, Lamivudine, and Emtricitabine. Tenofovir disoproxil fumarate (TDF) actually has some lipid lowering properties.[11] As a class the INSTIs including Raltegravir, Dolutegravir, and Bictegravir appear to be lipid-neutral. Changing therapy has become less necessary in the current era as most ART options are fairly lipid-neutral

Pharmacologic therapy for dyslipidemia is also similar for those living with and without HIV infection.[12] For hypertriglyceridemia, fibrates are the mainstay of therapy. Fenofibrate is preferred over gemfibrozil as it is dosed daily (versus twice daily) and there are less drug interactions with statins. Fish oil can also be utilized to lower triglycerides, but can be challenging due to the increase in additional pill burden. Some patients may find fish oil more preferable due to the perception that it is more natural than a pharmaceutical produced medication.

For mixed hyperlipidemia, statins are the recommended therapy to lower TC and LDL-cholesterol. The choice of statin should take into account the relative efficacy of the statin balanced, whether a high or moderate intensity statin is needed based on a patient's overall CVD risk score, and also one must consider potential side effects and drug-drug interactions. Some statins, specifically simvastatin and lovastatin have potential interactions with ART, leading to concerns for muscle and liver toxicity. My preferred choice is rosuvastatin, which is mainly due to its high potency. A second preference is atorvastatin and a reasonable option if rosuvastatin is not covered by insurance. While pravastatin is unlikely to interact with ART, it is much less potent than other statins.

Other non-statin options include ezetimibe, which has a synergistic effect with statins, bempedoic acid, and PCSK9 Inhibitors, a group of injectable medications given every two to four weeks, which preliminarily has shown significant reductions in LDL-cholesterol in people with HIV.[12] It must be noted that there are no data regarding the benefits of non-statin therapies on cardiovascular outcomes.

In conclusion, we have reviewed the clinical management of dyslipidemia in people with HIV and included practical tips based on my clinical experience. Keep in mind that there are some unique considerations when treating dyslipidemia in PWH. First of all, dyslipidemia may be more difficult to treat in those with HIV. In part, this is due to the fact that HIV itself may contribute to dyslipidemia, whether treated or not. The dyslipidemia may also be caused by the ART that is being used to treat HIV. There may not always be options to switch to other lipid-neutral ART due to drug resistance and/or intolerability to other medications.

Secondly, PWH may also need titration to higher doses of lipid-lowering drugs and more complex combination therapies, leading to potential increased toxicities. Thirdly, there are potential cytochrome P450 drug interactions with ART and statin therapies which can lead to increased toxicity even with standard or low dosing. Lastly, it is important to realize that dyslipidemia can evolve over time as our patients age along with changes in lipid, glucose, and fat metabolism. Continued periodic monitoring of patients is key in diagnosing and treating dyslipidemia to reduce the risk of CVD and related clinical events. **HIV**

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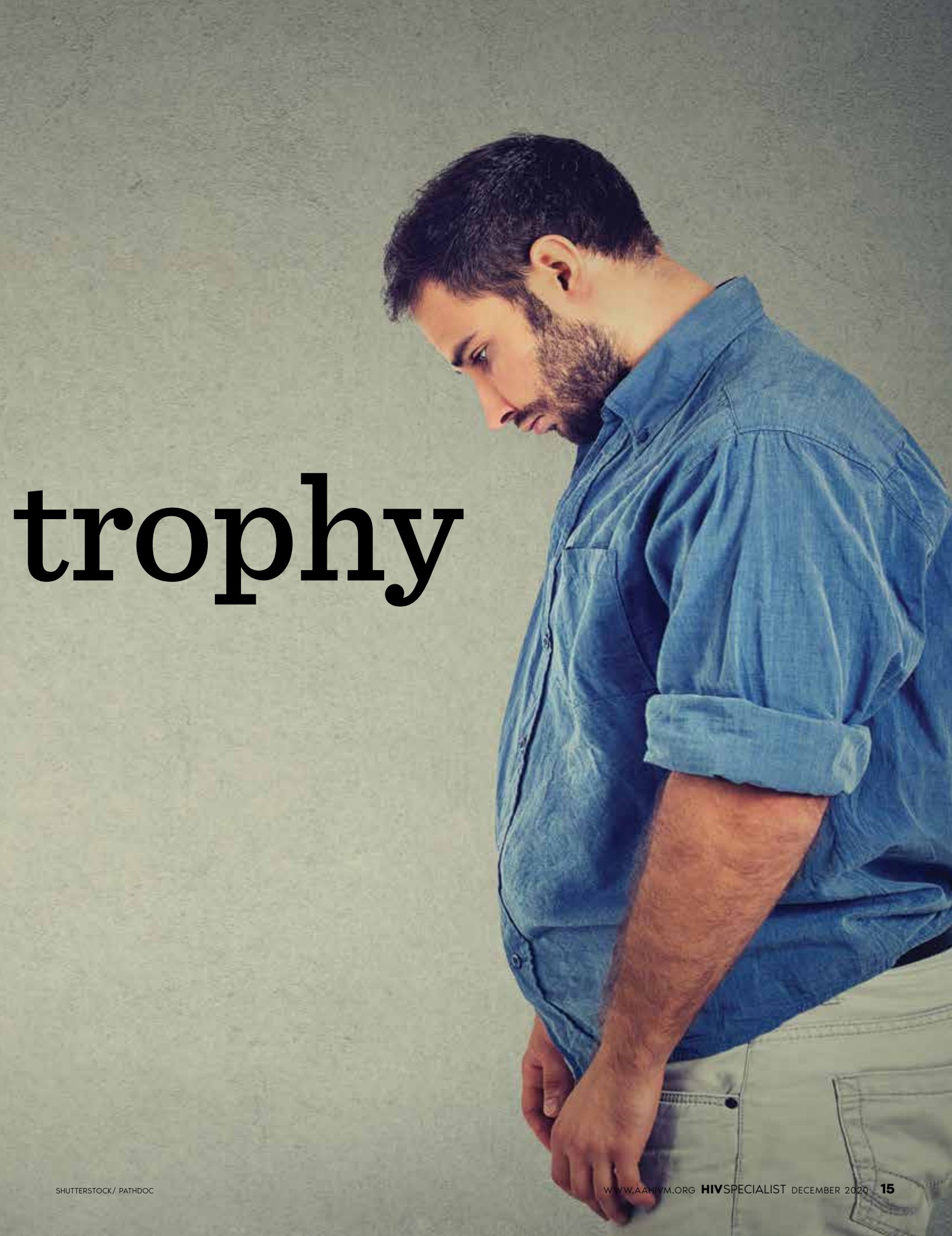
THE UPS AND DOWNS OF Lipodys

By Daniel Lee, MD, AAHIVS

LIPODYSTROPHY is a term used to describe the abnormal distribution of body fat that may occur in persons with HIV (PWH).[1] Lipodystrophy was much more common in the early days of the HIV epidemic, and was mainly associated with the use of older nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) such as indinavir. Some individuals may have evidence of mainly fat loss, known as lipoatrophy, while others may have evidence of fat accumulation, known as lipohypertrophy. However, most have a combination of both fat loss and fat accumulation. Often times, there are also cholesterol and/or glucose abnormalities associated with HIV lipodystrophy.

trophy



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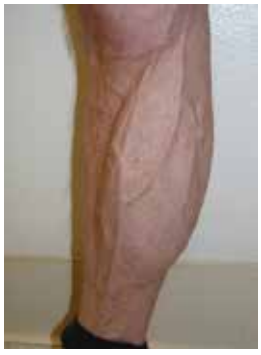
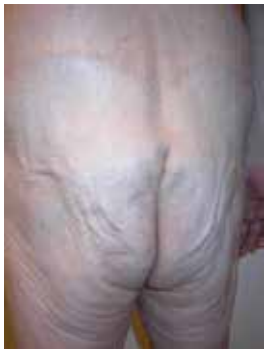
Lipoatrophy

Patients with lipoatrophy have loss of subcutaneous adipose tissue (SAT) in the face, arms, legs, and/or buttocks (see photos). The etiology of lipoatrophy is often associated with antiretroviral (ARV) use, especially older NRTI use, which includes zidovudine or stavudine. These medications were associated with causing mitochondrial toxicity.[2] If mitochondrial toxicity occurred in fat cells, then these fat cells would die, leading to lipoatrophy. Other risk factors of lipoatrophy include older age, disease severity (nadir CD4<200), and host factors.[1,3]





For the evaluation of someone with suspected lipoatrophy, the main focus is on the physical exam. The fat loss tends to be diffuse and widespread. While patients with lipoatrophy often report facial fat loss, as it is more stigmatizing, it is not uncommon to see evidence of global lipoatrophy with close examination. It is important for providers to pay attention and document the degree of facial fat loss, which can occur near the nasolabial folds or the bitemporal areas. Asking patients for an old photo, such as an old driver's license, can provide some historical perspective in assessing how severe the fat loss may be. Lipoatrophy can also occur in breast tissue and some women may report having a decreased bra cup size. Attention should also be paid to the thinning of the arms and legs, sometimes with the presence of visible veins due to loss of fat that usually covers the veins.

Lipoatrophy is distinguishable from wasting as the muscle mass in the extremities is preserved. In my opinion, the best area to look for evidence of lipoatrophy is at the medial (inner) thigh. There can be loss of significant fat in this area leading to an outline of the muscles of the lower quadriceps. Patients may also report having more pain with sitting down due to the loss of cushion from losing fat in the buttocks. On exam, loose, sagging skin may be seen rather than the standard roundness of the buttocks. On rare occasions, I have seen patients present with pain in the feet, only to find evidence of significant fat loss leading to loss of cushion, increasing the risk of stress fractures and exposure of nerves resulting in potential compression with walking.

The main treatment options for lipoatrophy are focused on reversing the causes of fat loss and prevention of future fat loss. In the majority of PWH, lipoatrophy was likely caused by the mitochondrial toxicity related to thymidine NRTIs. Thus, the cessation of these medications can further mitigate loss of fat. However, there is no single therapy that has been found to completely reverse lipoatrophy.[1] Several NRTl-substitution studies (switching away from the offending thymidine NRTIs to other NRTIs) have shown partial improvement but incomplete return of fat.[4,5] Insulin sensitizers, such as the thiazolidinediones (or "glitazones") were also studied as possible treatment options, but have produced mixed results.[1] What is often left as a treatment option is surgical intervention, such as injection of facial fillers, implants, or fat transfer.[6] While polylactic acid is FDA-approved for HIV lipoatrophy, in my experience, it is still difficult to find insurance coverage to cover the cost of this treatment and cover the fees of a plastic surgeon or dermatologist to perform the procedure.

Lipoatrophy is often deemed as a purely cosmetic condition, which is why my strong recommendation is for medical providers to document in the medical record how lipoatrophy affects their patient from a quality of life standpoint (i.e. mood, self-esteem). Facial fillers are also temporary fixes and may require future repeat touch-ups, which add additional costs over time.

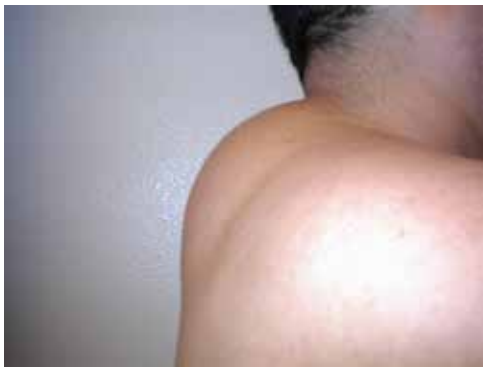
Lipohypertrophy

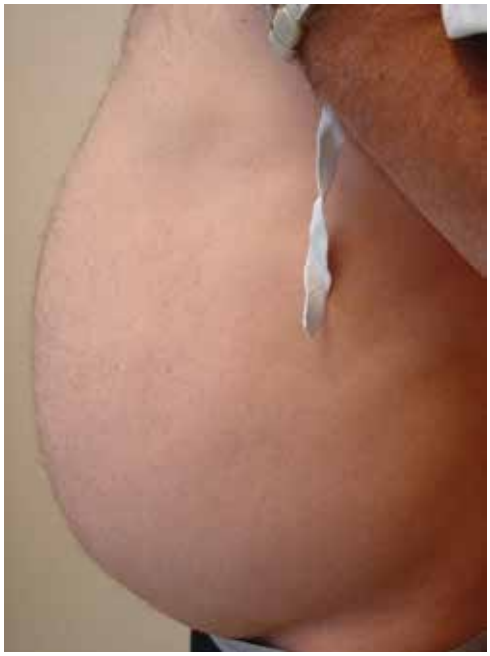
Patients with lipohypertrophy may present with fat accumulation in the central abdomen, mainly visceral adipose tissue (VAT), upper trunk, breasts, and/or the back of the neck (dorsocervical fat pad).[1] The etiology of lipohypertrophy is much more complicated, multifactorial, and less well defined. The role of antiretroviral therapy (ART), especially PIs, in the development of lipohypertrophy is supported by the literature, although there are anecdotal reports and clinical examples of people with lipodystrophy who have not taken PIs.[1,7] Other studies have suggested contributing factors may include advanced age, higher baseline body fat content, higher body mass index, white race, and low CD4 cell count at initiation of ART.[1,7]

The pathophysiology of HIV-lipohypertrophy is complex and multifactorial. There is a well-known "return to health" phenomenon that occurs with lipids, but in my clinical experience, there is also a "return to health" phenomenon that occurs with weight too.[8] In other words, the longer that someone has been HIV-infected prior to treatment, the more likely that person has a higher basal metabolic rate and higher resting energy expenditure, often associated with a greater weight loss. Thus, when this person is

PICTURES COURTESY OF DR. DANIEL LEE

started on ART, there is the potential for greater weight gain related to "return to health." It is my belief and clinical experience that the faster the rate of weight gain and perhaps the amount of weight gain over a short time period may lead to an unequal distribution of fat distribution favoring VAT over SAT. The development of lipohypertrophy may also be affected by the concurrent development of lipoatrophy, which prevents deposition of fat into the SAT depot, resulting in VAT accumulation.





There are often other factors that contribute to excess weight gain beyond "return to health" weight gain. These include poor diet with increased caloric intake to compensate for recent weight loss. Another important factor is lack of exercise or inability to exercise due to debility from recent illness or an opportunistic infection. One must also keep in mind that fat is also an "endocrine organ" that produces hormones, such as leptin and adiponectin.[9] Leptin is involved in the regulation of appetite, while adiponectin improves insulin sensitivity. Dysregulation of these adipocytokines may also influence fat accumulation. In addition, with HIV, there can be lower hormone levels of testosterone and growth hormone, which are associated with increased abdominal fat accumulation.[10,11] Thus, there are a myriad of factors that may contribute to the development of lipohypertrophy.

