Perspective  CME

HIV Infection: Advances Toward a Cure  121
Daniel C. Douek, MD, PhD
Hematopoietic Stem Cell Transplantation • Very Early Treatment • Shock and Kill • Immune Therapy • Gene Therapy • Broadly Neutralizing Antibodies Against HIV Envelope

Investigational Antiretroviral Drugs: What is Coming Down the Pipeline  127
Roy M. Gulick, MD, MPH
Nucleoside Analogue Reverse Transcriptase Inhibitors • Nonnucleoside Analogue Reverse Transcriptase Inhibitors • Integrase Strand Transfer Inhibitors • Entry Inhibitors

Management of Long-Term Complications of HIV Disease: Focus on Cardiovascular Disease  133
Judith S. Currier, MD
Survival and Comorbidities • CVD in HIV Infection • Pathways for Non-AIDS Diseases in HIV • Interventions to Reduce Non-AIDS Events in HIV

Maximizing the Benefits of HIV Preexposure Prophylaxis  138
Susan P. Buchbinder, MD
Effectiveness of PrEP • PrEP for HIV-Serodiscordant Couples • Initiation and Monitoring of PrEP • Is PrEP Scale-Up Reaching the Right People?

Opioids and HIV Infection: From Pain Management to Addiction Treatment  143
Chinazo O. Cunningham, MD, MS
Pain, Opioid Analgesics, and HIV • Current Guidelines for Opioid Treatment for Chronic Pain • Treatment of Opioid Use Disorder •
Topics in Antiviral Medicine™

Topics in Antiviral Medicine™ (formerly Topics in HIV Medicine) is published by the IAS–USA. This journal is intended to be a resource for practitioners and scientists who are actively involved in medical care and research.

Editorial Policy

The views and opinions expressed in this journal are those of the contributors and do not necessarily reflect the views or recommendations of the IAS–USA. Topics in Antiviral Medicine is supported through grants from several commercial companies that are committed to supporting continuing medical education on HIV, hepatitis C virus, and other viral infections. In the interest of an objective, balanced, and scientifically rigorous publication, the IAS–USA seeks funding that is pooled from companies with competing products; these companies have no input or control over the journal content or the selection of contributors.

Financial Disclosures

Financial disclosures for members of the IAS–USA Board of Directors and the Editorial Board of Topics in Antiviral Medicine are available online at www.iasusa.org.

Copyrights and Reprints

The contents of Topics in Antiviral Medicine are protected by copyright. We welcome reference to and use of portions of this journal, however, we do require that permission to reproduce or use any part of the journal be obtained from the IAS–USA. In the case of reprinted or adapted materials where the IAS–USA does not own the copyright, permission to reproduce these materials must be obtained directly from the original source. For more information about reprints, please send an e-mail to journal@iasusa.org.

Subscription Information

Topics in Antiviral Medicine is published 4 to 6 times a year. To obtain a subscription or notify the IAS–USA of a change in your e-mail address, please create or update your user profile at www.iasusa.org.

Correspondence

Topics in Antiviral Medicine welcomes editorial correspondence. Address correspondence to:

Editor, Topics in Antiviral Medicine
E-mail: journal@iasusa.org
Mail: IAS–USA
425 California St, Ste 1450
San Francisco, CA  94104-2120
Phone: (415) 544-9400
Fax: (415) 544-9401
Website: http://www.iasusa.org

On the Web

Current and previous issues of Topics in Antiviral Medicine (as well as Topics in HIV Medicine) are available online at www.iasusa.org/pub.

ISSN 2161-5853 (Online)

©2018 IAS–USA. All rights reserved

IAS–USA Board of Directors

Constance A. Benson, MD
Professor of Medicine
University of California San Diego

Peter C. Cassat, JD
Vice President and General Counsel
AutoTrader Group, Inc

Judith S. Currier, MD
Professor of Medicine
University of California Los Angeles

Carlos del Rio, MD
Professor of Medicine and Global Health
Emory University

Roy M. Gulick, MD, MPH
Professor of Medicine
Weill Cornell Medicine

Jeanne M. Marrazzo, MD, MPH
Professor of Medicine
University of Alabama at Birmingham

Douglas D. Richman, MD
Professor of Pathology and Medicine
University of California San Diego and Veterans Affairs San Diego Healthcare System

Michael S. Saag, MD
Professor of Medicine
University of Alabama at Birmingham

Grant Support

IAS–USA funding comes from a variety of sources. The largest single source of revenue is conference and participant registration fees.

This activity is part of the IAS–USA national educational effort that is funded, in part, by charitable contributions from commercial companies. Per IAS–USA policy, any effort that uses commercial grants must receive grants from several companies with competing products (see page 120). Funds are pooled and distributed to activities at the sole discretion of the IAS–USA. Grantors have no input into any activity, including its content, development, or selection of topics or speakers.
Perspectives

HIV Infection: Advances Toward a Cure 121
Daniel C. Douek, MD, PhD

Investigational Antiretroviral Drugs: What is Coming Down the Pipeline 127
Roy M. Gulick, MD, MPH

Management of Long-Term Complications of HIV Disease: Focus on Cardiovascular Disease 133
Judith S. Currier, MD

Maximizing the Benefits of HIV Preexposure Prophylaxis 138
Susan P. Buchbinder, MD

Opioids and HIV Infection: From Pain Management to Addiction Treatment 143
Chinazo O. Cunningham, MD, MS

Announcements

Continuing Medical Education (CME) Information 120
Upcoming Activities 126
Guidelines for Authors and Contributors 147
Mark Your Calendar Back Cover

Visit www.iasusa.org/tam/cme-issues or use the QR code in this issue to access the online posttest.
CME Information

The IAS–USA is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education (CME) for physicians.

The IAS–USA designates this enduring material for a maximum of 4.0 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is offered from April 6, 2018, to April 6, 2019. Participants who successfully complete the activity posttest and submit the evaluation and registration forms are eligible to receive CME credit. Physicians (MDs, DOs, and international equivalents) may receive CME credit for completing this activity. Other health care practitioners will receive a certificate of participation.

- CME credits available: 4.0 AMA PRA Category 1 Credits™
- Release date: April 6, 2018
- Expiration date: April 6, 2019

To claim CME credit, please read each article and successfully complete the posttest and evaluation form, which will help us evaluate this activity and plan future activities. Your responses will not affect your CME credit.

Learning Objectives

On completion of this activity, the learner will be able to:

- Describe the status of HIV cure research
- List the investigational drugs and formulations for potential HIV treatment
- Formulate strategies for identifying cardiovascular disease risk and management in HIV-infected patients
- Describe current guides for HIV preexposure prophylaxis with antiretroviral drugs
- Formulate plan for treating pain in HIV-infected patients

Intended Audience

This enduring material is designed for physicians and other health care practitioners who are actively involved in the medical care of people with HIV and HCV infections.

This activity is also relevant for other practitioners, including nurse practitioners, nurses, physician assistants, pharmacists, and others.

Disclosure of Financial Interests

In the interest of maintaining the independence of its CME activities, and in accordance with the policies of the Accreditation Council for Continuing Medical Education (ACCME), the IAS–USA requires all persons with control of content (ie, authors, IAS–USA Board members, and program staff) to disclose any financial relationships that they (or their spouses or partners) have had with commercial companies within the past 12 months. Any real or apparent conflicts of interest of those parties are resolved prior to the continuing medical education activity being delivered. Individuals who refuse to disclose financial interests may not participate in an IAS–USA CME activity.

Financial affiliations with commercial entities: Dr Buchbinder has participated in research trials that have received provision of medicines from Gilead Sciences, Inc. Dr Douek has no relevant financial affiliations to disclose. Dr Currier has received research grants awarded to her institution from Theratechnologies. Dr Gulick has no relevant financial affiliations to disclose. Dr Cunningham holds stock and stock options for Quest Diagnostics. Her spouse is employed by and holds stock and stock options for Quest Diagnostics.

Drug and Product Disclaimer

This activity may contain information about the investigational uses of drugs or products that are not approved by the US Food and Drug Administration. Please consult full prescribing information before using any medication or product mentioned in this activity.

The views and opinions expressed herein are those of faculty and do not necessarily represent the opinions or recommendations of IAS–USA.

Posttest

Use the QR code or visit www.iasusa.org/tam/cme-issues to complete the posttest and evaluation for this activity and claim CME credit.
Perspective
HIV Infection: Advances Toward a Cure

Achieving cure of HIV infection requires eliminating all replication-competent virus from the reservoir of latently infected cells or completely inhibiting infected cells from emerging from latency. Strategies include very early use of antiretroviral therapy; hematopoietic stem cell transplantation; “shock-and-kill” approaches; immune therapy with immune checkpoint inhibitors; gene therapy, including use of CC chemokine receptor 5–modified CD4+ T cells; and broadly neutralizing antibody therapy. Success is likely to require a combination of approaches. This article summarizes a presentation by Daniel C. Douek, MD, PhD, at the IAS-USA continuing education program held in Berkeley, California, in May 2017.

Keywords: HIV, cure, hematopoietic stem cell transplant, antiretroviral therapy, shock and kill, gene therapy, immune checkpoint inhibitors, broadly neutralizing antibody therapy, latent infection

People on suppressive antiretroviral therapy acquire a reservoir of quiescent HIV-infected T cells that persists for life. These cells can undergo clonal expansion and maintain or increase the size of the reservoir without producing virus. If antiretroviral therapy is interrupted, production of HIV by these cells is observed within 2 to 4 weeks. Thus in the absence of antiretroviral therapy, cells that harbor quiescent replication-competent virus can rekindle HIV replication and transmission. The task in achieving cure of HIV infection is to eliminate all replication-competent virus in the reservoir or to attain lifelong remission, that is, sustained atriemia in the absence of antiretroviral therapy over an individual’s lifetime.