When a PWH presents with abdominal fat accumulation, one must first distinguish lipohypertrophy from general obesity. In my opinion, general obesity tends to present as a combination of both SAT and VAT. The fat accumulation of HIV-lipohypertrophy, however, tends to consist more of VAT than SAT on physical exam. Because VAT tends to occupy the upper abdomen more commonly, those with lipohypertrophy tend to have more upper abdominal fat accumulation than lower abdominal fat accumulation.

As part of my clinical assessment to determine the difference between lipohypertrophy and obesity, I like to start with a "pinch test" on the side of the abdomen to determine how much subcutaneous fat that I can pinch. In those with lipohypertrophy, there is usually minimal subcutaneous fat that you can pinch because the majority of the fat accumulation is visceral fat, located under the peritoneum and surrounding the organs. I also examine the size of the abdomen and look to see if there is more fat accumulation above the umbilicus (associated more often with lipohypertrophy) versus below the umbilicus (associated more often with obesity). These two evaluations can be helpful especially in the absence of more objective direct measurements of SAT and VAT.

In addition to asking your patient about the evolution of the fat accumulation, I would recommend asking the following additional questions:

- How long do you think you have been HIV-infected?
- What was your normal weight before HIV infection?
- Does the fat accumulation cause any discomfort?
- What is the body habitus of family members?
- Do you have any life stressors?
- Can you tell me about your diet?
- Do you exercise regularly?

These additional questions can help with understanding why the fat accumulation may have happened in a particular patient. The rationale behind asking patients how long do they think that they have been HIV-infected is because this gets at what someone's "actual" date of HIV infection is (an estimation of when the patient thinks they were infected) versus the reported date of HIV infection (based on date of positive HIV antibody test). The "actual" date of HIV infection, by definition, is earlier than the reported laboratory confirmed date of HIV infection. This information can be used to determine if a particular patient will have a greater "return to health" weight gain with initiation of ARVs due to the high probability of the "actual" date of HIV infection being before the reported date of HIV diagnosis.

In addition, knowing a patient's normal weight before HIV infection will also give you a sense of what may be normal versus abnormal weight gain. It is also worthwhile to document whether or not the fat accumulation causes any discomfort, such as abdominal pain, heartburn, reflux, or limitation of range of motion (e.g. bending over to tie shoelaces). Another question to ask is about the body habitus of family members. If family members are obese and the patient has abdominal fat accumulation, the fat accumulation may be in part genetic. However, if the family members are thin, then the fat accumulation is likely more abnormal. In addition, assessing coping strategies during stressful times is useful as stress eating can be quite common. Lastly,

inquiring about the dietary and exercise habits of patients can provide opportunities for intervention.

For objective documentation of lipohypertrophy, body composition measurements can be performed. While skinfold caliper measurements can be used to predict the total amount of body fat, the main interest is in regional body fat. Thus, circumference measurements can be performed at the waist and hip and a waist-to-hip ratio can be calculated.[12] These measurements can be followed longitudinally over time and can easily be done in a clinical setting. Dual energy x-ray absorptiometry (DEXA) scans can be performed to look at fat, however, this measures only regional fat in the extremities versus truncal fat in the abdomen, and does not tell us anything about SAT or VAT. This testing modality is often not routinely available and may not be covered by third-party payers. Computerized Tomography (CT) scans and Magnetic Resonance Imaging (MRI) scans can be done to look specifically at SAT and VAT, but these are typically research tools as measuring the area of SAT and VAT is time-consuming and not done routinely. Old photographs and digital pictures may also be helpful to document changes in appearance over time.

Treating Lipohypertrophy

Given the multifactorial etiologies of lipohypertrophy, the treatment is less well-defined and is focused on general weight loss, with the hopes that this will also lead to loss of VAT. Improving diet and increasing exercise are always recommended. However, weight loss may be associated with a subsequent reduction of both SAT and VAT. ART substitution studies have not generally had favorable results in terms of reduction of VAT.[13] Metformin has been demonstrated to show a trend towards decreased VAT and abdominal fat accumulation in PWH. However, metformin promotes a general loss of weight, which may include a decrease in lean body mass and SAT.[14] Testosterone gel has also been studied but reduced SAT without significant improvement of VAT.[15]

The only currently FDA-approved medication for reduction of excess abdominal fat in HIV-infected patients with lipodystrophy is tesamorelin, or growth hormone releasing factor.[16,17] Tesamorelin is lipolytic and has been shown to reduce VAT preferentially over SAT, which makes this an ideal way to reduce VAT. This therapy is quite expensive, requires regular injections, and

Case Study

A 48-year old male with HIV with a CD4 of 310 cells with an undetectable viral load <20 comes to see you. He has been HIV-positive since 1993 and has been on multiple antiretroviral (ARV) regimens with known prior resistance in the past. His current antiretroviral regimen includes darunavir/cobicistat, dolutegravir, and tenofovir alafenamide/emtricitabine. He presents with a chief complaint of "lipodystrophy" and on physical exam, he has evidence of fat loss in his arms, legs, face, and buttocks. He also has some fat accumulation in the abdomen with a slight dorsocervical hump. He is interested in finding out what causes these body fat changes and what can be done to treat this condition. What are the causes of fat loss (lipoatrophy) and fat accumulation (lipohypertrophy)?

The patient was asked the following questions:

- How long do you think you have been HIV-infected?
- What was your normal weight before HIV infection?
- Does the fat accumulation cause any discomfort?
- Body habitus of family members?
- Stress?
- Diet?
- Exercise?

He stated that although he was diagnosed with HIV in 1993, he believes he was HIV-infected for much longer, at least since 1990, in his opinion. He also states that his normal weight was 170 lbs. prior to HIV infection, but that he had lost about 20 lbs. (down to 150 lbs.) which led to his HIV diagnosis in 1993. He was initially started in 1993 with zidovudine monotherapy and then switched to dual therapy and eventually switched to indinavir, stavudine, and lamivudine in 1996, which finally got his HIV under better control. This also suggests that then his "return to health" phenomenon in regards to weight, likely did not happen until 1996 or so, when his HIV became better controlled. By 1996, he had already noticed that his face was more gaunt from the weight loss related to poorly controlled HIV,

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must be given long term as fat accumulation may recur upon cessation. Lastly, surgical interventions liposuction may be used for removal of dorsocervical fat accumulation or lipomas, but are of limited use for abdominal lipohypertrophy.

I have reviewed the clinical management of lipodystrophy in PWH and included several practical tips based on my clinical experience. Although we may not see as much of the severe lipodystrophic changes as we once did, it is still important to understand how this condition came to exist. And although the changes are less, it remains a concern as the changes can have significant clinical consequences relating to other metabolic comorbidities, and deserves appropriate attention and management. **HIV**

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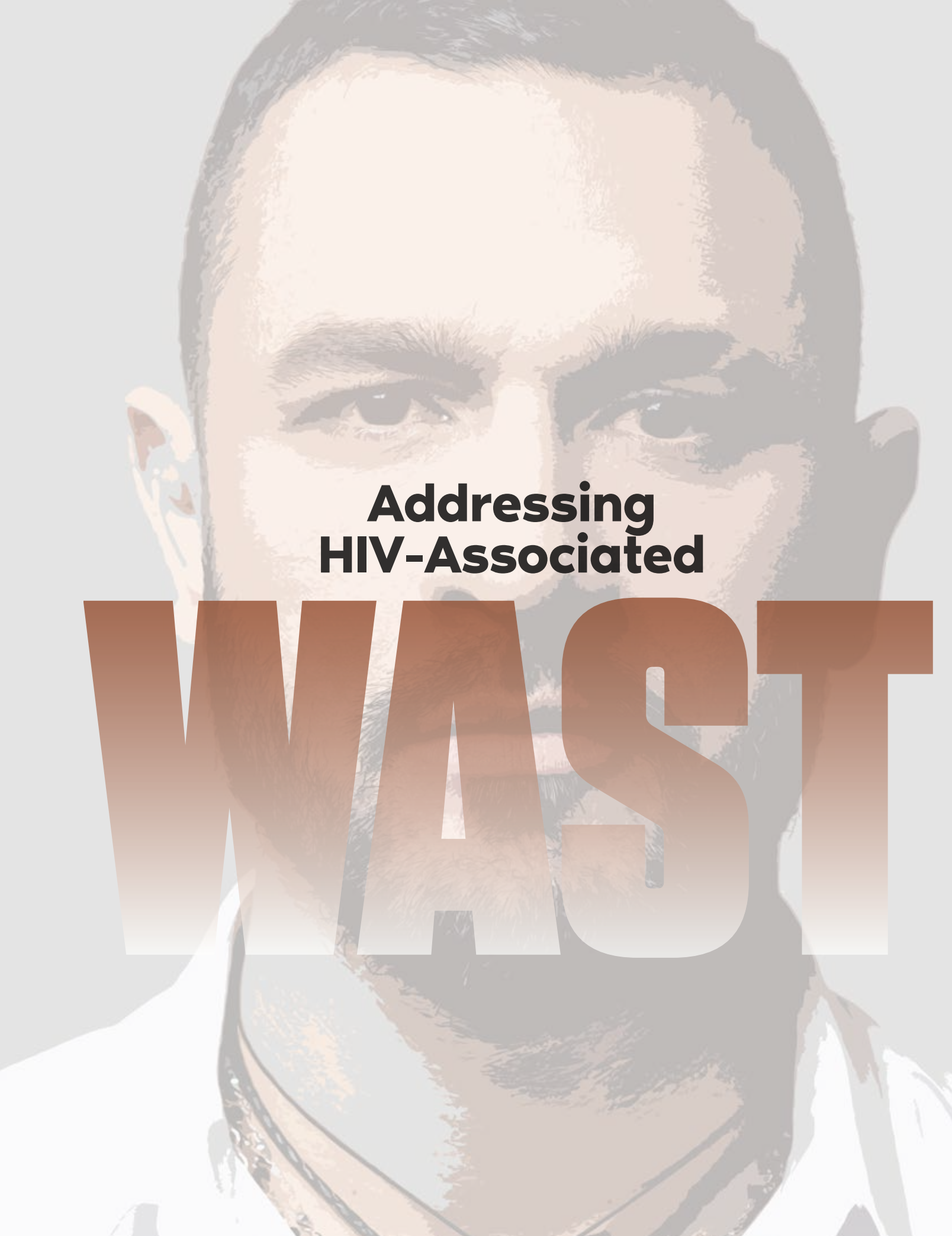
but also due to the lipoatrophy.

Once he had started the indinavir, he started noticing the weight gain, which coincides with the "return to health." The weight initially came back fairly quickly since starting the triple drug regimen in 1996. However, he continued to gain weight slowly over time and now weighed 210 lbs. now, which is 40 lbs. above his normal weight. As a result of this abnormal additional weight gain, he cites having some abdominal discomfort and difficulty breathing at times, due to the sheer size of his abdomen. He also has difficulty bending forward to tie his shoelaces due to the size of his abdomen. The body habitus of all of his family members were thin, suggesting that his lipohypertrophy is most likely abnormal. He cites having stress, anxiety, and depression, but denied stress eating as a coping mechanism. He has a good diet and goes to the gym 5 days per week and does cardio workout for 30 minutes and resistance training for 30 minutes. Despite all of his efforts to lose weight, he has not been successful.

This was actually a patient of mine. I explained to my patient that he had evidence of both lipoatrophy and lipohypertrophy. The global lipoatrophy that was seen throughout his body was caused by his older antiretroviral regimens in the past, as he stated that he had been on both zidovudine and stavudine for many years as part of his antiretroviral regimen. In addition, he had a normal "return to health" weight gain after starting an effective triple antiretroviral therapy regimen with indinavir-based regimen, followed by an abnormal weight gain of an additional 40 lbs.

The abnormal weight gain may also be in part due to a natural slowing of his metabolism with aging, which may be accelerated due to longstanding cumulative inflammation from HIV infection. In regards to treatment options, unfortunately, these were limited. For his lipoatrophy, the damage of his prior thymidine NRTIs had already caused irreversible fat loss. Facial fillers were his only option and a referral was made to the surgeon. For his lipohypertrophy, he was started on tesamorelin which led to a 5 cm decrease in abdominal size, which helped reduce his abdominal discomfort, reflux disease, and improved his range of motion to tie his shoelaces, as well as positively impacted his body image, self-esteem, and quality of life.



Addressing HIV-Associated WAST

HIV-ASSOCIATED WASTING. was a relatively common condition in the pre-antiretroviral therapy (ART) era in people with advanced HIV disease. HIV-associated wasting was formally defined as an involuntary weight loss of at least 10 percent of baseline body weight plus either chronic diarrhea or chronic weakness and documented fever for at least 30 days that is not attributable to a concurrent illness or condition other than HIV infection itself that could explain the findings.[1] However, in the current era of clinical practice, most clinicians anecdotally agree that wasting can be redefined by a 10 percent involuntary weight loss but without diarrhea and/or other constitutional symptoms.

HIV-associated wasting is a potentially life-threatening complication that is associated with significant morbidity and mortality.[2,3] The symptoms of wasting commonly include fatigue and lethargy with decreased physical functioning. Studies have shown that there is an increased risk of opportunistic infections and hospitalization in wasting patients.[4-6] Quality of life is also severely compromised. Death can occur when a patient reaches 66 percent of ideal body weight (IBW) or 54 percent of lean body mass (LBM)[2] and this is independent of other risk factors.[7]

By Daniel Lee, MD, AAHIVS

ING

With the introduction of highly active antiretroviral therapy (HAART) in the mid 1990's, now simply referred to as ART, persons with HIV (PWH) have significantly improved in regards to immune status, overall well-being and life expectancy. As a result, it is often assumed that AIDS wasting no longer remains a threat, as long as one remains on ART. Wasting is, therefore, often overlooked in the post-ART era.[8] To gain a better understanding of how HIV-infected patients can develop wasting, one must first examine the body's standard response to losing weight.

The body's normal response to weight loss typically results in the preferential loss of body fat and the preservation of LBM. Only in the late stages of starvation does LBM decrease. In contrast, HIV-associated wasting is associated with altered metabolism leading to the disproportionate loss of LBM greater than the loss of fat mass. In addition, HIV-associated wasting should be considered in most PWH, regardless of their immunologic and virologic indices. Wasting can still occur in patients otherwise doing well while receiving ART.[8] The focus, however, has shifted away from HIV-related wasting and attention has moved towards long-term complications of ART.

The development of lipoatrophy associated with some HIV medications, can closely mimic HIV-associated wasting, and thus, complicate the clinical diagnosis of wasting, especially in the setting of ART.[3] In HIV-associated wasting, a progressive decrease in body weight is seen which is characterized by a decrease in mean area circumference of the extremities and waist circumference. Bioelectrical impedance analysis (BIA) shows both a decrease in LBM and fat mass. In contrast, lipoatrophy may occur with or without changes in body weight. A decrease in mean area circumference is often seen, but may not necessarily be accompanied by a change in waist circumference. The use of BIA, however, is not reliable in the assessment of regional fat changes as it reports whole body changes in fat and LBM.[9]

The etiology of wasting and weight loss in PWH is often multifactorial.[3] A patient's weight represents a complex balance between caloric intake and metabolic rate. A decline in caloric intake or an increase in the basal metabolic rate may disrupt this balance leading to weight loss. Loss of appetite is a common cause

of inadequate nutrition and anorexia may be due to medications or systemic infection.

The clinical definition of HIV-associated wasting was developed by a Consensus Development Panel on Wasting.[3] This definition was redefined in an effort to improve early clinical diagnosis and treatment, in addition to providing assistance for reimbursement issues regarding justification of the appropriate use of therapies related to wasting. Patients must meet at least one of the following criteria to qualify for a diagnosis of HIV-associated wasting:

- 10% unintentional weight loss over 12 months
- 7.5% unintentional weight loss over six months
- 5% body cell mass (BCM) loss within 6 months
- In men: BCM <35% body weight and BMI <27 kg/m²
- In women: BCM <23% body weight and BMI <27 kg/m²
- BMI <20 kg/m2

Unintentional weight loss in PWH can have many different causes. The presence of untreated HIV-related opportunistic infections and/or malignancies can contribute to weight loss. Oral and esophageal infections, such as candidiasis, herpes, cytomegalovirus (CMV), and aphthous ulcers, can produce pain and dysphagia. Obstructive processes along the gastrointestinal tract can produce nausea, vomiting, abdominal pain and distention, in addition to inhibiting adequate absorption of nutrients. Infection with Cryptosporidium, Microsporidium, Isospora, CMV, or Mycobacterium Avium Complex may also cause malabsorption, leading to a secretory diarrhea. Depression, anxiety, HIV-associated dementia, and other neuropsychiatric disorders can result in anorexia and inadequate nutrition. Other medical conditions, such as hyperthyroidism and/or hypogonadism may lead to weight loss and/or loss of muscle mass, respectively. Lack of financial resources or access to food (i.e. food deserts) may also play a role in HIV-associated weight loss or wasting.

Clinical Assessment of HIV-Associated Wasting

The initial evaluation of a patient with possible HIV-associated wasting should start with a thorough history. The history should be directed towards eliciting information in regards to wasting. Suggested questions include:

- Have you lost any weight? How much? Over what period of time?
- How is your appetite? How many meals per day do you eat?
- Do you have problems with nausea or vomiting? Any problems with abnormal taste or smell?
- What does your diet consist of? What types of food are you eating? Do you snack in between meals?
- Do you have diarrhea? How much and how often? Is the diarrhea worse after eating a meal?
- Are you more tired and fatigued than usual? Has your strength decreased?
- Have you had any problems with performing your daily activities?
- What is your perception of your own body? What is your usual weight?
- Are you depressed or lonely? Are you anxious?
- Do you have money to buy food? Do you have adequate housing?

The answers to the above questions may be helpful in determining and mitigating (when possible) the potential causes of HIV-associated wasting.

A thorough and complete physical examination is also indicated. The physical examination should ideally be performed with the patient completely undressed, except for a gown. This allows the clinician to evaluate areas that may be covered by clothing. Evidence of atrophy in the limbs, abdomen, and buttock are suggestive of wasting. One must also look for signs of infections, malignancies, or other medical problems on physical examination which may contribute to the weight loss process.

A more objective way to track changes on physical examination over time include anthropometry and circumference measurements. Anthropometric measurements can be performed with a caliper to measure skinfold thickness. Typical sites to measure include triceps, biceps, subscapular, and suprailiac areas of the body. Circumference measurements can also be used to track the changes over time which may occur in the waist, hip, umbilical, mid-arm, and mid-thigh regions.

Body composition measurements can also be useful in the evaluation of wasting. Body mass index (BMI) as calculated in the clinical setting and is based on a patient's weight (in kilograms) divided by height (in meters) squared. These measurements should be obtained on all PWH at every office visit. IBW can also be determined based on a person's height with equations based on gender. Bioelectrical impedance analysis (BIA) can be used to assess body cell mass.[10,11] BIA is performed by sending a painless low-level current into the patient. Voltage changes are recorded via electrodes connected to a patient's hands and feet. Lean tissue conducts electric current more readily than fat because it contains most of the body's electrolytes. The results of the BIA along with knowledge of the patient's age, weight, height, and sex, allow for the calculation of body cell mass. The main obstacle in obtaining a BIA is finding a clinic that performs a BIA.

Assessment of wasting also includes the use of laboratory testing. The presence of wasting is commonly seen in PWH with advanced, untreated disease which is manifested by low CD4 counts and high

HIV viral loads. Hypogonadism is another potential cause of wasting in men with HIV and can be diagnosed by a low free or total serum testosterone level. Hypoalbuminemia also serves as a marker for long-term malnutrition or advanced liver disease. Weight loss can also be seen with hyperthyroidism due to an increased metabolic rate, so screening with a TSH level for patients with weight loss is reasonable.

Treatment of HIV-Associated Wasting

An important first step for patient with HIV-associated wasting is nutritional counseling. Instruction from a registered dietitian is helpful in the assessment of a patient's dietary intake. Patients with wasting may overestimate their food intake and may not realize that it is not adequately meeting their caloric needs. Others may lack knowledge as to what constitutes a healthy diet. Thus, nutritional counseling is useful in reviewing one's eating habits and dietary content.

The treatment of HIV-associated wasting should be individualized as the cause of wasting in each patient may be uniquely different.[3] Anorexia, if present, may be corrected with appetite stimulants. Agents which have been used effectively in PWH include megestrol acetate, dronabinol, and THC. Patients with wasting should also be counseled on ways to improve their nutritional intake. All PWH should be on ART, so if virologic suppression is not achieved, changing the existing regimen to achieve an undetectable viral load may help prevent further loss of body mass. Opportunistic infections, malignancies, and gastrointestinal infections should be treated when present. Consultation with a psychiatrist or other mental health provider may be helpful if there are underlying mental health issues which are common in PWH. Connection with a social worker or case manager is appropriate to assist patients with financial, housing, and/or transportation needs. Progressive resistance exercise can be useful in maintaining and increasing LBM in those who are able to exercise.

Patients with HIV-associated wasting and androgen deficiency may benefit from replacement therapy with testosterone.[12] For those without hypogonadism, the short-term use of anabolic steroids (e.g. oxandrolone; oxymetholone) may be helpful in improving lean body mass.[13] Lastly, the only FDA-approved treatment formally indicated for treating HIV patients with wasting or cachexia to increase LBM and body weight, and improve physical endurance is recombinant human growth hormone.[14]

In my clinical experience, while it is true that HIV-associated wasting is much less common in the post-ART era, this condition does still exist in some PWH. It presents more subtlety often as malaise or fatigue. Patients may experience a mild decrease in strength or physical functioning. They may also complain of difficulty with activities of daily living (ADLs) or instrumental activities of daily living (IADLs), such as standing to prepare and cook food, walking to a store, cleaning the house or doing laundry.

As PWH live longer, providers must consider also the onset of frailty that may begin to occur at younger ages than with our HIV-negative patients. This may be in part due to an accelerated aging process associated with HIV being a chronic inflammatory state. Thus, it is vital not to dismiss these subtle complaints often brought up by our patients and to consider the possibility of wasting in these individuals. With this in mind, I often start screening my patients for wasting and frailty when they reach the age of 40, by asking about and testing their functional abilities. I strongly encourage my patients to start or continue physical activity with the goal of preventing future wasting and frailty that often plagues my older patients. Current recommendations of the American Heart Association[15] include:

- At least 150 minutes per week of moderate-intensity aerobic activity or 75 minutes per week of vigorous aerobic activity, or a combination of both, preferably spread throughout the week.
- Add moderate- to high-intensity muscle-strengthening activity (such as resistance or weights) on at least two days per week.
- Spend less time sitting. Even light-intensity activity can offset some of the risks of being sedentary.
- Gain even more benefits by being active at least 300 minutes (five hours) per week.
- Increase amount and intensity gradually over time.

By being proactive, clinicians can improve their patients' quality of life as they age with HIV. **HIV**

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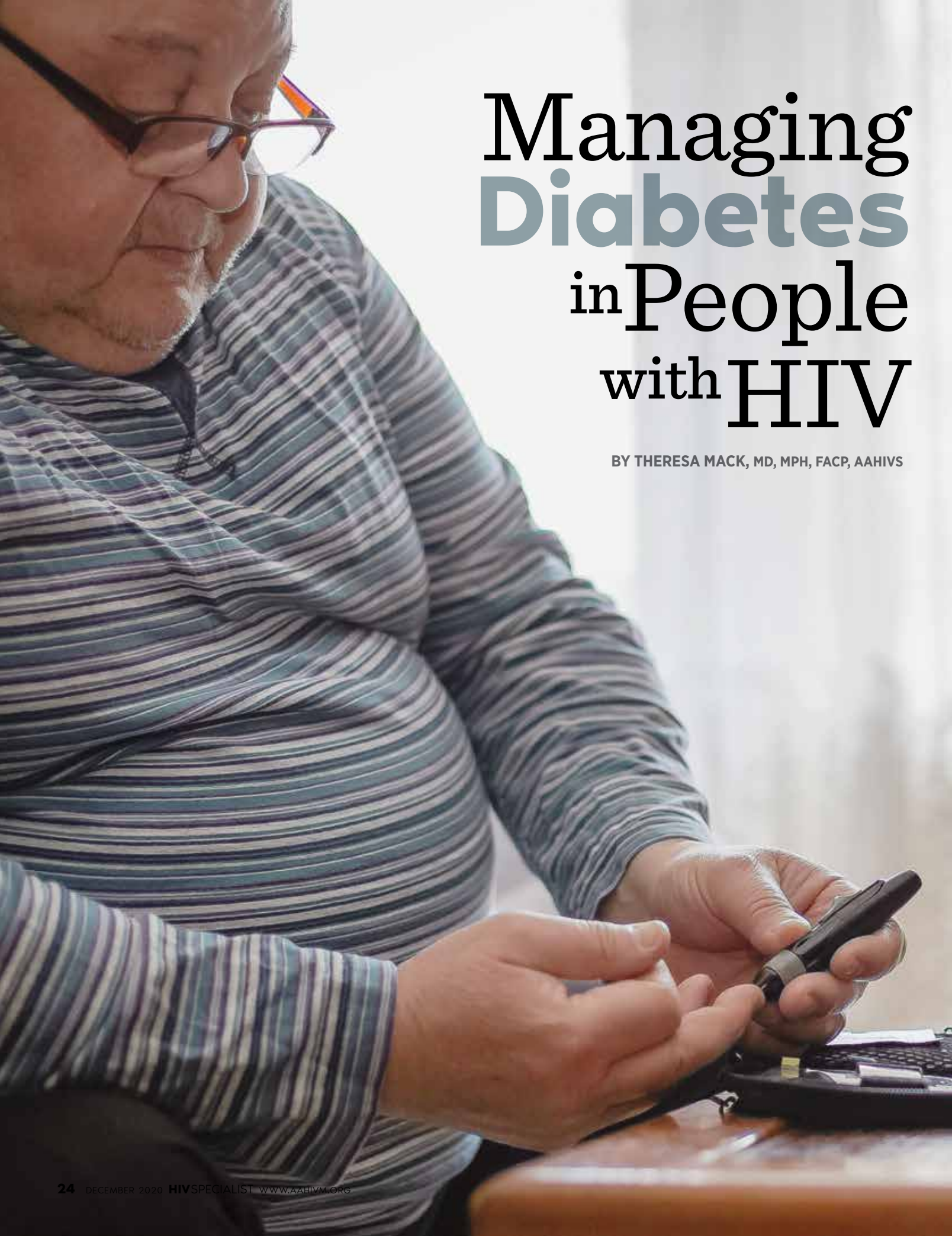

Managing Diabetes in People with HIV

BY THERESA MACK, MD, MPH, FACP, AAHIVS

DIABETES is a complex chronic illness characterized by hyperglycemia as a result of defective insulin secretion and/or decreased insulin sensitivity.[1] Management of diabetes requires continual medical care both to prevent the complications of uncontrolled diabetes and to improve quality of life for the patient. Infection with HIV also causes a complex chronic illness that requires continual medical care to prevent further destruction of the immune system and improve quality of life. Diabetes and HIV infection are both independent risk factors for cardiovascular disease (CVD). Hence, co-existence of these two diseases in a patient increases their CVD risk with potentially devastating consequences.[2] Treatment and successful management of these conditions will minimize additional risk of CVD and associated complications including myocardial infarction.

Diabetes is classified into a number of different subtypes:

- Type 1, in which autoimmune destruction of pancreatic beta cells leads to an absolute insulin deficiency. Although Type 1 DM is typically associated with juvenile diabetes, it may also be seen in people with HIV (PWH), who may develop autoimmune diseases after their immune system has been reconstituted.[3]
- Type 2, in which either a) the progressive loss of pancreatic beta cells to produce insulin or b) the periphery or the target cells no longer responding to insulin leads to insulin resistance.
- Gestational Diabetes, which refers to increased insulin resistance occurring after the first trimester of pregnancy due to placental hormones.
- Drug or chemical induced diabetes, in which hyperglycemia is induced by glucocorticoids, antiretroviral medications (ARVs) for HIV, or drugs used in patient who have undergone organ transplantation, among others.