How can we cure HIV-infected people? Numerous mechanisms account for HIV persistence. However, a unifying theme in cure strategies is to find and diminish the size of the HIV reservoir. Potential strategies include using early antiretroviral therapy to reduce seeding of the latent pool; reversing latency (“shock-and-kill” approach); increasing HIV-specific immune function (eg, with vaccines); reducing immune activation; using gene therapy to target the virus and the host; and using allogeneic hematopoietic stem cell transplantation. Combinations of these or other approaches may be necessary.

Hematopoietic Stem Cell Transplantation

Cure has only been achieved in 1 person, Timothy R. Brown, also referred to as the Berlin patient. He received a hematopoietic stem cell transplant from a donor whose cells were resistant to HIV infection (CC chemokine receptor 5 [CCR5] delta32/delta32). Brown, who has not received antiretroviral therapy for more than 10 years, has been doing well and has no evidence of replication-competent HIV. No viral DNA has been found in his peripheral blood mononuclear cells, and there is no convincing evidence for a nonartefactual signal in any assay for HIV nucleic acids, along with waning HIV antibodies and the absence of HIV-specific T cells. Although the transplantation approach is considered an important proof of concept in achieving cure, the risk associated with transplantation makes it unlikely that it will ever translate into an accessible method for all HIV-infected people.

In the case of 2 other individuals, known as the Boston patients, who received hematopoietic stem cell transplants from donors with cells susceptible to HIV infection, viral recrudescence was observed despite the 1000- to 10,000-fold reductions in viral reservoir size achieved. In one patient, viral rebound occurred after approximately 9 months off antiretroviral therapy and was attributed to a single virus. Thus, although kinetic modeling has indicated that a reduction of 100,000-fold in the reservoir is needed to achieve cure, the finding that a single virus may cause recrudescence suggests that cure is dependent on eliminating all latent replication-competent viruses or completely inhibiting their ability to emerge from latency.

Very Early Treatment

Can very early antiretroviral therapy reduce the size of the latent reservoir and play a role in cure? Studies of early reservoir dynamics in the absence of treatment indicate that about the time HIV RNA becomes detectable, the reservoir size begins to increase dramatically, with an apparent 100,000-fold increase over the next 2 weeks. The reservoir is largely established by week 4 of infection. However, very early antiretroviral treatment can substantially reduce the size of the reservoir. As shown in Figure 1A, initiation of treatment within 2 weeks of infection results in nearly undetectable reservoir size compared with initiation after 2 to 4 weeks of infection or during chronic infection. However, there is no clinically significant delay in time to viral rebound after stopping treatment. In the data shown in Figure 1B, median time to viral rebound was 14 days in chronic infection, 22 days in Fiebig stage III or IV infection, and 26 days in Fiebig stage I infection. Thus, it appears that there is a limit to the potential effect of even very early treatment in preventing recrudescence from a diminished reservoir.

Shock and Kill

The strategy of “shock and kill,” relies on a latency reversing agent (LRA) to reactivate HIV transcription in latently infected cells. The immune system then recognizes and kills
the infected cells. Administration of antiretroviral therapy throughout the shock-and-kill process protects against the propagation of new infection.

Many LRAs currently are being investigated, including epigenetic modifiers such as histone deacetylase (HDAC) inhibitors, toll-like receptor agonists, activators of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), disulfiram, immune checkpoint inhibitors, and agents that affect the STAT5 signaling pathway and mTOR signaling. However, studies to date indicate that compared with maximal T-cell activation, few LRAs work well ex vivo with cells from HIV-infected patients. In clinical trials of LRAs, increases in cell-associated and plasma HIV RNA have been observed, with the reservoir size increasing and no detection of infected cells being eliminated.

As to the “kill” part of the strategy, various studies have shown that neither the virus nor the immune system is effective in clearing infected cells after latency reversal; in one in vitro model, infected resting CD4+ T cells survived despite viral cytopathic effects. Further, because most of the virus has mutated to escape immune responses, escape variants dominate in the latent reservoir of people with chronic infection. Therapeutic vaccines to augment immune responses have resulted in transient expansion of T cells that do not recognize escaped HIV epitopes. At least 40 clinical trials of vaccines to increase the magnitude of HIV-specific immune response have been completed in the past 2 decades, and overall results show that vaccination is safe and immunogenic, but ineffective in eliminating virus.

A number of shock-and-kill studies have combined LRAs with approaches such as therapeutic vaccines, interferon, and broadly neutralizing antibodies to enhance immune response. In one study of 20 individuals on antiretroviral therapy who had a viral load below 50 HIV RNA copies/mL for more than 3 years, the combination of the HDAC inhibitor romidepsin and the HIV peptide vaccine resulted in no change in integrated DNA or infectious virus. A statistically significant decline in total HIV DNA was observed; however, the effect was clinically meaningless, because viral rebound after cessation of antiretroviral therapy was always observed within 2 to 4 weeks.

In a recent study, use of a different HIV vaccine in combination with romidepsin was associated with viral rebound within 4 weeks of interruption of antiretroviral drugs in 8 participants; 5 other participants exhibited sustained lower level viremia during the interruption.

Figure 1. Effect of early antiretroviral therapy on reservoir size (A) and time to rebound after therapy interruption by infection stage (B). Chronic HIV infection has a range of 5–29 days; median, 14 days; Feibig stage III or IV infection has a range of 14–77 days; median, 22 days; and Feibig stage I infection has a range of 13–48 days; median, 26 days. PBMC indicates peripheral blood mononuclear cells. Adapted from Rothenberger et al. 2015, Kroon et al. 2016, and Colby et al. 2017.

Figure 2. Log₁₀ change in viral load from individual baseline for 8 study participants longitudinally for 90 days after infusion of VRC01, a monoclonal antibody targeting the CD4 binding site of HIV Env (day 0). Adapted from Lynch et al. 2015.
Monoclonal antibodies that target PD-1, PD-L1, and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) may be used to block this interaction. These inhibitors have been shown to enhance HIV-specific T-cell responses in ex vivo studies. A number of small clinical trials are underway to evaluate the effects of the immune checkpoint inhibitors pembrolizumab, nivolumab, ipilimumab, and atezolizumab in HIV-infected individuals with malignancies. This strategy stands a good chance of reinvigorating HIV-specific immune response, perhaps when used in combination with LRA; however, the safety of these approaches is an ever-present consideration and remains the subject of much discussion.

**Gene Therapy**

The aim of gene therapy is to deliver a therapeutic agent to a cell using a gene; to inhibit or kill the HIV genome in the cell, such as with anti-HIV antisense RNA, targeted DNA nucleases, and transdominant Rev; or to remove something that HIV needs, such as CCR5, by using antisense RNA, intrabodies, or targeted DNA nucleases. As shown in the cases of the Berlin patient and the Boston patients, cure requires removing the virus and the target cells (eg, by inhibiting or eliminating CCR5).

A promising approach is nuclease-based gene therapy targeting CCR5. In this approach, CD4+ T cells or CD34+ hematopoietic stem cells are removed from HIV-infected individuals and treated with a zinc-finger nuclease that recognizes and cleaves the CCR5 gene. This results in cells that no longer express the CCR5 coreceptor. After these cells expand, they are infused back into the individual. The approach is minimally invasive, with low risk of severe adverse effects. It is also more accessible than hematopoietic stem cell transplantation, with no need for donors and no risk of graft-versus-host disease.

A number of gene therapy studies in HIV-infected individuals who are aviremic and on antiretroviral therapy are underway. Initial findings include the long-term persistence in vivo of CCR5-modified CD4+ T cells after a single infusion and

---

**Immune Therapy**

More promising are strategies that reverse the exhaustion of HIV-specific CD8+ T cells with the use of immune checkpoint inhibitors, which have become effective in treating a variety of malignancies. T-cell exhaustion may arise from the interaction of the cell surface marker PD-1 (programmed death-1) with PD-L1 (programmed death-ligand 1). This interaction serves to shut down the T-cell response to such infected cells. Immune checkpoint inhibitors such as monoclonal antibodies that target PD-1, PD-L1, and cytotoxic

---

**Figure 3.** Viral load after cessation of antiretroviral therapy in patients receiving VRC01, a monoclonal antibody targeting the CD4 binding site of HIV Env, in the AIDS Clinical Trials Group (ACTG) A5340 trial (A) and National Institutes of Health (NIH) (B) phase I trials. Percentage of viral suppression in the phase I trial participants compared with participants in previous ACTG trials (C) after treatment discontinuation. Adapted from Bar et al. 2016.15
durable increases in CD4+ T memory stem cells enriched for modified CCR5. A reduction in the size of the HIV reservoir was observed in all patients over 5 years, and viral kinetics suggest replacement of infected cells over time.

A reduction in the HIV set point was observed when antiretroviral therapy was interrupted at 6 weeks after infusion; this set point correlated with the amount of CCR5-modified CD4+ T cells in the infusion received by the individuals. At last reporting, 4 of 16 patients receiving treatment have remained off antiretroviral drugs for more than 22 weeks. These findings indicate that administering cells resistant to HIV infection when antiretroviral therapy is stopped reduces the size of the reservoir and the HIV set point. Although these early findings are extremely encouraging, a primary question is how scalable an approach this will prove to be.

**Broadly Neutralizing Antibodies Against HIV Envelope**

Broadly neutralizing antibodies that target the HIV envelope (Env) may be an approach to a cure because they can block viral entry into cells and mediate the killing of infected cells. Numerous monoclonal antibodies (mAbs) with varying inhibitory potency and breadth of coverage of diverse viruses have been discovered in recent years.

A phase I study evaluating VRC01, a mAb that targets the CD4 binding site of HIV Env, showed that a single infusion in viremic patients was associated with responses consisting of sustained suppression, transient suppression, or no suppression with the degree of suppression dependent upon the sensitivity of the virus to VRC01 (Figure 2). Additional phase 1 trials of VRC01 in individuals who interrupt antiretroviral therapy have shown that the majority of participants had viral rebound within 5 weeks, even with high plasma levels of VRC01, and rebound was associated with emergence of resistant virus. However, a modest but statistically significant delay in viral rebound was observed compared with historical controls, lending some optimism to the findings (Figure 3). Similar findings were made in a study of the 3BNC117 antibody.

To overcome the pitfalls of single-agent mAbs, desirable characteristics of second-generation mAb products include a 10-fold greater potency than current agents, coverage of 98% to 99% of virus envelope diversity to prevent escape, administration via subcutaneous injection once every 4 to 6 months instead of by intravenous infusion every 2 months with current products, and a cost comparable with antiretroviral drugs.

Greater potency and breadth of coverage can be engineered as well into mAbs. The 10E8 antibody, for instance, exhibits excellent breadth of coverage but has limited potency. A few amino acid mutations engineered into the antibody creates a product with the same breadth of coverage but at 1000 times greater potency. In addition, antibodies can be formulated into combined products that exhibit greater breadth of coverage and potency than that offered by a single antibody (Figure 4).

In addition, engineered mutations to the Fc portion of an antibody are capable of dramatically prolonging the product’s half-life, for example, by protecting it from endosomal degradation. In one approach, the addition of 2 amino acid mutations to VRC01 may extend the half-life of the antibody in healthy participants by at least 4-fold, with therapeutic levels appearing to be maintained for 6 months.

**Conclusion**

A greater understanding of the size, location, and maintenance of the HIV reservoir has been attained and is likely to improve strategies aimed at cure of infection. Reservoir size can be reduced with early antiretroviral therapy, but the clinical significance of such a reduction remains uncertain. Latency reversing agents have shown poor reactivation of virus and no reduction in reservoir size. Therapeutic vaccines generally have not shown promising effects in human studies. Hematopoietic stem cell transplantation has been shown to work in 1 patient, but it is not a scalable approach. Gene therapy may be used to target HIV and CCR5, and clinical studies show some reservoir reduction, but scalability is an issue. Env-specific mAbs are in promising proof-of-concept studies, with more potent combinations...
and bispecific mAbs being developed. Combinations of approaches may need to be used to increase the chances of achieving cure, including LRAs plus mAbs, gene therapy plus mAbs plus LRAs, and others.

Presented by Dr Douek in April 2017. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Douek in August 2017.

Financial affiliations in the past 12 months: Dr Douek has no relevant financial affiliations to disclose.

References


UPCOMING ACTIVITIES

Spring 2018

Interactive Webinars With IAS–USA Faculty

Live, interactive continuing medical education (CME) in the comfort of your home or office, free of charge. Participants can ask questions and receive responses in real time. Visit the IAS–USA website for details. Upcoming webinars will cover the following topics:

State-of-the-Art in Hepatitis C Virus (HCV) Diagnosis and Treatment—April 17, 2018
Presenter: Kristen M. Marks, MD

Are You Up to Date? Primary Care for HIV—April 24, 2018
Presenter: Steven C. Johnson, MD

Infectious and Other Complications of the New Immunobiologic Agents—May 10, 2018
Presenter: Peter Chin-Hong, MD

Pathogenesis of HIV Infection and Core Principles of Treatment—May 31, 2018
Presenter: Michael S. Saag, MD and David H. Spach, MD

Hepatitis B Virus (HBV) Infection—June 14, 2018
Presenter: Marion G. Peters, MD

IAS–USA Live Courses

Full- and half-day CME courses and workshops continue to feature cutting-edge, scientifically rigorous topics presented by leading experts in the fields of HIV and hepatitis C virus (HCV) medicine. Visit the IAS–USA website for up-to-date information and webcasts of prior courses. This spring, IAS–USA live courses focusing on the management of HIV infection will be held in:

Atlanta, Georgia—Friday, March 16, 2018—Georgia State University—Student Center East
Chairs: Jeffrey L. Lennox, MD, and Michael S. Saag, MD [Webcast Available]

New York, New York—Friday, March 30, 2018—NYU Skirball Center
Chairs: Gerald H. Friedland, MD, and Paul A. Volberding, MD [Webcast Available]

Los Angeles, California—Monday, April 9, 2018—The California Endowment Conference Center
Chairs: Constance A. Benson, MD, Raphael J. Landovitz, MD, and Ronald T. Mitsuyasu, MD

Washington, DC, Thursday—April 26, 2018—The National Press Club
Chairs: Henry Masur, MD, and Michael S. Saag, MD

San Francisco, California—Friday, May 11, 2018—San Francisco State University—Towers Conference Center
Chairs: Stephen E. Follansbee, MD, Annie Lukenmeyer, MD, and Robert T. Schooley, MD

Chicago, Illinois—Friday, May 18, 2018—Loyola University Chicago, Lake Shore Campus
Chairs: John P. Phair, MD, and Paul A. Volberding, MD

Cases on the Web

A series of web-based, case-driven CME activities, created to offer convenient online access to top-quality professional education. Visit the IAS–USA website for a full list of Cases on the Web activities. Recent activities address the following topics:

Immunizations for HIV-Infected Adults
Authors: Brian T. Montague DO, MPH, MS; Steven C. Johnson MD, University of Colorado

Diagnosis and Management of Major or Persistent Depression in the HIV-Infected Patient
Authors: Jameela J. Francine Cournos MD, Columbia University; Milton L. Wainberg MD, Columbia College of Physicians and Surgeons.
Release date: Monday, February 16, 2015.

Ending the Epidemic in New York City: From Blueprint to Implementation
Author: Demetre C. Daskalakis MD, MPH, New York City Department of Health and Mental Hygiene.
Release date: Wednesday, September 28, 2016.

Dates above may be subject to change. IAS–USA announcements are paperless, so please watch for e-mail updates or visit www.iasusa.org for course information, agendas, and online registration, or to access archives of educational resources from past activities.

These activities have been approved for AMA PRA Category 1 Credit™.
Perspective

Investigational Antiretroviral Drugs: What is Coming Down the Pipeline

Over the past 30 years, antiretroviral drug regimens for treating HIV infection have become more effective, safer, and more convenient. Despite 31 currently approved drugs, the pipeline of investigational HIV drugs remains full. Investigational antiretroviral drugs include the nucleoside analogue reverse transcriptase translocation inhibitor (NRTTI) MK-8591, a long-acting compound that could be dosed once weekly. Investigational nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs) include doravirine, which is active in vitro against NNRTI-resistant HIV and was potent and well–tolerated when used in combination with a dual–nucleoside analogue RTI (nRTI) backbone in treatment-naive individuals. New integrase strand transfer inhibitors (InSTIs) include recently approved bictegravir, which is active against InSTI-resistant viral strains in vitro and was potent and well–tolerated in combination regimens in treatment-naive individuals, and investigational cabotegravir, which is being studied with monthly parenteral dosing for HIV maintenance treatment and with bimonthly dosing for HIV preexposure prophylaxis (PrEP). Investigational HIV entry inhibitors include the new CD4 attachment inhibitor fostemvasivir, which targets HIV envelope glycoprotein 120, and recently approved ibalizumab, which binds the CD4 receptor. This article summarizes presentations by Roy M. Gulick, MD, MPH, at the IAS–USA continuing education program, Improving the Management of HIV Disease, held in Los Angeles, California, in April 2017, and at the 2017 Ryan White HIV/AIDS Program Clinical Conference, held in San Antonio, Texas, in August 2017.

Keywords: HIV, antiretroviral drugs, antiretroviral therapy, MK-8591, doravirine, bictegravir, cabotegravir, fostemvasivir, ibalizumab, investigational, nucleoside, nonnucleoside, integrase, entry inhibitor

Although currently recommended antiretroviral regimens are more effective, safer, and more convenient than ever before,1,2 the pipeline of investigational antiretroviral drugs for treating HIV infection remains full. New agents include compounds in existing classes—nucleoside analogue reverse transcriptase inhibitors (nRTIs), nonnucleoside analogue RTIs (NNRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitors (InSTIs)—as well as new classes of HIV entry inhibitors. Among a number of investigational drugs in the pipeline, 6 of those furthest along in development or that offer distinct advantages over currently available other drugs are discussed.

Dr Gulick is Rochelle Belfer Professor in Medicine at Weill Cornell Medicine in New York, New York.

Nucleoside Analogue Reverse Transcriptase Inhibitors

For nRTIs, drugs with more convenient dosing than current once-daily schedules could offer benefits. MK-8591 (or 4’-ethynyl-2-fluoro-2’-deoxyadenosine [EFDa]) is an investigational long-acting adenosine analogue currently in phase II studies.3 MK-8591 exhibits potent activity against HIV-1 in vitro, as well as activity against HIV-2 and multidrug-resistant HIV strains,4 and has a prolonged half-life of 150 to 160 hours. It is a nucleoside nonobligate chain terminator that inhibits HIV reverse transcriptase by preventing translocation of the enzyme, and hence has been termed a nucleoside reverse transcriptase translocation inhibitor (NRTTI).5 In a study of 30 HIV-infected treatment-naive individuals, single oral doses of 0.5 to 30 mg of MK-8591 reduced plasma HIV RNA levels by up to 1.7 log10 copies/mL at 10 days, with no emergence of viral resistance, indicating that convenient weekly dosing may be possible.6

Other formulations of MK-8591 may be administered parenterally and have the potential to be combined with other antiretroviral drugs. In animal studies, a single parenteral dose of MK-8591 produced persistent target drug levels for more than 180 days7 and the compound accumulated in target sites, including lymph nodes and vaginal and rectal tissues.8 MK-8591 also prevented simian-human immunodeficiency virus (SHIV) infection when used as in PrEP macaques.9

Nonnucleoside Analogue Reverse Transcriptase Inhibitors

NNRTIs with less toxicity, better tolerability, fewer drug interactions, and activity against NNRTI-resistant viruses are needed. The investigational NNRTI furthest along in development is doravirine (MK-1439), which has been evaluated in phase III trials. Preclinical studies showed that doravirine is potent at low doses against HIV and active against viral strains with common NNRTI-resistance–associated substitutions such as K103N, Y181C, G190A, E101K, E158K, and K103N/Y181C.10 Doravirine is metabolized by cytochrome P4503A4 (CYP3A4) but is not a CYP450 inhibitor nor inducer, and thus has less potential for drug interactions than other NNRTIs.