ISTOCK/ JAKOVO

Diagnosis

Diabetes is defined as a fasting plasma glucose greater than or equal to 126 mg/dl, a hemoglobin A1c (HbA1c) level of 6.5 percent or greater or any patient with polyuria and polydipsia with a random plasma glucose over 200 mg/dl has diabetes. Pre-diabetes is defined as a fasting blood glucose from 100-126 mg/dl or a normal fasting plasma glucose less than 99 mg/dl.

There are three subgroups of patients with diabetes and HIV.[3] All patients are treated for their diabetes according to the American Diabetes Association (ADA) guidelines. The subgroups are:

1. Patients with preexisting diabetes who are living with HIV. These patients can be treated with the same diabetic medications used prior to their HIV diagnosis. The patient is educated about the possible adverse effects of HIV medications, namely lactic acidosis and hyperglycemia. Insulin may be initiated rather than increasing the oral medication if adverse effects occur.[3]
2. Patients who are newly diagnosed with both diabetes and HIV. These patients are treated for diabetes according to ADA guidelines for non HIV- infected patients. Unless contraindicated, metformin is first line of treatment. Insulin is an alternative if metformin is not used.[3]
3. PWH who develop hyperglycemia after the start of HIV treatment. These patients are treated with metformin if there are no contraindications. However, insulin may be necessary until glycemic control is obtained.[3]

It may be appropriate to consider discontinuing the offending ARV medication if there is an alternative one.[5]

Nearly 34 million Americans are afflicted with some form of diabetes, resulting in an annual cost of approximately $325 billion dollars for treating this condition and its complications.[6]

There are also nearly 1.2 million Americans living with HIV, resulting in an annual medical cost of approximately $28 billion dollars.[7]

The financial burden of disease from these two illnesses is astronomical, but ultimately it is a cost that can be prevented.[1] Effective and proven prevention strategies include successful treatment of pre-diabetes to prevent diabetes, and the utilization of HIV pre- and post-exposure prophylaxis (PrEP and PEP) to remain HIV negative.

Although an HIV diagnosis was once considered a death sentence, PWH now have a much longer life expectancy and better quality of life because of much improved HIV medications. Currently, treatment with the newer antiretroviral therapies (ART) has transformed HIV into a manageable chronic illness, and PWH who receive appropriate care have a normal life expectancy. However, the prevalence of diabetes is higher in PWH (14%) compared to the general population (9%),[9] in part because PWH are at a higher risk for developing pre-diabetes and diabetes due to some of the ARVs used for HIV treatment. [11]

The ADA as well as the Department of Health and Human Services (DHHS) HIV treatment guidelines recommend that PWH should be screened for diabetes and pre-diabetes with fasting glucose before starting ART, at the time of switching ART and three to six months after starting or switching therapy. If the initial screening results are normal, fasting glucose should be checked annually.[11]

Risk factors

The risk factors for acquiring pre-diabetes and diabetes in PWH include the traditional ones (diet, obesity, etc.) in addition to those associated with HIV infection and ARVs. Those who are co-infected with the Hepatitis C virus (HCV) are prone to insulin resistance due to the inflammatory effect of this co-infection.[1,3] The established risk factors of unhealthy diet, obesity and physical inactivity must be addressed to prevent diabetes. Advancing age and obesity are causes of diabetes in the general population as well.[1,2]

Inflammation from HIV infection also contributes to the risk of developing diabetes. Extensive observational data and other studies have linked immune activation and inflammation from HIV with an increased cardiovascular risk. There is also evidence that CD4/T- cells can impair glycolysis (glucose metabolism) causing hyperglycemia.[10] The persistent viremia with untreated HIV, immune suppression (i.e., low CD4 count) and the duration of HIV infection all contribute to the increased risk of CVD.[12]

Some ARVs may cause insulin resistance, decrease insulin secretion or an increase in pro-inflammatory substances like C-reactive protein, Tumor Necrosis Factor, and interleukin 6 that are associated with hyperglycemia. Some of the older protease inhibitors cause insulin resistance via the apoptosis of the pancreatic beta cells.[11] The nucleoside reverse transcriptase inhibitors may affect fat distribution leading to lipo-hypertrophy and lipo-atrophy. Both of these fat distribution changes have been associated with insulin resistance.[11]

While the older ARVs, (first generation protease inhibitors, nucleoside reverse transcriptase inhibitors) contributed to insulin resistance and body composition changes, the newer ARVs (integrase inhibitors) appear to have subtle effects on glucose and fat metabolism.[9] Based on data from many clinical trials, the new drugs appear to be less toxic than prior medications. However, in general HIV infection and ART continue to be associated with mitochondrial dysfunction, altered glucose/fatty acid metabolism, and insulin resistance.[9]

Diabetic treatment in PWH

The medical therapies discussed in this article are for type 2 diabetes. Persons with type 1 diabetes require treatment with insulin and is beyond the scope of this article. As noted above, the mechanism that PWH develop diabetes is mainly through insulin resistance and the majority of type 2 diabetics can be managed with oral therapy.[10]

Once diabetes is diagnosed, treatment is initiated to prevent complications including nephropathy, neuropathy, and retinopathy.[2] Diabetes is diagnosed in PWH the same way as for patients without HIV by using the fasting blood glucose.[8] Per the most recent 2020 HIV Primary Care Guidelines—Random or fasting blood glucose and hemoglobin A1c (HbA1c) should be obtained prior to starting ART. If random glucose is abnormal, fasting glucose should be obtained. After initiation of ART, only plasma glucose criteria should be used to diagnose diabetes. Patients with DM mellitus should have an HbA1c level monitored every six months with an HbA1c goal of <7%, in accordance with the American Diabetes Association Guidelines.[13]

The management of diabetes in PWH follows the same ADA guidelines as HIV uninfected patients.[4] The ADA guidelines are the standard of care. Clinicians, however, must be cognizant of how HIV infection and its treatment may impact diabetic disease and adjust the treatment regimens accordingly if clinically appropriate.

Just as with HIV, a patient-centered team approach has better clinical outcomes.[8] The initial management begins with lifestyle changes. Consultation with a certified diabetic educator and/or nutritionist is recommended for all patients. Physical activity is recommended at least three times a week and should optimally be at least 150 minutes per week of moderate intensity aerobic activity or 75 minutes per week of vigorous aerobic activity spread throughout the week. Dietary recommendations include monitoring carbohydrate intake, limiting consumption of sugar sweetened beverages and following a Mediterranean style diet.[8]

If glycemic control (normalization of HbA1c) is not accomplished with these lifestyle changes, then medical therapy is indicated.[8]

ISTOCK/ RICH CANO

Metformin

The preferred medication for type 2 diabetes treatment is metformin (Glucophage, Glumetza). It is an oral medication that is inexpensive, and it improves insulin sensitivity by reducing hepatic glucose production and peripheral glucose uptake.[9] Common side effects include nausea and diarrhea that may be improved with extended release preparations.[8] Historically, metformin has been contraindicated in chronic kidney disease due to an increased risk of lactic acidosis, however newer data has shown this drug can be safely used in patients with a GFR of >30 ml/min.[14]

Metformin is also recommended for pre-diabetic patients who are overweight, with a family history of diabetes, and women with a history of gestational diabetes.[10] Dolutegravir, an integrase inhibitor, raises the concentration of metformin and increases the risk of lactic acidosis.[1]

Second line treatments include the following classes of medications: sulfonylureas, thiazolidinediones, incretin mimetics, glifozins, meglitinides, and insulin.

Sulfonylureas

Sulfonylureas, glimepiride (Amaryl), glyburide (Diabeta), and glipizide (Glucotrol) stimulate insulin release from pancreatic beta cells.[1,8] They are inexpensive but can cause weight gain and hypoglycemia. There are no HIV-specific considerations with these agents.

Thiazolidinediones

Thiazolidinediones, rosiglitazone (Avandia) and pioglitazone (Actos), lower blood glucose by improving the cellular response to insulin.[1] Many of the protease inhibitors are inhibitors of the cytochrome P450 system and may increase the serum levels of rosiglitazone and pioglitazone, leading to toxicity. Pioglitazone increases HDL cholesterol which portrays a cardiovascular benefit.[1,8] However, they are expensive and have been associated with an increased risk of bladder cancer.[8]

Incretin Mimetics

Glucagon-like peptide-1 (GLP-1) receptor agonists, liraglutide (Victoza) and exenatide (Byetta), increase insulin secretion and decrease postprandial glucagon secretion.[1] They are expensive and the main disadvantage is gastrointestinal side effects.[1] There are nonspecific HIV considerations. GLP-1 receptor agonists are injectable medications.

Dipeptidyl peptidase 4 (DPP-4) inhibitors, sitagliptin (Januvia), saxagliptin (Onglyza), vildagliptin (Galvus), and linagliptin (Tradjenta) increase insulin synthesis and release from pancreatic beta cells. They also decrease hepatic glucose production. The dose of saxagliptin (Onglyza) must be reduced when used with cytochrome P450 inhibitors like, ritonavir to prevent toxicity.[1] The DPP-4 inhibitors are oral anti-diabetic medications.

Gliflozins

The gliflozins are oral anti-diabetic medications. The sodium glucose co-transporter 2 (SGLT2), dapagliflozin (Farxiga) and canaglifozin (Invokana) block the reabsorption of glucose by increasing the excretion of glucose in the urine.[1] The glycosuria may increase the risk of urinary tract infections and genital fungal infections.[1] There are no specific HIV considerations for dapagliflozin. However, canagliflozin dose must be increased when administered with ritonavir since ritonavir decreases the serum levels of canagliflozin.[1]

Meglitinides.

Meglitinides, repaglinide (Prandin) and nategliide (Starlix) are oral anti-diabetic medications that stimulate insulin release from pancreatic beta cells.[1] They are short-acting and are taken prior to a meal.[8] Some of the protease inhibitors are CYP450 inhibitors and may increase the serum levels of repaglinide (Prandin)/nategliide (Starlix) causing toxicity. The recommendation is to decrease the dose of the repaglinide and nateglide when used with ritonavir.

Insulin

For PWH with type 2 diabetes mellitus who cannot achieve glycemic control with oral therapy, insulin can be used in combination with other anti-diabetic medications. It is generally recommended for patients with hemoglobin A1c over nine percent, or those with severe liver disease or chronic kidney disease. There are no specific HIV considerations regarding the use or dosing of insulin. The early introduction of insulin is also considered if there is ongoing weight loss, the hemoglobin A1c is greater than 10 and the fasting blood glucose level is consistently greater than 300 mg/dL.[5]

Basal insulin is slow-acting insulin and is initiated at bedtime. Basal insulin provides a constant supply of insulin to lower resting blood glucose levels. NPH (Humulin N, Novolin N), Detemir (Levemir) and Glargine (Basaglar, Lantus) are examples of basal insulin.

If the desired fasting blood glucose is greater than 120 mg/dL, the basal insulin can be titrated every two to three days. Adding a short-acting insulin (bolus) before meals may be beneficial if the glucose goal is not achieved with the slow acting basal insulin. Aspart (Novolog), Lispro (Humalog) and Glulisine (Apidra) are examples of bolus insulin. Insulin can cause hypoglycemia and is associated with weight gain. **HIV**

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Integrase Strand Transfer Inhibitors

By Milena Murray,
PharmD, MSc, BCIDP, AAHIVP

INTEGRASE STRAND TRANSFER INHIBITORS (INSTIs) are recommended as first-line therapy and switch therapy for people living with HIV (PLWH). While these agents are preferred for reasons such as a relative lack of drug-drug interactions and a high genetic barrier to resistance, challenges remain with treatment using this particular class. Weight gain after antiretroviral (ARV) initiation is concerning as it may lead to an increased risk of cardiovascular disease, diabetes, and other comorbidities. Weight gain occurs with all ARV classes; however, the INSTIs appear to have the strongest association.[1] Notably, dolutegravir has the most significant effect on weight; however, the role of the nucleoside reverse transcriptase inhibitor (NRTI) backbone needs to be elucidated. Ongoing research continues to shed light on metabolic issues associated with INSTIs.

A pooled analysis of ARV naïve patients enrolled in eight clinical trials, which included over 10,000 years of person-year follow-up, reached several conclusions regarding ARV therapy and its effects on weight changes.[2] INSTIs as a class were associated with more weight gain than the protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) classes. Within the INSTI class, elvitegravir boosted with cobicistat had an association with less weight gain than dolutegravir and bictegravir.

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A study of two cohorts was undertaken to explore the effects of pharmacogenetics, including UGT1A1 and CYP2B6 metabolism, on weight gain.[3] UGT1A1 polymorphisms may increase the plasma concentrations of INSTIs due to an impact on metabolism. While these polymorphisms affect the area under the curve, maximum concentration, and trough concentration, there are no dosage adjustments recommended if UGT1A1 polymorphisms are present. It is worth mentioning that elvitegravir is primarily metabolized by CYP3A4. CYP2B6 polymorphisms are relevant to efavirenz and are associated with an increased risk of suicidality and the need for discontinuation due to central nervous system adverse effects. Of note, using these genetic tests clinically is not done regularly.

The first cohort analyzed pharmacogenetics in PLWH who were switching ARV therapy.[3] This observational study reported weight gain at 48 weeks after a switch from efavirenz-based to INSTI-based therapy. There was no association between UGT1A1 and weight gain. CYP2B6 slow metabolizers had more weight gain after switching to elvitegravir or raltegravir; however, not switching to dolutegravir. While univariate analyses of multiple patient characteristics showed an association with CYP2B6 genotype and average weight gain, a multivariable analysis, controlling for age, sex, and weight at ARV switch, revealed no such association.

In the second cohort of ARV naïve PLWH, three AIDS Clinical Trial Group studies were combined to analyze the effects of weight gain at 48 weeks.[3] Of note, none of the participants in these trials were randomized to INSTIs; the impact of UGT1A1 genotype was not analyzed. In this cohort, CYP2B6 slow metabolism was associated with less weight gain at 48 weeks in PLWH receiving efavirenz with tenofovir disoproxil fumarate but not efavirenz with abacavir.

Case studies of raltegravir and dolutegravir suggest an association of INSTIs with new-onset diabetes mellitus (DM). To further explore this relationship, a study of almost 20,000 patients examined the incidence of DM over eight years.[4] The authors concluded that incident DM was not associated with INSTI use. However, there was a recommendation that clinicians monitor for this potential metabolic adverse event.

A second study of new-onset DM in approximately 23,000 PLWH revealed an increased risk of incident DM after initiating an INSTI vs. an NNRTI-based regimen.[5] The same association was found with PIs compared to NNRTIs. Overall, the effect was the greatest with raltegravir. This study postulated that weight gain might affect the risk of new-onset DM when beginning an INSTI or PI-based regimen.