In a phase I study of antiretroviral therapy–naive individuals, 7 days of treatment with doravirine produced a rapid decrease of 1.5 log10 copies/mL in plasma HIV RNA levels.11 In a double-blind phase II trial, 216 antiretroviral therapy–naive participants with HIV RNA levels of 1000 copies/mL or higher and CD4+ cell counts of 100/µL or higher were randomly assigned to receive coformulated (indicated with a /) tenofovir disoproxil fumarate (TDF)/emtricitabine plus either doravirine (n = 108) or efavirenz (n = 108).12 At 48 weeks, 78% of the doravirine group and 79% of the efavirenz group had HIV RNA levels below 40 copies/mL.
Two phase III registrational trials were recently completed and presented. In the first trial, 769 treatment-naive participants with HIV RNA levels of 1000 copies/mL or higher and no resistance to study drugs by genotypic testing were randomly assigned to receive 2 nRTIs (mostly TDF-based combinations) plus either double-blinded doravirine 100 mg or the PI darunavir 800 mg boosted with ritonavir 100 mg. At 48 weeks, 84% of the doravirine group and 80% of the darunavir/ritonavir group had HIV RNA levels below 50 copies/mL. Protocol-defined virologic failure was uncommon, and no resistance mutations were identified in cases of virologic failure. Treatment was discontinued due to adverse events in 2% and 3% of participants, respectively.

The second trial randomly assigned 728 treatment-naive participants to receive double-blinded doravirine/TDF/lamivudine or efavirenz/TDF/emtricitabine. At 48 weeks, 84% of the doravirine group and 81% of the efavirenz group achieved virologic suppression (HIV RNA level < 50 copies/mL) and fulfilled prespecified noninferiority criteria (Figure I). There were differences in the proportions of participants who reported dizziness (9% in the doravirine group vs 37% in the efavirenz group) and sleep disorders (12% in the doravirine group vs 26% in the efavirenz group), although rates of study drug discontinuation were similar.

These studies are under review by the US Food and Drug Administration (FDA) with a target action date of October 2018 and could support approval of doravirine. To date, there are no clinical data on the effects of a doravirine-based regimen in individuals with NNRTI-resistant virus.

**Integrase Strand Transfer Inhibitors**

For InSTIs, agents with more convenient dosing or with activity against InSTI-resistant viral strains are needed. The recently approved InSTI bictegravir is active against InSTI-resistant virus in vitro and has a half-life of approximately 18 hours, with no pharmacokinetic boosting required for once-daily dosing. Bictegravir does not inhibit or induce CYP3A4 or uridine 5'-diphospho (UDP)-glucuronosyltransferase, indicating a low potential for drug interactions.

In a phase 1 study, 20 participants who were treatment-naive or had been off antiretroviral therapy for at least 12 weeks and had not previously taken an InSTI, with HIV RNA levels of 10,000 to 400,000 copies/mL and CD4+ cell counts above 200/µL, received 10 days of bictegravir once daily at 5 mg, 25 mg, 50 mg, or 100 mg and experienced dose-related decreases in HIV RNA levels of 1.45 log_{10} to 2.43 log_{10} copies/mL. In a phase II study, 98 treatment-naive participants who had HIV RNA levels above 1000 copies/mL and CD4+ cell counts of 200/µL or higher were randomly assigned to receive tenofovir alafenamide (TAF)/emtricitabine plus either bictegravir (n = 65) or dolutegravir (n = 33). At 48 weeks, 97% of the bictegravir group and 91% of the dolutegravir group had HIV RNA levels below 50 copies/mL. Virologic failure occurred in 2% and 6%, respectively, with no drug resistance observed in these individuals. Adverse events and abnormal laboratory test results were similar between the 2 groups.

Phase III registrational studies of bictegravir were recently completed and presented. In one study, 645 treatment-naive participants with HIV RNA levels of 500 copies/mL or higher and glomerular filtration rates of 50 mL/min or higher who were negative for the HLA-B*5701 allele were randomly assigned to receive double-blinded bictegravir/TAF/emtricitabine or dolutegravir/abacavir/lamivudine. At 48 weeks, 92% of the bictegravir group and 93% of the dolutegravir group had achieved virologic suppression (HIV RNA levels < 50 copies/mL), fulfilling prespecified noninferiority criteria. Adverse events (all grades) were similar between the 2 regimens, with the exception of nausea (10% in the bictegravir group vs 23% in the dolutegravir group).

---

**Figure 1.** Rates of virologic suppression among treatment-naive HIV-infected individuals treated with coformulated (indicated with a /) doravirine/tenofovir disoproxil fumarate (TDF)/lamivudine or efavirenz/TDF/emtricitabine in a phase III trial. CI indicates confidence internal. Adapted from Squires et al. 14

**Figure 2.** Rates of virologic suppression at 48 weeks in 2 phase III trials of HIV-infected individuals treated with coformulated nucleoside analogue transcriptase inhibitors (nRTIs) tenofovir alafenamide (TAF)/emtricitabine plus either the investigational drug bictegravir or plus dolutegravir. 15, 16
In a second study, 645 treatment-naive participants with HIV RNA levels of 500 copies/mL or higher and glomerular filtration rates of 30 mL/min were randomly assigned to receive a double-blinded regimen of bictegravir/TAF/emtricitabine or of dolutegravir. Cabotegravir demonstrates potent activity against HIV in oral formulation at a range of doses and is also formulated (indicated with a /) abacavir/lamivudine orally for 20 weeks (induction phase), followed by continued cabotegravir 400 mg plus rilpivirine 900 mg intramuscularly every 8 weeks, or cabotegravir 30 mg plus abacavir/lamivudine orally daily (maintenance therapy) in the phase II LATTE-2 (Long-Acting Antiretroviral Treatment Enabling–2) trial. Adapted from Margolis et al.24

Figure 3. Rates of virologic suppression among HIV-infected individuals treated with the investigational drug cabotegravir 30 mg plus coformulated (indicated with a /) abacavir/lamivudine orally for 20 weeks (induction phase), followed by continued cabotegravir 400 mg plus rilpivirine 600 mg intramuscularly every 4 weeks, cabotegravir 600 mg plus rilpivirine 900 mg intramuscularly every 8 weeks, or cabotegravir 30 mg plus abacavir/lamivudine orally daily (maintenance therapy) in the phase II LATTE-2 (Long-Acting Antiretroviral Treatment Enabling–2) trial. Adapted from Margolis et al.24

In a phase I study, cabotegravir administered parenterally exhibited a half-life of 21 to 50 days, which supports monthly or bimonthly dosing.21 In the phase II ECLAIR study of HIV-seronegative men,22 14 (16%) of 86 participants had detectable levels of study drug 1 year after their last injection.23

In the phase IIb LATTE-2 (Long-Acting Antiretroviral Treatment Enabling–2) study, 309 treatment-naive HIV-infected participants received run-in treatment with oral cabotegravir 30 mg plus abacavir/lamivudine for 20 weeks. Participants with virologic suppression were then randomly assigned to receive either intramuscular cabotegravir 400 mg plus intramuscular rilpivirine 600 mg every 4 weeks (n = 115), intramuscular cabotegravir 600 mg plus intramuscular rilpivirine 900 mg every 8 weeks (n = 115), or continue oral cabotegravir 30 mg plus abacavir/lamivudine daily (n = 56).24 At 96 weeks, HIV RNA levels were suppressed below 50 copies/mL in 87% in the group that received the injectable regimen every 4 weeks, 94% in the group that received the injectable regimen every 8 weeks, and 84% in the group that received the oral regimen daily (Figure 3). Adverse events were limited to injection site reactions, which occurred in most participants but were generally mild or moderate in intensity (lasting a median of 3 days), and led to treatment discontinuation in only 2 (1%) participants. Subsequent analysis revealed a few cases of virologic breakthrough in the group that received intramuscular treatment every 8 weeks. Thus, cabotegravir with monthly intramuscular dosing is currently being examined as maintenance treatment in phase III studies.25