It is currently not recommended to change initial therapy due to concern over metabolic adverse events with INSTIs.[6] After weight gain has occurred, patients are usually switched to another class of ARV therapy. A case report of a female patient living with HIV described a return to baseline weight after discontinuing elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide and returning to therapy with efavirenz/emtricitabine/tenofovir disoproxil fumarate.[7] Larger studies of the effects and timeline for a potential return to baseline weight after discontinuation of an INSTI are needed.

Many of the mechanisms suggested in the summarized literature cannot explain differences in weight gain among cohorts, particularly those seen with differing NRTI backbones. As clinicians grapple with these adverse events, more data are needed to fully elucidate potential risk factors and the populations most likely to experience weight gain and other metabolic effects. A validated risk scoring system would allow the prospective prescribing of INSTIs to the most appropriate patient populations.

As more patients become aware of this potential adverse effect upon initiating or switching to an INSTI-based regimen, clinicians must be ready to appropriately counsel regarding the risks and benefits of therapy with an INSTI. Furthermore, relationships and risk factors regarding treatment-emergent obesity are needed. Prospective clinical trials controlling for diet, lifestyle, and other factors may fill the current research and clinical gaps. **HIV**

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New Course Dives Deep into HIV and Aging

Amy C. Min, PharmD, BCACP, AAHIVP

THE ACADEMY has launched an "Intensive Course in HIV & Aging" program, providing a select group of participants with a unique opportunity for hands-on learning that will improve their ability to care for older adults with HIV, enhance their expertise as HIV providers, and foster lifelong learning through a community of like-minded clinicians.

Led by Academy National Board Chair Dr. Jonathan Appelbaum and Dr. Aroonsiri Sangarlangkarn, the free, virtual eight-week program is only taking a very limited number of participants on a first come, first served basis. Participants (MD/NP/PA/PharmD eligible) will receive CME/CNE credit with a certificate of completion from AAHIVM at the end of the course.

If you're interested in applying, we will begin accepting applications for the March 2021 program on December 29, 2020. Please visit https://aahivm.org/hiv-aging-course for more information.

Following is an interview with recent participant Amy C. Min, PharmD, BCACP, AAHIVP, Clinical Assistant Professor and HIV Pharmacotherapy Specialist in the Department of Pharmacy Practice at Temple University School of Pharmacy:

Tell us a little about your background.

I graduated from the University of Maryland School of Pharmacy and then completed a post-graduate year 1 (PGY1) pharmacy residency at Penn Presbyterian Medical Center and a PGY2 in HIV Ambulatory Care/Clinical Pharmacogenetics at the University of Houston College of Pharmacy. After residency training, I joined Temple University School of Pharmacy as Clinical Assistant Professor.

As a pharmacist, how did you come to specialize in HIV?

After completing a PGY1, I knew I wanted more training in HIV and decided to pursue a PGY2 in HIV. During my PGY2, my time was split between an adult HIV practice in Houston as well as a pediatric HIV clinic at Texas Children's Hospital.

What experience have you had with working with older people with HIV?

The Temple Comprehensive HIV Program offers primary medical and specialty HIV care. As a HIV Clinical Pharmacy Specialist, I provide support to those patients who struggle with medication adherence and those who may have drug-resistance mutations. As with patients living with HIV (PLWH) in the US, PLWH in North Philadelphia are aging and I have had the opportunity to work with many long-term survivors.

Why did you decide to take this course?

I decided to take the HIV & Aging course because I wanted to become more knowledgeable about working with the geriatric patient population. As patients age, there are different priorities and comorbidities that we need to be more mindful of. Since I don't have a geriatric background, I wanted to take this course to be better equipped to take care of aging PLWH.

How was the experience?

I really enjoyed being in the first cohort of this course! The patient cases were very well developed and the questions generated great discussions. The facilitators are experts in HIV geriatric care and I was able to learn a lot from their experiences. Being able to lead a topic was also a good experience and gave learners an opportunity to share their interests and expertise.

What was the most useful thing you learned in the course?

I really learned a lot in the faculty-led discussion on advanced care planning and learned about the "respecting choices" model. This was a very unfamiliar area to me, so it was very interesting to learn more about how to approach these discussions with aging patients. The facilitators were able to speak from their experiences and provide best practice tips.

Do you feel more prepared to work with your older patient population?

Yes, with each of the module discussions, I've learned so much from the facilitators and other learners. There are geriatric issues that I feel much more comfortable with and have gained perspectives on patient management. This course really brought to light the special care and attention we need to provide to our aging HIV population. **HIV**

Uncharted Epidemics

Lessons from the Height of HIV

BY DONNA SWEET, MD, MACP, AAHIVS

WHEN THE FIRST CASES OF AIDS were reported in the United States, I was working as an Internal Medicine Resident Physician in Wichita, Kansas. Despite my many years of training and seeing patients, nothing could have prepared me for the height of the HIV epidemic. I know many healthcare professionals are feeling the same type of anxiety and uncertainty right now as they serve on the front lines of the coronavirus disease 2019 (COVID-19) pandemic. As we navigate our clinical response to COVID-19, I want to share five key things I've learned over my nearly 40 years fighting the HIV epidemic that may prove useful in the days ahead.

1 Communication is our most powerful tool

When I first started seeing patients with HIV and AIDS back in the early 1980s, there were so many unknowns. People would come in with opportunistic infections because there was no test and no way of knowing what might help. HIV was a relentless killer, and misinformation made matters worse.

The same is true of COVID-19. There is still so much we don't know, and health professionals are responding to a rapidly evolving situation. Meanwhile, patients want clear answers and consistent guidance about how to protect themselves and their families. As clinicians, it's important to be truthful and honest with patients about what we know and what we don't know. It's okay to not have all the answers or to change your recommendations based on the latest science and official guidelines.

Be clear with patients about the evidence we do have, including information about physical distancing and wearing masks to prevent transmission. Encourage patients to follow evidence-based public health experts and associations, like Dr. Anthony Fauci, for updates they can trust.

2 Fear and stigma are challenging barriers

In the early days of the HIV epidemic, fear was everywhere. I remember clinicians trying to convince people that HIV wasn't spread by touch and to combat the stigma being directed toward people with HIV. Fear breeds the belief that someone is to blame, and the public blamed patients with HIV instead of the virus itself. The widespread belief was that if someone had HIV, it was their fault, and they were labeled "bad people." In actuality, HIV crosses the boundaries of sexual orientation, gender, age, race, and ethnicity, and no one is to blame for acquiring HIV.

Similarly, I think people assume that if someone gets COVID-19, they did something wrong. But just like with HIV, individuals aren't to blame. As clinicians, we can help our patients reframe their stigma and fear as determination to protect themselves and their communities.

I recently saw a woman in her 90s who was so fearful of airborne coronavirus spread that she avoided coming in for care and let her atrial fibrillation go untreated. I reassured her that there were actions she could take to protect herself from COVID-19 when she left her home and that coming in for acute care needs to remain a priority.

3 Prevention is an uphill battle

Despite there being a few key actions people can take to prevent transmission, convincing people to adopt protective behaviors remains a challenge. With HIV, we learned that condoms were protective, but many people still opt not to wear them. For COVID-19, we know that masks and face coverings help decrease spread, but some people are resistant to wearing them or don't wear them consistently.

As healthcare providers, we can set a positive example by wearing masks, practicing physical distancing, washing our hands frequently, and encouraging patients to adopt these proven ways to protect themselves and their communities.

4 Hold onto hope

We are living through unprecedented times, and it may feel easier to despair than to hope, but I encourage colleagues to keep the HIV

People Marching on the Capital protesting lack of support for Aids Medical research funding. March on Aids took place on July 22, 2012 in Washington DC

epidemic in mind as a story of success. Back in the 1980s, HIV was a lethal disease, and we had no understanding of how it affected the body or how it might be treated. Now, in 2020, we have treatment that is easier than I would have ever imagined. Patients with HIV take an antiretroviral therapy pill, which has relatively low toxicity and very few side effects, once a day. The average lifespan for patients with HIV is currently upward of 80 years old.

It's reasonable to expect that we can get to a treatment for COVID-19 much faster than we did for HIV, because there is already a significant research base for diseases caused by RNA viruses like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) that can inform the development of coronavirus (SARS-CoV-2) treatment. I am hopeful that we can come up with good therapy, just like we did with HIV.

5 We are stronger together

Now more than ever, we need to turn to the clinician communities we trust for up-to-date evidence and resources. I trust the Centers for Disease Control and Prevention's *HIV Nexus* website for the latest data and national guidelines about COVID-19 and HIV, as well as the medical associations I am a part of. The American College of Physicians provides a free COVID-19 website with facts and answers to frequently asked questions from patients, and the American Medical Association morning report is another key source for the latest news.

Above all, I encourage healthcare providers to lean on each other for support. We are in this together, and I know someday we will look back on this time and tell stories similar to the ones I have from the height of the HIV epidemic. **HIV**

DONNA SWEET, MD, MACP, AAHIVS, has been treating people living with HIV since 1983 and has spent the entirety of her medical career in practice at the University of Kansas, School of Medicine in Wichita. Dr. Sweet is a delegate to the American Medical Association, a member of the leadership for the American College of Physicians, and past president of the ACP Board of Regents.

ISTOCK/ LA GUY2

Thumbs Down to HIV

The Latest Advances in Vaccine Research

BY AMELIA ESCOLANO, PhD

ACCORDING TO UNAIDS, 38 million people globally were living with HIV-1 in 2019, and 1.7 million became newly infected. Despite tremendous efforts by the scientific community and funding agencies, an efficacious vaccine that can broadly protect against HIV-1 infection is still elusive.

Three large clinical trials are currently testing different experimental vaccines for safety and their ability to confer protection against HIV-1 infection: HVTN 706 (or Mosaico) in North America, Latin America and Europe, HVTN 705 (or Imbokodo) in Sub-Saharan Africa, and HVTN703/704 (or AMP study) in Sub-Saharan Africa, the U.S. and South America (https://www.hvtn.org/en/science/HVTN-studies.html). The results of these trials will be critical for evaluation and guidance of the current vaccine design efforts.

On February 3, 2020, the results of the clinical trial, HVTN 702 or Uhambo (journey in Zulu), were released. Despite high expectations based on the efficacy achieved by the related vaccine regimen tested in the RV144 trial in Thailand (31.2% efficacy)[1,2], the Uhambo vaccine did not show any signs of efficacy, and the National Institute of Allergy and Infectious Diseases (NIAID) stopped its experimental administration. In light of these results, further investigation will be necessary to design efficacious vaccine approaches that can confer protection against HIV-1.

In recent years, novel technologies and methodologies are providing new insight into the HIV-1 virus and the immune responses mounted against HIV-1 by infected individuals. Identifying the vulnerabilities of the HIV-1 virus and understanding the mechanisms that our immune system uses to fight infection is key to design preventative and therapeutic strategies against HIV-1.

Hide and seek with HIV-1

The HIV-1 virus exposes one single protein of viral origin on its surface, the Envelope protein or Env. Env is therefore, the only candidate for the design of vaccines aiming to induce antibody responses against HIV-1.

Env is a trimeric glycoprotein. The peptidic component of Env is covered by a dense shield of glycans derived from the glycosylation machinery of the host infected cell. The glycan shield protects HIV-1 from recognition by the host immune system, which recognizes these glycans as self.[3] Moreover, HIV-1 mutates at very high rates. By the time our immune system produces an antibody response against the infecting HIV-1 virus, HIV-1 has already mutated and produced versions that can no longer be neutralized by the elicited antibody response. This high mutation rate allows the virus to escape from the host antibody system and results in a large diversity of different viral strains.

A small fraction of HIV-1 infected individuals develops, after several years of infection, antibodies of extraordinary potency and breadth against HIV-1 Env.[4] Although these broadly neutralizing antibodies (bNAbs) cannot protect the individuals who developed them due to continuous viral mutation and escape, bNAbs confer protection against infection with a simian-human immunodeficiency virus (SHIV) when administered to macaques, suggesting that a vaccine that elicits this type of antibodies would be protective in humans.[5-7]

Previous and current efforts to design immunization strategies against HIV-1 have used animals such as mice, rabbits and macaques as pre-clinical models to evaluate vaccine candidates. Although the antibody responses mounted by mice and rabbits qualitatively differ from those in humans, these animal models have been of great value to understand the response to vaccination with HIV-1 immunogens and advance towards the design of an efficacious vaccine. Macaques are believed to be a more suitable model to evaluate vaccine candidates for humans, however, very limited information was available about their ability to elicit bNAbs.

Our recent studies in the Nussenzweig laboratory at The Rockefeller University, together with the Martin laboratory at the National Institute of Health (NIH) and the Björkman laboratory at Caltech have shown that, in fact, macaques develop antibodies of great neutralization potency and significant breadth in response to SHIV infection. Moreover, ours studies show that these antibodies closely resemble human bNAbs in terms of antibody sequence and mechanism

of binding to Env, thus, these results validate the use of macaques in pre-clinical studies aiming to evaluate vaccine candidates for humans.[8]

Antibody responses to HIV-1, 'The Good, the Bad and the Ugly'

The analysis of bNAbs isolated from infected individuals revealed that these antibodies target regions of Env that are conserved among different HIV-1 strains.[9] Therefore, the goal of current antibody-based vaccine design efforts is to design immunization strategies to elicit antibody responses that specifically target conserved regions of Env, so that they can broadly neutralize HIV-1.

However, to date, most immunization protocols using Env-based immunogens in animal models have induced antibody responses that target only non-conserved regions of Env or regions that are not exposed during natural infection.[10,11] Hence, the elicited antibodies do not broadly neutralize HIV-1.

A main caveat of these studies was that the Env immunogens used to immunize these animals had a poor antigenic profile since they did not recapitulate the trimeric structure of the native Env. An important advance in the field has been the design of trimeric Env proteins that more closely mimic the native structure and glycosylation of Env.[12]

Immunization with native-like Env proteins induces significantly reduced responses to certain non-conserved regions of Env, however, these immunogens are ineffective to initiate responses towards the conserved regions of interest.[12-19]

Subject of further consideration are other antibody responses that target the conserved regions of Env but do not have the right features and potential to develop into bNAbs. These antibodies may interfere with the induction and development of bNAbs by masking their binding sites.