An injectable formulation of cabotegravir is also being investigated for HIV preexposure prophylaxis (PrEP). The phase II HIV Prevention Trials Group (HPTN) 077 study enrolled 199 low-risk, HIV-uninfected participants (66% women, 54% men) and randomly assigned them (3:1) to receive oral cabotegravir for 4 weeks followed by intramuscular cabotegravir 800 mg every 12 weeks or 600 mg every 8 weeks (or matching placebos).26 There were no differences in safety or tolerability except for injection site reactions occurring in 54% of those who received cabotegravir and in 2% of those who received a placebo injection. Drug concentrations were lower with cabotegravir 800 mg given every 12 weeks,
and investigators concluded that cabotegravir 600 every 8 weeks was optimal. These results support the design and implementation of the HPTN 083 study, with a target population of 4500 high-risk men who have sex with men and transgender women who have sex with men who are randomly assigned to receive double-blinded daily oral TDF/emtricitabine or intramuscular cabotegravir every 8 weeks. The primary endpoint of HPTN 083 is incident HIV infections over an expected duration of 4.5 years, and the study is fully powered for noninferiority with a margin of 25%. The first study participant was enrolled in December 2016. A parallel study will enroll at-risk, HIV-uninfected African women. In a phase II study, treatment-experienced participants who previously received at least 1 antiretroviral drug for at least 1 week and who had virus susceptible to temsavir (IC50 <100nM) were randomly assigned to receive TDF and raltegravir plus fostemsavir 400 mg twice daily (n = 50), 800 mg twice daily (n = 50), 600 mg once daily (n = 50), or 1200 mg once daily (n = 50), or plus atazanavir/ritonavir (n = 50). At week 48, 61% to 82% of the fostemsavir groups and 71% of the atazanavir/ritonavir group had HIV RNA levels below 50 copies/mL in a modified intent-to-treat analysis. Fostemsavir 1200 mg daily was selected as the dose for the open-label continuation study after week 48 for all participants who received fostemsavir. At week 96, virologic suppression was observed in 61% of the fostemsavir group and 53% of the atazanavir/ritonavir group. Treatment-related grade 2 to 4 adverse events were observed in 9% of the fostemsavir group and 37% of the atazanavir/ritonavir group, with hyperbilirubinemia observed in 12% of the latter group. Adverse events led to treatment discontinuation in 2.5% and 10.0%, respectively. In recognition of its novel mechanism of action, fostemsavir was granted “breakthrough status” by the FDA in July 2015. A phase III trial of fostemsavir enrolled 272 heavily-experienced participants who continued their regimens and randomly added 3:1 fostemsavir or placebo. At 8 days, the primary endpoint of the study, HIV RNA decreased 0.8 log10 copies/mL (fostemsavir) vs. 0.2 (placebo, P < .0001). Participants then optimized their background regimens and continued or added fostemsavir 600 mg bid. At 24 weeks, 54% had HIV RNA levels below 40 copies/mL and 12 (4%) had discontinued study medications due to adverse events.

The recently approved monoclonal antibody ibalizumab binds not to HIV but to the host cell at the second domain of the CD4 receptor, thereby preventing conformational changes and HIV entry. Ibalizumab has been in development for more than 10 years, with parenteral formulations given every 1 to 4 weeks in different study populations. In a phase II study of 113 treatment-experienced individuals with resistance to 3 antiretroviral drug classes, approximately 40% achieved virologic suppression (HIV RNA level <50 copies/mL) with an ibalizumab-containing optimized background regimen. Ibalizumab was evaluated in 40 individuals who had resistance to antiretroviral drugs from 3 classes, with HIV RNA levels above 1000 copies/mL on stable antiretroviral therapy for at least 6 months, and had sensitivity to at least 1 antiretroviral drug. Participants continued their current antiretroviral regimens, and then received ibalizumab 800 mg intravenously on day 7 and were assessed for virologic responses at day 14, the primary endpoint of the study. At that

---

**Figure 4.** Mechanisms by which HIV entry inhibitors block virus from entering a cell. Fostemsavir and ibalizumab are investigational drugs. Enfuvirtide and maraviroc have been approved by the US Food and Drug Administration. CCR5 indicates CC chemokine receptor 5; CXCR4, C-X-C chemokine receptor type 4; gp, glycoprotein. Adapted from Moore et al. Currently available entry inhibitors are the CCR5 receptor antagonist maraviroc and the fusion inhibitor enfuvirtide.

**Entry Inhibitors**

Entry inhibitors with novel mechanisms of action and greater convenience in dosing would be useful. The 3 steps of HIV entry are: 1) HIV binding to the CD4 receptor; 2) subsequent binding to the chemokine receptor (either CC chemokine receptor 5 [CCR5] or C-X-C chemokine receptor type 4 [CXCR4]); and 3) fusion of the viral and host cell membranes (Figure 4). Currently available entry inhibitors are the CCR5 receptor antagonist maraviroc and the fusion inhibitor enfuvirtide.

A new class of HIV entry inhibitors, CD4 attachment inhibitors, targets the first step of entry. Fostemsavir is a small molecule inhibitor that binds HIV envelope glycoprotein 120 (gp120) and prevents virus from binding to the CD4 receptor. Fostemsavir is an oral prodrug of temsavir, the active compound, with potent activity in vitro against HIV, and pharmacokinetics that support once-daily dosing with no need for pharmacologic boosting. In a phase I dose-escalation study in 48 participants who were treatment-naïve or had been off antiretroviral treatment for 8 weeks or longer, higher doses of fostemsavir led to a reduction in HIV RNA level of 1.5 log10 copies/mL. Twelve percent of participants had baseline envelope polymorphisms that rendered fostemsavir inactive, raising the issue of the need for patient screening for polymorphisms.

---

In a phase II study, treatment-experienced participants who previously received at least 1 antiretroviral drug for at least 1 week and who had virus susceptible to temsavir (IC50 <100nM) were randomly assigned to receive TDF and raltegravir plus fostemsavir 400 mg twice daily (n = 50), 800 mg twice daily (n = 50), 600 mg once daily (n = 50), or 1200 mg once daily (n = 50), or plus atazanavir/ritonavir (n = 50). At week 48, 61% to 82% of the fostemsavir groups and 71% of the atazanavir/ritonavir group had HIV RNA levels below 50 copies/mL in a modified intent-to-treat analysis. Fostemsavir 1200 mg daily was selected as the dose for the open-label continuation study after week 48 for all participants who received fostemsavir. At week 96, virologic suppression was observed in 61% of the fostemsavir group and 53% of the atazanavir/ritonavir group. Treatment-related grade 2 to 4 adverse events were observed in 9% of the fostemsavir group and 37% of the atazanavir/ritonavir group, with hyperbilirubinemia observed in 12% of the latter group. Adverse events led to treatment discontinuation in 2.5% and 10.0%, respectively. In recognition of its novel mechanism of action, fostemsavir was granted “breakthrough status” by the FDA in July 2015. A phase III trial of fostemsavir enrolled 272 heavily-experienced participants who continued their regimens and randomly added 3:1 fostemsavir or placebo. At 8 days, the primary endpoint of the study, HIV RNA decreased 0.8 log10 copies/mL (fostemsavir) vs. 0.2 (placebo, P < .0001). Participants then optimized their background regimens and continued or added fostemsavir 600 mg bid. At 24 weeks, 54% had HIV RNA levels below 40 copies/mL and 12 (4%) had discontinued study medications due to adverse events.

The recently approved monoclonal antibody ibalizumab binds not to HIV but to the host cell at the second domain of the CD4 receptor, thereby preventing conformational changes and HIV entry. Ibalizumab has been in development for more than 10 years, with parenteral formulations given every 1 to 4 weeks in different study populations. In a phase II study of 113 treatment-experienced individuals with resistance to 3 antiretroviral drug classes, approximately 40% achieved virologic suppression (HIV RNA level <50 copies/mL) with an ibalizumab-containing optimized background regimen. Ibalizumab was evaluated in 40 individuals who had resistance to antiretroviral drugs from 3 classes, with HIV RNA levels above 1000 copies/mL on stable antiretroviral therapy for at least 6 months, and had sensitivity to at least 1 antiretroviral drug. Participants continued their current antiretroviral regimens, and then received ibalizumab 800 mg intravenously on day 7 and were assessed for virologic responses at day 14, the primary endpoint of the study. At that
time, 60% of patients experienced at least a 1 log_{10} copies/mL decrease in HIV RNA level. Subsequently, participants optimized their antiretroviral regimen based on treatment history and drug resistance testing and received ibalizumab 800 mg intravenously on day 21 and then every 2 weeks thereafter. With this strategy, at week 24, participants experienced a mean decrease in HIV RNA level of 1.6 log_{10} copies/mL and 43% experienced suppressed HIV RNA levels below 50 copies/mL. Twenty-seven of these participants continued ibalizumab and their optimized background regimen in an open-label extension study and 59% had HIV RNA levels below 50 copies/mL at 48 weeks. These data supported FDA approval of ibalizumab for heavily treatment-experienced adults with multidrug resistant HIV-1 infection in whom their current regimen had failed.

Presented by Dr Gulick in April and August 2017. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Gulick in March 2018.

Financial affiliations in the past 12 months: Dr Gulick has no relevant financial affiliations to disclose.

References


39. Emu B, Fessel WJ, Schrader S, et al. 48-Week Safety and Efficiency On-Treatment Analysis of Ibalizumab in Patients with Multi-Drug Resistant HIV-1. ID Week 10-6-2017; San Diego, California, USA.
**Perspective**

**Management of Long-Term Complications of HIV Disease: Focus on Cardiovascular Disease**

HIV-infected individuals on effective antiretroviral therapy experience a number of non-AIDS noncommunicable diseases, such as cardiovascular disease, more frequently than uninfected individuals. Common pathways for such diseases are chronic immune activation and inflammation, including the prolonged inflammation associated with lower nadir CD4+ cell count. Prevention and treatment of non-AIDS conditions include treatment of traditional risk factors, lifestyle interventions, earlier initiation of antiretroviral therapy, and potentially therapies specifically targeting inflammation and immune activation (eg, statins). This article summarizes a presentation by Judith S. Currier, MD, at the IAS–USA continuing education program, Improving the Management of HIV Disease, held in New York, New York, in February 2017.

**Keywords:** HIV, non-AIDS diseases, cardiovascular disease, CVD, heart failure, immune activation, inflammation, CD4+ cell count, interleukin-6, IL-6, statins

As HIV-infected individuals on effective antiretroviral therapy are living longer, a range of other health issues is emerging among these persons. A number of conditions, including cardiovascular disease (CVD), non–AIDS-related cancers, bone disease, diabetes, frailty, liver disease, lung disease, renal disease, and cognitive disorders, occur with more frequency in HIV-infected persons with viral suppression on antiretroviral therapy than in the general population. Efforts to determine how best to prevent and treat such conditions and whether they share underlying contributing causes are ongoing.

**Survival and Comorbidities**

Data from a study in the Netherlands indicate that the survival rate for treated HIV-infected individuals aged 50 years or older has steadily increased from the period from 1996 to 1999 to the period from 2006 to 2014 and is approaching the survival rate among uninfected individuals in this age group (Figure 1). However, even when survival analysis is limited to HIV-infected persons who had no comorbidities before initiating antiretroviral therapy and who have maintained viral suppression throughout treatment, there remains a gap between the survival rates of such persons and the general population (Figure 1).

Dr Currier is Professor of Medicine, Chief of the Division of Infectious Disease, and Associate Director of the Clinical AIDS Research and Education Center at David Geffen School of Medicine, University of California Los Angeles in Los Angeles, California, and is a member of the IAS–USA Board of Directors.

The prevalence of comorbidities is increasing as the population of individuals with HIV infection ages. Data from another study in the Netherlands indicate that the proportion of persons living with HIV infection aged 50 years or older will increase from 28%, as of 2010, to 73% by 2030. Over this time, the proportion of HIV-infected persons with at least 1 noncommunicable disease from among CVD (including hypertension, hypercholesterolemia, myocardial infarction [MI], and stroke), diabetes, chronic kidney disease, osteoporosis, and non-AIDS malignancies is estimated to increase from 29% to 84%. It is estimated that by 2030, 28% of HIV-infected individuals will have more than 3 noncommunicable diseases and that 54% will be on medications to treat these conditions.

**CVD in HIV Infection**

A US study showed that between 1999 and 2013, the proportion of mortality attributable to circulatory CVD among HIV-infected individuals aged 25 years or older increased from 2.1% to 3.8% in women and from 1.9% to 4.9% in men. These increases occurred during a period when mortality attributable to CVD decreased in the general population and among persons with other inflammatory diseases such as inflammatory polyarthropathies.

Some data indicate that the relative risk of CVD in HIV-infected individuals has decreased over time. In a cohort study from Kaiser Permanente Northern California, the adjusted MI rate ratio for HIV-infected versus uninfected persons decreased from 1.8 (95% confidence interval [CI], 1.3-2.6; incidence rate [IR], 276/100,000 vs 136/100,000 person-years) in the period from 1996 to 1999 to a nonsignificant 1.0 (95% CI, 0.7-1.4; IR, 195/100,000 vs 165/100,000 person-years) in the period from 2010 to 2011; rate ratios were 1.7, 1.3, and 1.3 for the periods from 2000 to 2003, 2004 to 2007, and 2008 to 2009, respectively. This cohort likely reflects a population with well-managed HIV infection and access to preventive care, suggesting that such care may contribute to reducing CVD risk.

HIV infection adversely affects cardiac function. Studies using cardiac magnetic resonance imaging (MRI) have shown a high burden of myocardial fibrosis and cardiac steatosis among asymptomatic HIV-infected individuals, decreased systolic function in HIV-infected individuals compared with controls, and increased pericardial fat among HIV-infected individuals with lipoaccumulation.

Clinical studies have shown an increased risk of heart failure among HIV-infected persons. In a study of 27,363 HIV-infected and 55,125 HIV-uninfected persons without CVD conducted between 2003 and 2012, HIV-infected persons had...
a statistically significantly elevated risk of heart failure with preserved ejection fraction (EF) (EF, ≥40%; RR, 1.21; 95% CI, 1.05-1.40) and with reduced EF (EF, <40%; RR, 1.58; 95% CI, 1.36-1.89).11

Pathways for Non-AIDS Diseases in HIV

There may be common contributing factors for non-AIDS events in HIV infection, involving host genetics and lifestyle, HIV replication with resulting immune activation, and antiretroviral therapy. Measures of these risk factors include innate immune activation (eg, soluble CD14 [sCD14], sCD163, monocyte activation); history of low nadir CD4+ cell count—“area under the curve of chronic inflammation” or a low CD4 to CD8 ratio; copathogens (eg, cytomegalovirus [CMV] immune responses or CMV-specific T-cell responses); and abnormalities in coagulation (eg, tissue factor expression).

Single measurements of the coagulation marker D-dimer and the inflammation marker interleukin (IL)-6 were predictive of serious non-AIDS events or death in HIV-infected individuals over a period of 10 years (Figure 2).12-14 In a biomarker analysis of the SMART (Strategies for Management of Antiretroviral Therapy) and ESPRIT (Evaluation of Subcutaneous Aldesleukin in a Randomized International Trial) trials that compared highest with lowest quartiles of IL-6, D-dimer, and the inflammatory marker highsensitivity C reactive protein (hs-CRP), IL-6 was the strongest predictor for both non-AIDS malignancy and CVD among HIV-infected persons (Figure 3).14 Similar associations have been found in cohort studies of immune activation. Higher levels of innate immune activation have been associated with all-cause mortality, CVD and thromboembolic disease,15 non-AIDS cancers and lymphoma,16 osteoporosis,17 type 2 diabetes,18 frailty,19 chronic obstructive pulmonary disease,20 bacterial pneumonia,21 and neurocognitive dysfunction.22 With regard to adaptive immune activation, T-cell activation predicted morbidity and mortality in a multinational case-cohort study,23 and in a study among persons in Uganda.24

A high proportion of persons with HIV infection are coinfected with CMV. CMV infection may be responsible for some of the increased immunosenescence and increased proliferation of CD8+ T cells linked to comorbidities in the context of coinfection with HIV. Whether immunization or more effective therapy for CMV infection might reduce immune activation and immunosenescence in the context of HIV/CMV coinfection, thus reducing the risk of associated comorbidities, remains unknown.

The harms of untreated HIV disease clearly outweigh any excess risk of CVD associated with antiretroviral therapy. Longer duration of treatment with older HIV protease
inhibitors (eg, indinavir, ritonavir-boosted lopinavir) was associated with increased MI risk in observational studies. However, no association between antiretroviral drugs and evidence of plaque on computed tomography (CT) angiography has been observed. Abacavir has been associated with increased relative risk of MI. The most consistent evidence of this association has been found among individuals with additional risk factors, and the mechanism of the association remains unclear. Recent evidence suggests a possible role for platelet reactivity as the underlying mechanism.

AIDS Clinical Trials Group (ACTG) A5260s, a substudy of the ACTG A5257 study, examined the effects of newer antiretroviral regimens on CVD biomarkers and changes in carotid intima-media thickness (CIMT). Antiretroviral treatment–naive participants with no known CVD, diabetes, or use of lipid-lowering medications (n = 328) were randomly assigned to receive emtricitabine/tenofovir disoproxil fumarate (slash indicates coformulation) plus ritonavir-boosted atazanavir, raltegravir, or ritonavir-boosted darunavir. At 96 weeks, raltegravir was associated with a persistent decline in IL-6, whereas atazanavir and darunavir were not. A decline in D-dimer was observed with atazanavir or darunavir but not with raltegravir. Measures of T-cell activation declined in each group, but changes in monocyte activation were inconsistent. Progression of CIMT was observed in each group over 144 weeks, although the rate of progression was lower in the atazanavir group than in the darunavir group, and the rate in the raltegravir group was intermediate. A bilirubin level of 0.6 mg/dL or higher at weeks 4 and 24 was associated with a reduced rate of progression of CIMT. Increases in bilirubin (which is an antioxidant) are characteristic of atazanavir.

The findings above raise the question of whether atazanavir may have a protective effect against CVD in the context of HIV infection. Higher bilirubin levels were associated with lower risk of type 1 MI and stroke but with higher risk of type 2 MI (resulting from oxygen supply/demand mismatch, such as during sepsis) in the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort. Atazanavir was associated with reduced risk (hazard ratio, 0.66) for MI but not for stroke in a US Veterans Affairs study. Atazanavir is no longer considered a preferred drug because of side effects, including rash and severe hypersensitivity reactions.

Interventions to Reduce Non-AIDS Events in HIV

Interventions that may reduce non-AIDS events in persons with HIV infection include lifestyle changes, earlier initiation of antiretroviral therapy, and treatments for inflammation and immune activation. Lifestyle interventions include smoking cessation, as smoking may synergize with HIV to increase mortality; screening for and treating hypertension and diabetes; diet and exercise; use of aspirin; and use of statins and other lipid-lowering treatments. It is notable that deaths related to smoking may outnumber those due to HIV-related diseases. 

Data from the START (Strategic Timing of Anti-Retroviral Treatment) trial, which examined initiating treatment at a CD4+ cell count above 500/µL or waiting until it dropped below 350/µL, showed benefits in reducing non-AIDS endpoints, not including differences in risk of CVD, in neurocognitive performance, or in risk of chronic obstructive pulmonary disease. The population of this trial was relatively young, and the 3-year follow-up period may have been too short to capture differences in some outcomes. However, some of the non-AIDS conditions may be linked to immunologic changes associated with immunodeficiency, including exposure to lower CD4+ cell count nadirs and greater levels of inflammation. Opportunistic infections (OIs) and CVD events increased with lower nadir CD4+ cell count among individuals whose antiretroviral treatment was interrupted in the SMART trial, which compared continuous treatment with interrupting treatment when CD4+ cell count was above 350/µL and restarting it when CD4+ cell count fell below 250/µL (Figure 4).

In the START trial, nadir CD4+ cell count was much higher among participants whose antiretroviral treatment was delayed than in those who treatment was interrupted in the SMART trial, and there were fewer OIs and CVD events. However, there still appears to be a benefit associated with the higher nadir CD4+ cell count among those who initiate antiretroviral treatment immediately compared with those whose treatment is delayed. Thus, although CVD is not generally thought to be linked to immune deficiency, nadir CD4+ cell count and history of long-term immune activation may contribute to CVD risk. There is also evidence of impaired vascular function and increased arterial inflammation even in early HIV infection, suggesting that there may be a continuum of CVD risk in this setting.