Currently, considerable efforts are concentrated on the design of stable native-like Env immunogens, and immunization strategies, that can elicit "the Good" bNAb responses against conserved regions of Env, while preventing "the Bad" responses that target non-conserved regions and "the Ugly" responses that cannot develop into potent and broad neutralizing antibodies.

Step by step maturation of anti HIV-1 broadly neutralizing antibodies.

B cells are the cells of our immune system that produce antibodies. B cells express antibodies on the cell surface, the B cell receptors, which recognize foreign antigens in our bodies. When B cells encounter foreign antigens, such as viruses, they get activated and proliferate. Activated B cells join the germinal centers, the anatomical sites within secondary lymphoid organs where B cells proliferate and differentiate. Also in the germinal centers, B cells undergo affinity maturation, the process by which their B cell receptors mutate and diversify, and are subsequently selected based on their affinities for the foreign antigen.[20]

Analysis of bNAbs isolated from infected individuals showed that these antibodies

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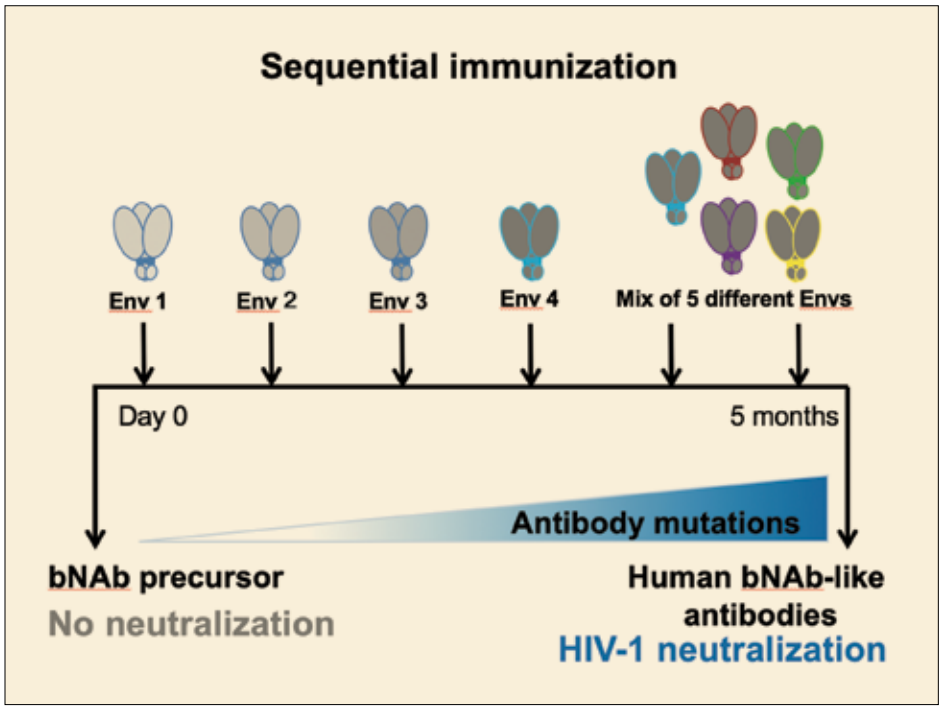

Figure 1. Sequential immunization to induce anti HIV-1 bNAbs. The graph illustrates the sequential immunization regimen that induced bNAbs against HIV-1 in a transgenic mouse model expressing a human bNAb precursor antibody. The sequential immunization protocol involved a series of immunizations with different engineered and native-like Env proteins in a time period of 5 months. At the end of the protocol, these transgenic mice developed broad and potent neutralizing antibodies against HIV-1 that were highly mutated and very closely resembled human bNAbs.

were extraordinarily mutated and that the mutations were necessary for the neutralization activity against HIV-1.[21-27] The high number of mutations indicated that bNAbs developed after a long process of affinity maturation in the germinal centers in response to a constantly mutating HIV-1 virus during the course of natural infection.[25]

Common vaccination regimens involving repeated immunization with single immunogens do not induce the high number of mutations found in anti HIV-1 bNAbs. This suggested that bNAb development would require a novel form of vaccination to induce prolonged periods of affinity maturation in the germinal centers and therefore high numbers of mutations. We hypothesized that immunization protocols using series of slightly different Env proteins that recapitulate the evolving HIV-1 Env protein during natural infection would induce continuous affinity maturation and lead to bNAb development.

To test this hypothesis, we designed, in the Nussenzweig laboratory, a transgenic mouse that had the ability to produce a single "Good" antibody, thus, the "Bad" and "Ugly" antibody responses could not interfere with the bNAb maturation process.[18] The antibody produced in this mouse targeted one of the conserved regions of Env and was the precursor of a bNAb isolated from an infected individual. We used this mouse to design immunization strategies that could induce the maturation of this antibody to become a bNAb. Our work in collaboration with the Schief laboratory at The Scripps Institute, showed that a sequential immunization protocol using a series of different engineered and native-like Env proteins induced the maturation of this bNAb precursor to acquire potent and broad neutralization activity against HIV-1 (Figure 1). The antibodies elicited by this step-wise immunization protocol were highly mutated and very closely resembled human bNAbs. This work was the first demonstration that bNAbs against HIV-1 can be elicited by vaccination and established the paradigm for current efforts in HIV-1 antibody-based vaccine design.[18]

Current work in the Nussenzweig laboratory is focused on the design of sequential immunization strategies that can elicit bNAbs in non-genetically modified animals and humans.

Up-to-date reported immunization protocols using series of different Env- based immunogens have induced antibody responses of only limited neutralization potency and breadth against HIV-1 and none of these regimens was shown to confer protection against viral infection.

The Nussenzweig laboratory, in collaboration with the Bjorkman laboratory at Caltech, and the Martin laboratory at NIH, have designed a new set of Env-based immunogens, called RC1, that initiate specific antibody responses to a conserved region of Env in mice, rabbits and macaques.[28] These set of immunogens has been recently licensed by Gilead Sciences. Our current efforts are directed to design sequential immunization strategies that can induce the maturation of these initial antibodies to become bNAbs.

Despite significant advances towards the development of a vaccine against HIV-1 in the last 30 years, to date, no immunization regimen has induced bNAbs against HIV-1 in animals or humans, which evidences the magnitude of this endeavor. Similarly, despite years of investigation, no universal vaccine exists against the influenza virus, and a seasonal vaccine needs to be reformulated every year. The socio-politico-economic consequences that the current SARS_COV2 pandemic is having worldwide, and the likelihood of emergence of other pathogenic threats with similar consequences in the future, advise a stronger international commitment to vaccine design. **HIV**

AMELIA ESCOLANO, PHD, is a current Research Associate in Michel Nussenzweig laboratory at The Rockefeller University in New York. She obtained her PhD from the Autonoma University of Madrid working under the supervision of Juan Miguel Redondo at the National Cardiovascular Research Center. She has been recently recognized as a finalist of the annual Blavatnik award in the category of Life Sciences for her achievements working on the design of a vaccine against HIV-1.

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UPDATE

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FEATURED LITERATURE:

Saag MS, Gandhi RT, Hoy JF et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2020 Recommendations of the International Antiviral Society–USA Panel. *JAMA*. Published online October 14, 2020. doi:10.1001/jama.2020.17025

The results of clinical trials of antiretroviral therapy (ART), including new drugs and formulations for HIV treatment and prevention are presented and/or published on a continual basis. This paper is the updated **IAS-USA Guidelines** which historically have been published in JAMA concurrently with the biannual IAS meeting. This is an update of the July 2018 guidelines. The authors reviewed over 5000 citations on ART and included 549 that were published or presented at peer-reviewed conferences. A panel of 15 experts in HIV research and patient care reviewed these new data which are the basis for updates to previous IAS-USA guidance. Specific areas addressed included: recommendations for initiating ART, monitoring patients starting on therapy, changing ART regimens, special considerations for older PWH, and preventing HIV infection for persons at risk. The guidelines continue to recommend starting ART as soon as possible for all individuals with HIV with detectable viremia. Initial therapy can be with a 3-drug or a 2-drug regimen, which should include an integrase strand transfer inhibitor. Effective and safe options are available for patients who are pregnant and those with specific clinical conditions, such as kidney, liver, or cardiovascular disease. For the first time, the guidelines recommend long-acting ART (*rilpivirine and cabotegravir*) injected once every 4 weeks or 8 weeks pending FDA approval and availability. For individuals at risk for HIV, PrEP with an oral regimen either daily or "on-demand" is recommended and pending FDA approval, with an IM injection of cabotegravir every 8 weeks. As in the past, clinical and laboratory monitoring before and during ART for safety and efficacy is recommended. Switching ART due to virological failure is uncommon these days and recommendations for switching therapies for convenience and other reasons are included. Lastly, the guidelines address issues related to HIV care amidst the COVID-19 pandemic.

COMMENTARY:

The IAS-USA HIV treatment guidelines remain a solid and complementary adjunct to the more detailed DHHS HIV guidelines. The IAS guidelines have some very good and concise recommendations related to ART use and comorbidities including bone, liver and renal disease, weight gain, and organ transplantation. Injectable formulations of ART are endorsed for prevention and treatment while FDA approval is pending. There are also excellent tables discussing when and how to switch ART. As in the past, there are certain clinical nuances in the IAS guidelines that differ from the DHHS recommendations. I would recommend that all HIV care providers review the full document which is available at the link above and incorporate these recommendations into their clinical practices.

FEATURED LITERATURE:

A Corma-Gómez, A. et al. HIV infection is associated with lower risk of hepatocellular carcinoma after sustained virological response to direct-acting antivirals in hepatitis C infected-patients with advanced fibrosis. *Clin Infect Dis 2020, published August 7th, ciaa1111*, https://doi.org/10.1093/cid/ciaa1111

Most HIV/HCV co-infected persons in the U.S. have been treated with direct acting antiviral agents (DAAs) and achieved a sustained virologic response (SVR) following completion of therapy. There is little data however regarding the risk of hepatic complications, including hepatocellular carcinoma (HCC) after HCV cure. This multisite cohort study from Spain included HCV-monoinfected and HIV/HCV-coinfected patients. Inclusion criteria were: 1) SVR after 12 weeks with DAA-based combination; 2) Pre-treatment liver stiffness (LS) by elastography of ≥9.5 kPa; 3) LS measurement done at the SVR time-point. The primary endpoint was the de novo occurrence of HCC. The secondary endpoint was development of liver decompensation other than HCC. There were 1035 HCV-infected patients in the cohort, 667 (64%) were coinfected with HIV. After a median follow-up of 43 months, 11 (3.0%) of the HCV-monoinfected and 8 (1.2%) of the coinfected individuals developed HCC. **In the multivariable analysis, HIV co-infection was associated with a lower adjusted risk of developing HCC.** Predictors of HCC included age, HCV genotype 3, MELD score at SVR>10 and LS value at time of SVR. Approximately 3 percent of patients in both groups experienced hepatic decompensation.

AUTHOR'S COMMENTARY:

The findings of this study are rather surprising and the inverse of what was seen in the pre-DAA era. Moreover, the HIV/HCV coinfected patients in this study actually had more advanced liver disease at baseline. The authors cite several possible reasons for their findings including a possible protective role of ART and that the monoinfected patients may have had a longer time of exposure to HCV. In addition, concomitant causes of liver diseases, such as alcoholic or non-alcoholic fatty liver disease were not analyzed in this study. Regardless, these data provide some reassurance for HIV/HCV patients who have attained an SVR after treatment with DAAs.

FEATURED LITERATURE:

Lataillade, M et al. Safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced individuals: Week 96 results of the phase 3 BRIGHTE study. *Lancet HIV. November 2020;7(11): e740-51.*

Fostemsavir (Rukobia®), is a first-in-class attachment inhibitor that binds directly to the HIV envelope glycoprotein 120. It was approved in July 2020 by the FDA for treatment-experienced patients with multidrug-resistant HIV-1. The 48-week data were previously published (*N Engl J Med* 2020; 382:1232). This paper is the analyses through week 96. The BRIGHTE study enrolled heavily treatment-experienced PWH failing ART. The average number of prior ART regimens was five. One randomised cohort included patients with one or two fully active ARV drugs who received oral fostemsavir (600 mg bid) or placebo in combination with their ART regimen for 8 days. This was followed by fostemsavir plus optimized background ART. The 2nd cohort included patients with no remaining ART options who received oral fostemsavir plus optimized background ART starting on day one. Over an 18-month time period, 371 participants were enrolled, including 272 in the randomised arm and 99 in the non-randomised arm. **In the randomised cohort, virological suppression increased from 53 percent at week 24 to 60 percent at week 96.** Viral suppression in the non-randomised cohort was 37 percent at week 24 and week 96. After 96 weeks the mean increase in CD4 count from baseline was 205/mm3 cells in the randomised cohort and 119 cellsmm3 in the non-randomised cohort. There was drug discontinuation in 7% of all subjects. There were 12 deaths in the randomised cohort and 17 in the non-randomised cohort respectively and those who died had median baseline CD4 count of only 11 cells/mm3.