Other strategies for targeting immune and inflammatory mechanisms include CC chemokine receptor 5 (CCR5)
antagonists, IL antagonists, methotrexate (which can lower IL-6), and statins. CCR5 antagonists and the investigational CCR2 antagonist cenicriviroc (which also targets CCR5) are currently being evaluated for potential cardiovascular benefits in clinical trials. IL-1β inhibition with the monoclonal antibody canakinumab, which was recently shown to reduce CVD events in 10,061 patients without HIV infection who had a prior episode of myocardial infarction and an elevated high sensitivity C-reactive protein level. A pilot study in 10 individuals showed a reduction in arterial inflammation after a single infusion of canakinumab, and a reduction in IL-6 but no change in T-cell activation.

Some studies have suggested that current American College of Cardiology (ACC) and American Heart Association (AHA) guidelines for statin use may underestimate risk for cardiovascular events in HIV-infected individuals. In one study, only 25% of participants with coronary plaque with 1 or 2 high-risk morphologic features on CT angiography met the 2013 guideline eligibility criteria for statin therapy. In another study which analyzed the ability of the Framingham Risk Score, ACC/AHA Pooled Cohort Equation, Systematic Coronary Risk Evaluation (SCORE), and the HIV-specific D:A:D (Data Collection on Adverse Effects of Anti-HIV Drugs) study equation to predict CVD events in the HIV Outpatient Study population, Framingham Risk Score performed best but still underestimated the incidence of CVD events. A larger study in the CNICS cohort found that the ACC/AHA Pooled Cohort Equation accurately predicted MI risk among white men but underpredicted events among black men and women. White women had too few events to assess predictive accuracy.

Statin therapy improves traditional and immune-related risk factors in HIV-infected individuals. Lowering of low-density lipoprotein (LDL) cholesterol level with statin therapy is similar in persons with or without HIV infection. Statin therapy has also been shown to dampen immune activation. In one study, rosuvastatin treatment substantially reduced monocyte activation over 48 weeks compared with placebo, as indicated by decreases in circulating levels of sCD14 and the macrophage-derived lipoprotein-associated phospholipase A2 (Lp-PLA2), as well as improved CIMT.

Safety of statins continues to be of concern in long-term use, particularly with regard to their effect on glucose control and potential interactions with HIV protease inhibitors. Recent data on pitavastatin indicate no adverse effects on blood glucose levels and no interactions with protease inhibitors, suggesting that this drug might be appropriate for HIV-infected individuals. The effects of pitavastatin on CVD events is currently being evaluated in the large-scale REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) trial. In REPRIEVE, a target population of 6500 HIV-infected participants who do not meet criteria for statin therapy are randomly assigned to receive pitavastatin or placebo. Substudies are examining the effects of pitavastatin on CT angiography outcomes, differences in outcome by sex, renal outcomes, and effects on muscle function.

**Summary**

Non-AIDs events are a growing cause of morbidity and mortality among persons with treated HIV infection. Inflammation and immune activation may be contributing to the prevalence of non-AIDS events among HIV-infected persons, and measurement of biomarkers of inflammation and immune activation may have utility in predicting risk and informing interventions. Traditional CVD risk factors remain important and should be the focus of interventions. Optimal methods for predicting CVD risk are undefined at present. Novel interventions to reduce inflammation for persons on antiretroviral therapy remain an important area of investigation.

**References**


Perspective
Maximizing the Benefits of HIV Preexposure Prophylaxis

Preexposure prophylaxis (PrEP) with tenofovir/emtricitabine (slash indicates coformulation) is highly effective in preventing new HIV infections. PrEP efficacy is strongly associated with adherence. In clinical trials, PrEP has been more effective in men who have sex with men and HIV-serodiscordant heterosexual couples than in women, likely reflecting pharmacokinetic differences between levels of tenofovir disoproxil fumarate in vaginal and rectal tissues, and poorer adherence in studies in women. Current guidelines recommend daily PrEP for men and women; however, PrEP taken at least 4 days per week for men may be as effective as daily PrEP, and women must take PrEP 6 to 7 days per week to maximize efficacy. Data are accumulating on the effectiveness of pericoital PrEP for men who have sex with men, but it is not yet recommended in the United States. PrEP is underprescribed for younger individuals, black individuals, and Hispanic and Latino individuals. This article summarizes a presentation by Susan P. Buchbinder, MD, at the IAS–USA continuing education program, Improving the Management of HIV Disease, held in Chicago, Illinois, in May 2017.

Keywords: HIV, prevention, preexposure prophylaxis, PrEP, tenofovir, TDF, emtricitabine, adherence, preventive efficacy, men who have sex with men, MSM, women

Preexposure prophylaxis (PrEP) is highly effective in preventing HIV infection. Tenofovir disoproxil fumarate (TDF)/emtricitabine (slash indicates coformulation) is the only form of PrEP currently approved by the US Food and Drug Administration.

Which persons may benefit most from PrEP can be gleaned from data on new HIV infections in the United States. From 2010 to 2014, 81% of new HIV diagnoses were among men. In 2015, man-to-man sexual contact and heterosexual sexual contact were responsible for 82% and 9%, respectively, of new HIV diagnoses among men, and heterosexual contact was responsible for 86% of new HIV diagnoses among women (Figure 1). Between 2008 and 2014, estimated annual new HIV infections decreased by 18%, and HIV incidence decreased among persons who inject drugs (PWID), heterosexual persons, and some groups of men who have sex with men (MSM). Annual HIV incidence has decreased among MSM aged 13 to 24 years but has increased among MSM aged 25 to 34 years. Annual HIV incidence has decreased among white MSM, remained stable among black MSM, and increased among Latino and Hispanic MSM. In 2015, 22% of HIV infections were among persons aged 13 to 24 years, 33% among those aged 25 to 34 years, 19% among those aged 35 to 44 years, and 25% among those aged 45 years or older. These data highlight the urgent need to provide PrEP and other highly effective prevention to MSM, particularly men of color. Although HIV infection is increasing among those aged 25 to 34 years, high infection rates are still observed in younger and older age groups, serving as a reminder that practitioners should obtain sexual histories on all of their patients and should counsel about the potential benefits of PrEP for all persons who may be at risk of HIV acquisition.

Effectiveness of PrEP

The highest levels of PrEP efficacy were achieved with daily TDF/emtricitabine in the PROUD (Preexposure Option for Reducing HIV in the UK) study of MSM (effectiveness, 86%) in the United Kingdom, event-driven TDF/emtricitabine in the IPERGAY (Action to Prevent Risk Exposure By and For Gay Men) study of MSM in France and Canada (effectiveness, 86%), and daily TDF/emtricitabine in the Partners PrEP study of HIV-serodiscordant heterosexual couples in Uganda and Kenya (effectiveness, 75%).

The effectiveness of PrEP correlates with adherence to PrEP (Figure 2). Adherence to and effectiveness of PrEP have been higher in studies of MSM, heterosexual couples, and combined populations of heterosexual men and women than in several studies of women only. Although social and environmental factors may have contributed to lower adherence among women in some studies, pharmacodynamics also likely contributed to reduced PrEP effectiveness in these populations.

Several studies in clinical rather than research settings have documented high PrEP effectiveness among MSM. In a cohort study from Kaiser Permanente Northern California, there were no new HIV infections among 952 men and 20 women despite a 42% annual cumulative incidence of sexually transmitted infections (STIs). Two new HIV infections occurred in the study population after participants discontinued PrEP. Similarly, in the US PrEP Demonstration Project among 557 MSM and transgender women in San Francisco, California, Miami, Florida, and Washington, DC, no new HIV infections were observed despite an overall STI rate of 51%, although 2 new HIV infections occurred after the individuals had discontinued PrEP.

Rare cases of breakthrough HIV infection in MSM despite high adherence to PrEP have been reported, including 2 MSM who were infected while being treated for hepatitis B virus (HBV) infection with daily TDF. 2 MSM infected with multidrug-resistant virus while taking TDF/emtricitabine, and 1 man who has sex with men who was infected with wild-type virus while highly adherent to daily TDF/emtricitabine. The latter report of a breakthrough infection with wild-type virus occurred in a man who reported 40 to 75 anal sex

Dr Buchbinder is Clinical Professor of Medicine and Epidemiology at University of California San Francisco and Director of Bridge HIV at San Francisco Department of Public Health in San Francisco, California.
partners per month. Assessment of dried blood spots from this individual showed a high TDF level near the time of infection, indicating daily adherence to the PrEP regimen. This case suggests that even high levels of adherence to PrEP may be overwhelmed by very high levels of exposure to HIV, along with other potentially contributory factors.

Modeling of the frequency of PrEP dosing versus its effectiveness using data from the placebo-controlled iPrEx (Chemophrophylaxis for HIV Prevention in Men) and STRAND studies indicated an estimated preventive efficacy of 96% (95% confidence interval [CI], 90%-99%) with 4 doses per week, 99% (95% CI, 96%-99%) with 7 doses per week, and 76% (95% CI, 56%-96%) with 2 doses per week.12 These data suggest that even missed doses 2 to 3 times per week for MSM prescribed daily PrEP may not negatively impact its effectiveness because of its long intracellular half-life and high concentrations in rectal tissue.