AUTHOR'S COMMENTARY:

These data support the efficacy and durability of fostemsavir in PWH with multi-class drug resistance. Response rates were reduced among patients with high baseline viral loads (>100,000 copies/mL) or a very low baseline CD4+ T-cell count (<20 cells per/mm3). The rates of virologic suppression were similar whether the patients had one or two antiretroviral drugs in their initial optimized background therapy. Due to fostemsavir's novel mechanism of action there is no cross-resistance to currently available classes of ART. The most recent IAS-USA guidelines note "fostemsavir can be used when creating a salvage regimen for individuals with extremely limited treatment options." The cost of fostemsavir is about $8000.00 for a one-month supply. There will be more data forthcoming as the BRIGHTE study completion date is December 2024. (NCT02362503)

FEATURED LITERATURE:

Smeaton LM et al. Screening and Enrollment by Sex in Human Immunodeficiency Virus Clinical Trials in the United States. *Clin Infect Dis 2020;71(5):1300–5. DOI: 10.1093/cid/ciz959.*

Approximately 25 percent of adults and adolescents with HIV in the U.S. are women but they have been underrepresented in HIV research studies. Key reasons may be ineligibility due to pregnancy or breastfeeding potential or refusal to participate after screening. This study was a retrospective, cross-trial analysis to determine if women screened for HIV clinical trials ultimately enrolled at lower rates than men. The authors looked at screening and subsequent enrollment in 31 clinical trials conducted at 99 ACTG sites from 2003 -2012. The primary outcome measured was "screen-out" defined as an individual who was formally screened for a trial but subsequently did NOT enroll. There were 10,744 persons with HIV screened of whom 18.9 percent were women. The percentage of women screened out was 27.9 percent compared to 26.5 percent of men (P = .19). The difference did not significantly vary by age, ethnicity, or race. The two most common reasons for screening out were not meeting eligibility criteria (30–35%) and subject opting out (23%), and these did not differ by sex. Some individual-level factors not addressed regarding trial participation were socioeconomic and employment status, caregiving status of dependents, and level of education. The authors believe approaching a greater number of women to screen for HIV clinical trials may be one approach to increasing participation in these studies

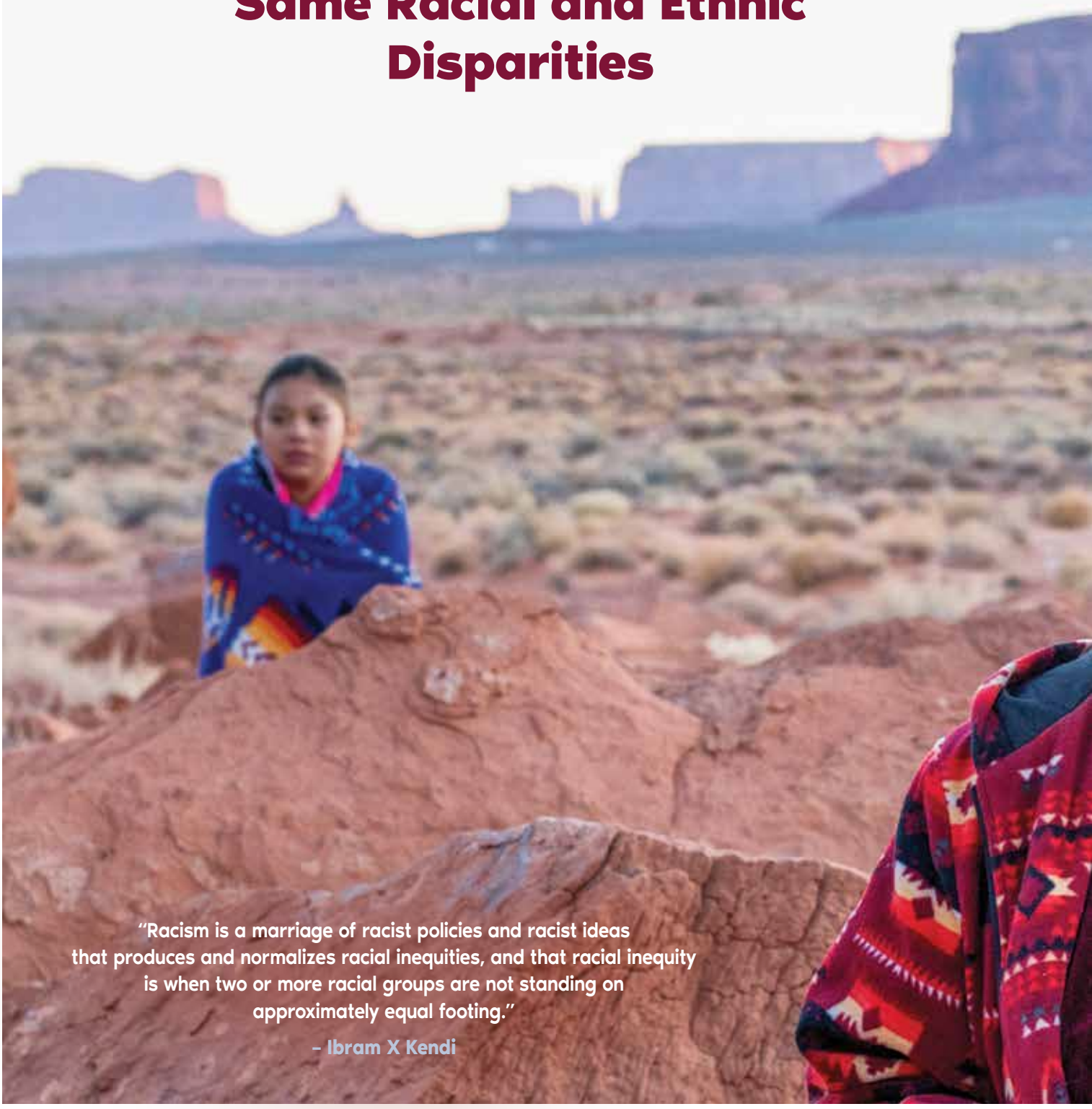
AUTHOR'S COMMENTARY:

The underrepresentation of women in HIV research has resulted in significant knowledge gaps regarding differences in ART responses, adverse drug reactions, and other important clinical outcomes. A prior study published in AIDS found the median proportion of women was 19.2 percent in 395 treatment trials and only 9.9 percent in "cure" trials. The Women's Interagency HIV Study (WIHS), a prospective, observational cohort started in 1993 has produced invaluable data but as the authors of this study note, greater outreach efforts are needed to screen and enroll women in clinical trials. One recent example from the ACTG – "Follow Your Heart," was a campaign to increase enrollment of women into the REPRIEVE trial of statin therapy. A recent paper in JID reported an enrollment of 31 percent female. **HIV**

HIV and COVID-19

Two Pandemics

Same Racial and Ethnic Disparities



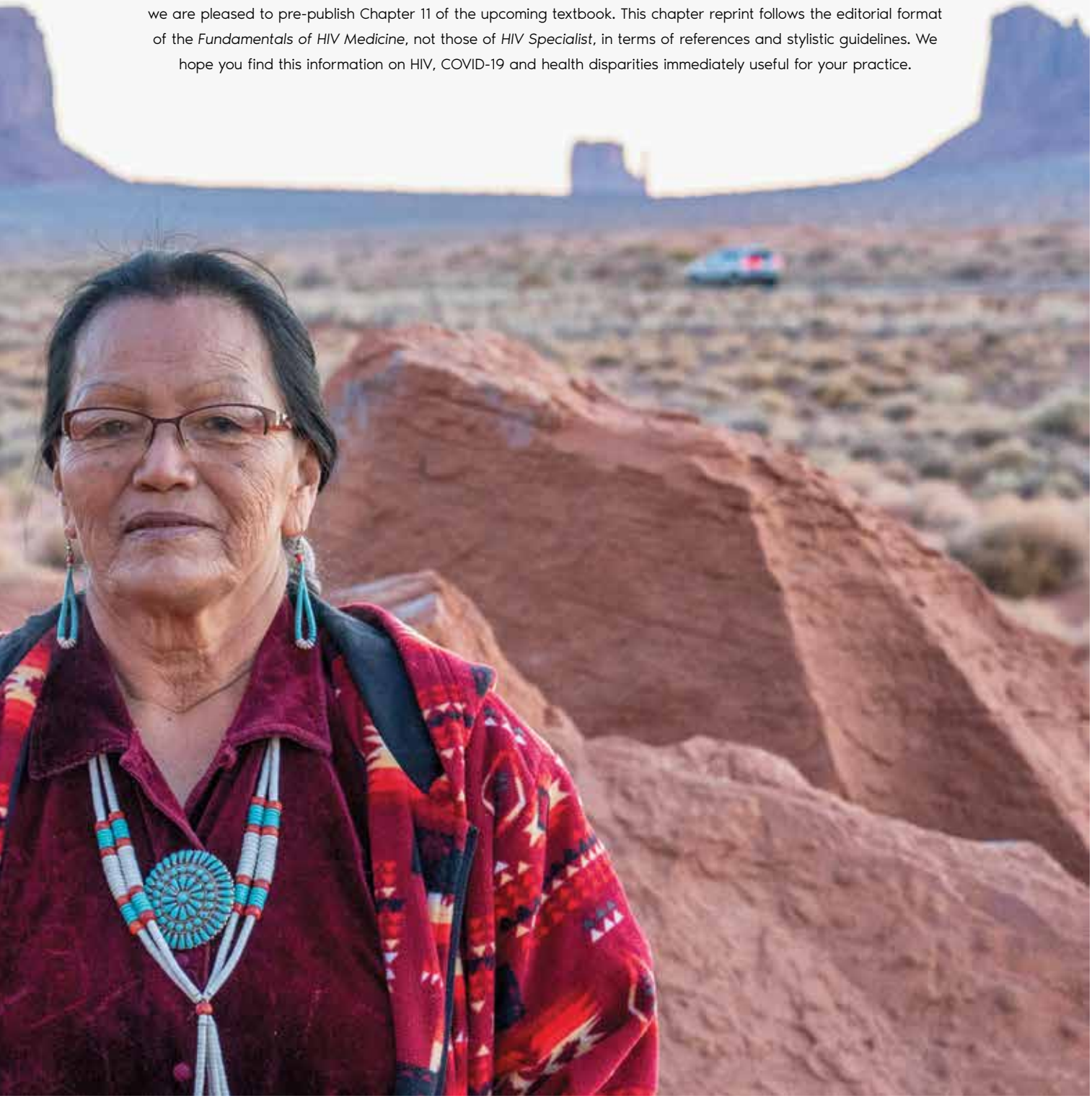
"Racism is a marriage of racist policies and racist ideas that produces and normalizes racial inequities, and that racial inequity is when two or more racial groups are not standing on approximately equal footing."

– Ibram X Kendi

ISTOCK/ GRANDRIVER

By Gary F. Spinner, PA, MPH, AAHIVS

Editor's Note: The American Academy of HIV Medicine will be releasing the 2021 *Fundamentals of HIV Medicine* publication in the Spring of next year. However, given the timely nature of the following content, and in follow up to the September 2020 issue of *HIV Specialist* which focused on health disparities, we are pleased to pre-publish Chapter 11 of the upcoming textbook. This chapter reprint follows the editorial format of the *Fundamentals of HIV Medicine*, not those of *HIV Specialist*, in terms of references and stylistic guidelines. We hope you find this information on HIV, COVID-19 and health disparities immediately useful for your practice.



THE DUAL PANDEMICS of HIV, caused by the RNA virus Human Immunodeficiency Virus and COVID-19, caused by the RNA virus SARS-CoV-2, share much in common beyond their viral etiologies. Both HIV and COVID-19 disproportionately affect Black and Latinx populations far more than Whites. Yet the health disparities in these two pandemics have nothing to do with any known biological differences or virus pathology. These disparities are directly related to social determinants of health, racial and ethnic health inequities, and societal policies that have either created or failed to address these unequal conditions. While PWH do not appear to be at greater risk of becoming infected with SARS-CoV-2 (Park, 2020), nor do they appear to have worse outcomes than HIV-uninfected people, people of color are significantly more likely to become infected with SARS-CoV-2, and have higher rates of mortality. To understand the similarities of these two pandemics is to recognize how social determinants of health create health inequity among people of color, leading to worse outcomes among those with HIV, COVID-19, or many other health conditions. The importance of knowing why racial and ethnic minorities are more likely to acquire HIV can help the HIV specialist become a more culturally competent and ultimately a better health care provider.

This chapter on caring for diverse populations has been updated during the COVID-19 pandemic, which is concurrent with an increase of social activism through the Black Lives Matter movement intensified by the killing of George Floyd at the hands of the Minneapolis police. The interconnection of a protest movement for racial justice and the devastation that both HIV and COVID-19 have on persons of color will be explored, contextualizing the health disparities of both pandemics and how social determinants of health adversely impact the health and well-being of people of color. According to the World Health Organization, "Social determinants of health (SDH) are the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life. These forces and systems include economic policies and systems, development agendas, social norms, social policies and political systems."

ISTOCK/ IOSEPH

Blacks, Latinxs, and Native Americans all experience significant health disparities in the United States. A health disparity is "a particular type of health difference that is closely linked with social, economic, and/or environmental disadvantage." Health disparities adversely affect groups of people who have systematically experienced greater obstacles to health care based on their racial or ethnic group; religion; socioeconomic status; gender; age; mental health; cognitive, sensory, or physical disability; sexual orientation or gender identity; geographic location; or other characteristics historically linked to discrimination or exclusion (U.S. Department of Health and Human Services, 2020). While unequal access to health care can be one determinant of less-than-equal health outcomes, the disparities go far beyond access to care. For example, even with equal access to health care in the Veterans Health Administration, there were mortality disparities for Black veterans with stage 4 chronic kidney disease, colon cancer, diabetes, HIV, rectal cancer, and stroke, for Native American and Alaska Native veterans undergoing noncardiac major surgery, and for Latinx veterans with HIV (Peterson, 2018).

What follows are examples of the racial and ethnic disparities for HIV and for COVID-19, and why it is important for HIV specialists to have a sound understanding of these disparities and how they affect clinical outcomes. Healthcare provider attitudes, biases, and beliefs will also be addressed, as it is important for the HIV specialist to recognize how racial and ethnic biases, whether conscious or unconscious, can have a profound impact on the health outcomes of patients.

HIV: RACIAL AND ETHNIC DISPARITIES

Black and Latinx populations account for a vastly disproportionate percentage of PWH. According to CDC data (CDC, 2020), while Blacks account for only 13.4% of the U.S. population, they comprised 42% of all newly diagnosed PWH in the U.S. in 2018. Latinxs comprise 18.5 % of the U.S. population, but accounted for 28% of HIV incidence in 2018. Black men and women have higher rates of some sexually transmitted diseases than other racial/ethnic groups, increasing risk for HIV acquisition and transmission (CDC, 2018). The lifetime risk of acquiring HIV is 6 times higher for Black men, and nearly three times higher for Latino men, than for Whites. Black women have a 14 times higher lifetime risk of HIV and Latina women have 3 times higher lifetime risk of acquiring HIV as compared with Whites. Among men who have sex with men (MSM) one of every two black MSM has a lifetime risk of HIV acquisition, compared with 1 in 6 Latino MSM and 1 in 11 White MSM (CDC, 2016).

Blacks and Latinxs have higher rates of HIV transmission, have higher risk of infection, are less likely to be virally suppressed when on antiviral therapy, and are less likely to be offered HIV prevention with PrEP than Whites.

In every category, comparing viral suppression between Whites and Blacks, Whites are more likely to be virally suppressed (Crepaz, 2018). While 56% of whites were suppressed, only 41% of Blacks were suppressed, and this held true by gender, by age, among MSM, and people-who-inject-drugs.

Pre-exposure prophylaxis (PrEP) is 99% effective in the prevention of HIV when taken optimally, yet while Blacks and Latino MSM have the highest risk of acquiring HIV, PrEP is far more likely to be offered to Whites (Kanny, 2019). This disparity between White and Black MSM persisted among those who had health insurance and had a usual source of healthcare.

In summary, Blacks and Latinxs have higher rates of HIV transmission, have higher risk of infection, are less likely to be virally suppressed when on antiviral therapy, and are less likely to be offered HIV prevention with PrEP than Whites.

COVID-19: RACIAL AND ETHNIC DISPARITIES

Like HIV, COVID-19 disproportionately affects people of color, who are more likely to become infected with COVID-19 than Whites, and more likely to have severe disease and death. A New York Times analysis of data from the CDC, looking at the characteristics of 640,000 persons with COVID-19, found that Latinxs and Blacks in the US were three times more likely to have COVID-19, and are twice as likely to die from this disease (Oppell Jr., 2020).

Although the CDC data are incomplete, missing racial and ethnic data for many patients, a study analyzing county data through mid-April 2020 (Millett, 2020a) in which there are disproportionately more Blacks residing, found that 97% of predominantly Black counties had at least one COVID-19 case compared to 80% of other counties. They also found that 49% of Black counties had at least one COVID-19 death compared with 28% in all other non-majority Black counties. The predominantly Black counties tended to have lower rates of insurance, higher rates of unemployment, crowded housing, poor air quality, and reduced ability to practice social distancing. In addition, employed persons in predominantly Black counties were more likely to be classified as essential workers, use public transportation, and have jobs that did not allow working from home. When using the same methodology to look at Latinx majority counties, a similar outcome of disproportionately high COVID-19 cases and deaths was found.

In a safety-net hospital in Chicago, (Parra-Rodriguez, 2020), 53% of Latinxs and 44% of Blacks had severe COVID-19 disease, as compared with 22% of Whites. A CDC analysis (Wortham, 2020) found that almost one third of U.S. non-Whites who die with COVID-19 are younger than 65, more than twice the proportion in Whites, according to analysis of over 10,000 deaths in 15 U.S. states and New York City. These data also showed that twice as many Latinxs under age 65 died from COVID-19 as compared to Whites. The authors of this study speculated that non-Whites were more likely to have jobs that precluded social distancing.

In California, where Latinxs account for 39% of the state population, they accounted for 46% of all COVID-19 deaths as of July 2020. Latinxs also account for a disproportionate share of COVID-19 deaths in Florida and Arizona through July 2020 (Thebault, 2020).

Native Americans have also been impacted disproportionately by COVID-19. While CDC data on race and ethnicity for COVID-19 have been incomplete and problematic, a New York Times article (Conger, 2020) found that in New Mexico, Native Americans accounted for nearly 40% of virus cases even though they make up 9% of the population. In the Phoenix, Arizona area, Native Americans were infected at 4 times the rate of Whites. "The disparities we see there with COVID-19 are aligned with those that we see for hospitalizations and deaths due to influenza and other respiratory viruses," said Allison Barlow, director of the Center for American Indian Health at Johns Hopkins University.

"Native Americans—particularly those living on reservations—are more prone to contract the virus because of crowded housing conditions that make social distancing difficult," she said, along with years of underfunded health systems, food and water insecurity, and other factors that contribute to underlying health conditions that can make the illness more severe once contracted.

Among the social factors most likely contributing to the increased morbidity and mortality of COVID-19 in racial and ethnic minorities are poverty, high density and crowded

housing, and employment that precludes working from home, and the higher likelihood of being employed as essential services workers. Other factors include reliance on public transportation, over-representation in jails, prisons, homeless shelters and detention centers where social distancing is not possible, living in multigenerational households where it is difficulty to protect older family members, not having sick leave (which increases the likelihood that someone keeps working while ill), lack of health insurance, distrust of the health care system, along with racism, stigma, and systemic inequities (CDC, 2020).

COVID-19, HIV AND THEIR LINK TO SYSTEMIC RACISM

Health equity (US Department of Health and Human Services definition) is the attainment of the highest level of health for all people. It requires valuing everyone equally with focused and ongoing societal efforts to address avoidable inequalities, historical and contemporary injustices, and the elimination of health and health care disparities (DHHS, 2010).

The significant health disparities experienced by people of color are examples of health inequity. The unequal adverse health impact of HIV and COVID-19 holds true for other health conditions as well, including certain cancers, respiratory diseases, diabetes, hypertension, and other conditions, along with worse health care outcomes for most of these conditions. Infant mortality for Black infants is 2.5 times higher than for white infants (CDC, 2016). A Black man has a nearly 5-year shorter life expectancy than a white man (CDC, 2017), is 30% more likely to die from heart disease, twice as likely to be diagnosed with diabetes, twice as likely to have a stroke, 40% more likely to have hypertension, but 10% less likely to have it under control (Graham, 2015).

The Black Lives Matter movement taking place at the time of this writing is not only about Blacks being more than 2.5 times as likely to be killed while in the hands of the police (Roper, 2020) or incarcerated at 5.1 times the rate for Whites, (Nellis, 2016) but also about these health inequities, among other issues comprising systemic racial injustice.

To truly understand the racial and ethnic disparities of the pandemics of HIV and COVID-19 one must recognize the pandemic of racism. According to Ibram Kendi, (Kendi, 2019) a scholar of race and discriminatory policy in America, "Racism is a marriage of racist policies and racist ideas that produces and normalizes racial inequities, and that racial inequity is when two or more racial groups are not standing on approximately equal footing. A racist policy is any measure that produces or sustains racial inequity between racial groups."

The social conditions that lead to adverse health conditions; including poverty, lack of access to health care, lower wage employment, segregated and overcrowded housing, educational disadvantages among many other inequities; are systemic problems related either to policies that have created these disadvantages or a lack of appropriate policies to address and eliminate these disadvantages.

Systemic racism, also known as institutional racism, is a form of racism that is embedded as normal practice within society or an organization that can lead to such issues as discrimination in employment, housing, health care, political power, criminal justice, education, among other issues. Systemic racism must be recognized for causing many of the social inequities that people of color experience. Crowded, high density housing, low wage essential service jobs that preclude working from home, and reliance on public transportation are linked to COVID-19. There are a multitude or programs and policies that can be traced back to the racial and ethnic discrimination. For example, the practice of banks denying housing loans to Blacks, or charging them higher rates of interest with stricter repayment terms, has led to fewer Blacks than Whites owning homes. Historically, Federal Housing Administration's refusal to insure mortgages in Black neighborhoods, and their requirement of developers receiving subsidized loans to build sub-divisions that specifically exclude Blacks, are systemically racist policies that created segregated and more densely populated housing and denied Blacks of one of the most common ways to build personal wealth, home ownership. (Rothstein, 2017)

Another example of systemic racism relates to unemployment benefits for workers laid off due to COVID-19. Almost a quarter of Black workers live in the South, where 52% of all new HIV infections currently occur, and where race has long played a role in limiting safety net program. During the COVID-19 pandemic, the US unemployment rate has skyrocketed, but the unemployment insurance program is state controlled, and many Southern states have excluded from unemployment programs many of the jobs that are more likely to employ Blacks and Latinxs. The average high school educated White is twice as likely to receive unemployment benefits as the average high school educated Black (Nichols, 2012) and Blacks receive lower rates of compensation than Whites, according to Kathryn Edwards of the Rand Corporation (Badger, 2020).

Despite the significant progress in treating PWH, there continues to be approximately 38,000 new HIV infections each year. While people of color are far more likely to acquire HIV, and PrEP is 99% effective in preventing infection when taken optimally, people of color are less likely to be offered it. "Ending the HIV Epidemic: A Plan for America" is the current administration's effort to address some of the geographic disparities where people are at greatest

risk of acquiring HIV. It targets the 48 counties along with 7 rural communities with greatest risk for HIV (HRSA, 2020). However, the social determinants of health faced by people of color threaten to undermine the plan's intended progress. A modeling study of HIV incidence (Nosyk, 2020) suggests the goal of ending the HIV epidemic is unlikely to be met due to many barriers including lack of access to health care, proposed cutbacks to and/or outright elimination of the Affordable Care Act, and failure to expand Medicaid in many of the Southern states. Millet pointed out at the AIDS 2020 conference (Millett, 2020b) that income inequality, poverty, and the degree of Black/White segregation, housing instability, and homelessness are associated with HIV in certain communities where poverty, vacant housing, unemployment, and isolation are most prevalent.

WHAT NEEDS TO BE DONE?

The Ryan White Program has been a hugely successful program with significantly better outcomes in Ryan White-funded clinics compared with other HIV clinics in the U.S. Serving over half a million patients with HIV, 73.6% of whom are racial and ethnic minorities, and 62.8% of whom are living below the federal poverty level, the highest measure of HIV treatment success- viral suppression, was 87.1% for Ryan White-funded clinics compared with the national average of 62.7% (Cheever, 2019, Hall, 2015). Ryan White clinics are funded to address barriers many patients face, such as lack of transportation, primary medical care, food bank services, housing, linguistic services, child care services, emergency financial services, substance use treatment services, case management, and a host of other services. Through the Ryan White clinics efforts to address these barriers, the level of health equity for patients served by this program is raised. The program success can be attributed to its intent to specifically address the racial and ethnic disparities impacting people of color, as well as other marginalized groups.

PROVIDING CULTURALLY COMPETENT CARE

It is not uncommon for health care providers to harbor false beliefs about biological differences between Blacks and Whites. One study of medical students and residents found that half of those surveyed believed one or more false statements about biological differences between Blacks and Whites, including the belief that Blacks to not feel pain the same way that Whites do, or that black skin is thicker than white skin (Hoffman, 2016). These prejudices alienate patients, who rightfully perceive the racism and implicit bias that their care health care providers harbor.

Several studies found health care providers associating poor adherence and noncompliance to Latinx patients and two studies found moderate amounts of bias against darker skinned patients than lighter skinned patients.

Provider bias, and sometimes overt racism, can lead to longer waiting times for people of color as compared with Whites, taking patient concerns less seriously, doing a less thorough workup of problems, recommending different treatment options based on a perceived lack of patient adherence, along with many other differences in the treatment of some racial and/or ethnic groups than others. A systematic review of 15 peer-reviewed studies to identify implicit racial and ethnic bias among health care providers found that in 14 of those 15 studies, most health care providers demonstrated implicit bias through more favorable attitudes towards Whites and negative attitudes towards Blacks and Latinxs (Hall 2015). Four studies found that health care providers saw Blacks as less cooperative, less compliant, and less responsive to medical advice. Several studies found health care providers associating poor adherence and noncompliance to Latinx patients and two studies found moderate amounts of bias against darker skinned patients than lighter skinned patients.

Even healthcare providers who sees themselves as providing equitable care may unknowingly be interacting with their patients of color differently and less effectively than with their White patients. Clearly, our system of medical education needs to more actively address issues of race and ethnicity in the training of physicians, nurses, and other healthcare workers. Unless we acknowledge and change our individual racist and ethnic biases, and work to implement health and social policies that eliminate racism and ethnic bias, we will continue to perpetuate the health disparities we see with HIV, COVID-19, and a multitude of other health conditions. **HIV**

****In the full chapter that will appear in the Spring edition of* Fundamentals of HIV Medicine, *this chapter continues with further examples of the diversity of patients with HIV, and how we can elevate our awareness and appreciation of the those who entrust us with their healthcare.*

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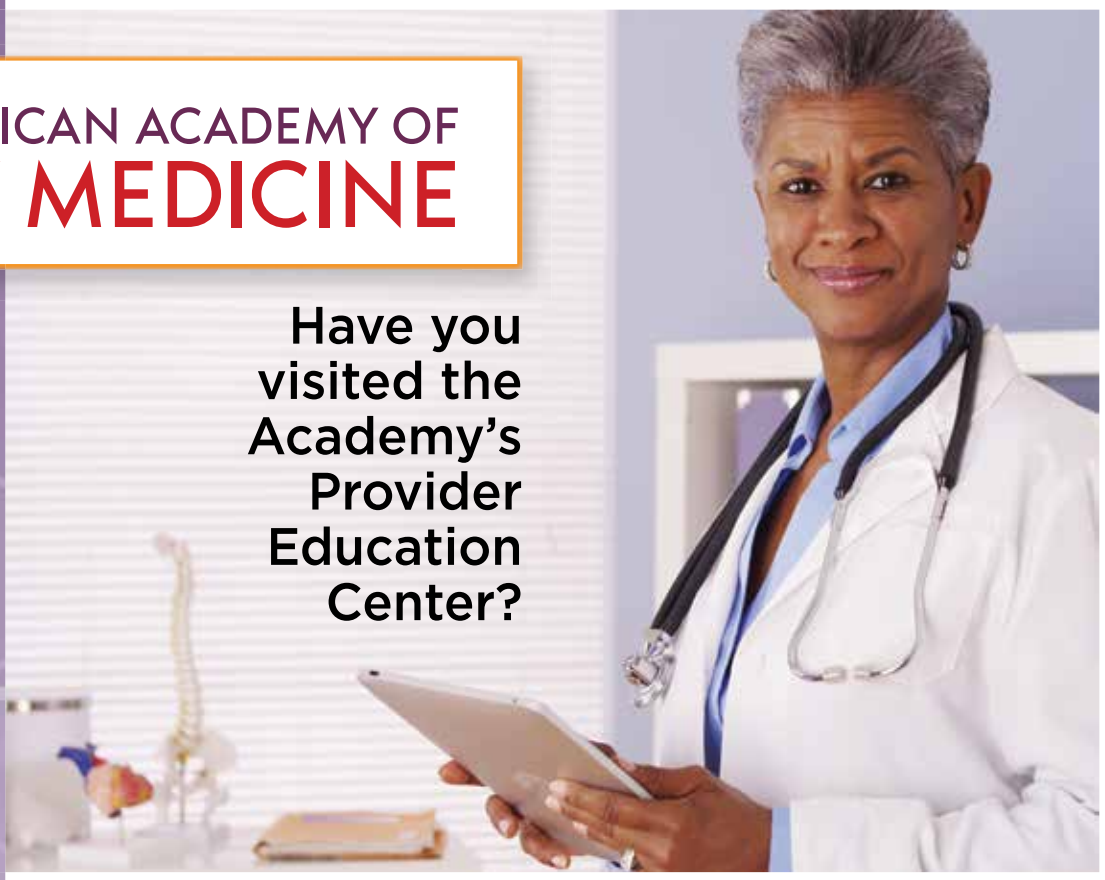

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