The placebo-controlled IPERGAY study examined the use of sex event–driven PrEP among MSM. Participants took 2 doses of TDF/emtricitabine 2 to 24 hours before sex and 1 dose each 24 and 48 hours after the first dose. If more sexual episodes occurred, participants took PrEP daily until 48 hours after the last sexual encounter. This strategy of event-driven or “on-demand” PrEP had a preventive efficacy of 86% in the double-blind portion of the trial. In the open-label portion of the trial, when participants knew they were receiving active drug, the preventive effectiveness compared with placebo in the double-blind phase increased to 97%.13 Participants took a median of 18 doses of PrEP per month, equal to more than 4 doses per week. Given that dosing 4 times per week is likely as effective as daily dosing for MSM, it remains unclear whether this trial fully evaluated a more intermittent on-demand PrEP strategy. The Centers for Disease Control and Prevention (CDC) continues to recommend daily dosing of PrEP, although the on-demand approach may be useful in some situations.14

To evaluate the extent to which sex is planned among high-risk MSM, an online survey was conducted in 1013 sexually active MSM. Approximately half of the men reported that their last anal sex act was planned. However, when asked how far ahead sex was planned, 17% indicated it was planned only minutes before sex and 45% reported planning several hours before sex, suggesting that a majority of MSM may have difficulty adhering to event-driven regimens that require taking PrEP a minimum of 2 hours before sex occurs.15 In a separate online survey of 3217 MSM, 46% reported engaging in unplanned condomless anal sex within the prior 3 months, reiterating that other strategies may need to be implemented to ensure adequate PrEP uptake for those who are not planning their sexual encounters.16 A study of 92 MSM asked to predict daily for 1 month whether or not they would have sex the next day found that participants were much better at predicting if they would not have sex than when they would.17 However, intermittent PrEP may be particularly useful during intermittent periods of heightened sexual activity, such as planned vacations. In another online survey of 7505 MSM, 26% reported engaging in condomless anal sex with new partners while on vacation.18

To explore biologic explanations for poorer PrEP efficacy in several PrEP trials in women, investigators from the CAPRISA (Center for the AIDS Programme of Research in South Africa) 004 study of PrEP with tenofovir gel assessed the impact of perturbations of the vaginal microbiome at baseline on PrEP effectiveness. In this analysis, topical PrEP was only effective in women with a Lactobacillus–dominant vaginal microbiome.19 There was no statistically significant topical PrEP efficacy among those with microbial dysbiosis, characterized by dominance of other bacteria, higher pH, and more inflammatory changes. Another study directly examined the impact of baseline vaginal microbiota on topical PrEP efficacy.

Among 41 HIV-uninfected women who received daily tenofovir gel or film for 7 days, those with a Lactobacillus–predominant vaginal microbiome showed higher levels of tenofovir in vaginal fluid, cervical tissue, and plasma, and those with vaginal dysbiosis had lower tenofovir levels in these compartments.20 These findings suggest limitations in the effectiveness of tenofovir gel; other analyses have found no substantial effect of baseline vaginal dysbiosis or bacterial vaginosis on the efficacy of systemic PrEP, taken orally.

An analysis of the Partners PrEP study showed no statistically significant difference (P = .9, for interaction) in the preventive efficacy of PrEP versus placebo according to bacterial vaginosis indicated by Nugent Score; efficacy was 73% (P = .001) among women who had a score of 0 to 3, 63% among women who had a score of 4 to 6 (P = .2), and 77% among women who had a score of 7 to 10 (P = .04).21 The lower effectiveness of systemic PrEP in women than in MSM may be attributable, in part, to differences in tenofovir levels in vaginal versus rectal tissue. Available data suggest that women need 6 to 7 doses of PrEP per week to achieve and maintain protective drug levels, whereas MSM need 4 to 7 doses per week.22
In one study assessing how long daily PrEP should be taken in advance of HIV exposure to provide sufficient concentrations of tenofovir, 89% achieved a 90% effective concentration (EC<sub>90</sub>) in blood after 7 doses and 98% achieved an EC<sub>90</sub> after 13 doses. These data have been used to support the current CDC recommendation that MSM initiate PrEP 7 days before sexual activity and continue it for 28 days after. For women, the number of daily doses of PrEP needed to achieve protective drug concentrations remains unknown, because at similar doses, tenofovir concentrations in vaginal tissue are 10- to 100-fold lower than in anal tissue. The CDC currently recommends that women take PrEP for 21 days before sexual activity. Given the possibility of missed doses, a strategy of daily dosing of PrEP for men and women is most prudent at this time.

PWID appear to require high levels of adherence to achieve the same protective effects of PrEP seen in MSM. (Of note, many female PWID also have sexual risk factors for HIV infection.) It is possible that the reduced efficacy seen in PWID in the only efficacy trial of this approach was because TDF alone was used rather than TDF/emtricitabine. In that study, 97.5% adherence under directly observed therapy was needed to achieve greater than 80% effectiveness. It is also possible that PrEP is less effective against parenteral than sexual exposure. Five of 11 breakthrough infections occurred despite apparent complete adherence.

### PrEP for HIV-Serodiscordant Couples

The HIV Prevention Trials Network (HPTN) 052 study showed that the likelihood of HIV transmission among HIV-serodiscordant couples is exceedingly low once the infected partner has maintained full viral suppression. Data from the Partners PrEP study suggested that HIV transmission risk was very low only after 6 months on antiretroviral treatment. In counseling patients about the risk of HIV acquisition from a sexual partner with full viral suppression, the durability of viral suppression and the consistency of medical care of the partner must be understood. In a cohort of more than 14,000 individuals at 6 US HIV clinics followed for a median of more than 3 years, more than half had HIV RNA levels above 1500 copies/mL at some point, with viral loads above this level accounting for 23% of observation time in the study (average of 85 days per person).

PrEP is effective as a bridge to antiretroviral therapy among HIV-serodiscordant couples. In the Partners PrEP study, HIV-seropositive partners were offered antiretroviral treatment and HIV-seronegative partners were offered PrEP for the first 6 months that their partners were on therapy. If an HIV-seropositive partner declined treatment initially, the HIV-seronegative partner continued PrEP until the HIV-seropositive partner initiated treatment and remained on it for 6 months. Overall, there was a 95% reduction in new HIV infections compared with the expected rate.

### Initiation and Monitoring of PrEP

Individuals who are candidates for PrEP based on risk assessment should undergo testing for HIV infection, including viral load testing, if any signs or symptoms of an acute viral illness are present. Initiating PrEP before HIV serostatus is known could result in emergence of resistance to TDF or emtricitabine if the person is already HIV infected. Creatinine levels should be measured, and individuals with a creatinine clearance below 60 mL/min should not begin PrEP. After PrEP is initiated, creatinine clearance should be monitored at 3 months and every 6 months thereafter. HBV serostatus should be confirmed, as individuals-chronically infected with HBV may experience viral rebound when TDF is stopped. Individuals should be screened for STIs and pregnancy before initiating PrEP and at 3 month intervals thereafter. HIV testing should be repeated every 3 months during PrEP, with individuals counseled not to stop and restart PrEP on their own. Individuals
and renal effects were more likely with older age. Recent injection drug use had no effect on creatinine levels, during PrEP use, with reductions appearing to level off at PrEP is discontinued. Data indicate that creatinine levels return to near normal after returning to baseline after PrEP is discontinued.

6 months.

true renal effects whether testing is done every 3 versus every repeat testing and that there was no difference in detecting 75% of increases in creatinine level were unconfirmed on

ners Demonstration Project studies indicated that more than

ular filtration rate (eGFR) (below 90mL/min) , persons older than 50 years, and those weighing less than 55 kg were at increased risk for experiencing an apparent diminution of eGFR while on PrEP. Analysis of the Partners PrEP and Partners Demonstration Project studies indicated that more than 75% of increases in creatinine level were unconfirmed on repeat testing and that there was no difference in detecting true renal effects whether testing is done every 3 versus every 6 months. In the Thai study of PWID referenced above, recent injection drug use had no effect on creatinine levels, and renal effects were more likely with older age. Available data indicate that creatinine levels return to near normal after PrEP is discontinued.

Decreases in bone mineral density have been observed during PrEP use, with reductions appearing to level off at approximately 1% to 2% loss and density measurements returning to baseline after PrEP is discontinued. Because there is no evidence of adverse clinical outcomes associated with PrEP use, such as fracture, there is no recommendation to monitor bone mineral density before or during PrEP use.

Although use of PrEP may have contributed to the increase in STIs observed over the past several years among high-risk populations, there is no evidence from randomized or open-label studies that STIs lower the efficacy of PrEP. The incidence of syphilis in the iPrEx trial was 7.3 cases per 100 person-years, with no statistically significant interaction with

PrEP efficacy observed. Similarly, no difference in PrEP efficacy was observed among participants with versus without STIs in the Partners PrEP study. In the PROUD study, 73% of participants had STIs at baseline and PrEP effectiveness was 86%. In the PrEP Demonstration Project, the incidence of STIs was 90 per 100 person-years and the rate of new HIV infections was 0.43 per 100 person-years. Modeling data indicate that STI screening every 3 months for persons taking PrEP may actually reduce transmission of STIs, as many STIs are asymptomatic.

Is PrEP Scale-Up Reaching the Right People?

The CDC estimates that, as of 2015, approximately 1.2 million persons have indications for PrEP, including approximately 540,000 MSM and 470,000 heterosexual women (Table). Only a fraction of this population is currently receiving PrEP. Available data indicate that younger, black, and Hispanic and Latino populations are undertreated in this regard. Data from 2013 through the first quarter of 2016 indicate that among 3485 women initiating PrEP, only 12.7% were younger than 25 years, and among 24,594 men initiating PrEP, only 5.9% were younger than 25 years. White women were 3.8 and 4.4 times more likely and white men were 8.3 and 6.7 times more likely to initiate PrEP than their black and Hispanic or Latino counterparts, respectively.

In annual surveys of 1500 primary care practitioners from 2009 through 2015, awareness of PrEP increased from 25% to 67%; however, in 2015, only 7% had prescribed PrEP. When PrEP efficacy was described as being greater than 75%, more than 90% of practitioners indicated a willingness to prescribe it. Practitioners indicated that they were most likely to prescribe PrEP for patients in stable HIV-serodiscordant partnerships and least likely to prescribe it for patients with STIs; however, HIV-serodiscordant partnerships in which the HIV-seropositive partner has achieved stable viral suppression are unlikely to benefit from PrEP, while persons with STIs may benefit substantially from PrEP. Practitioners may fear that PrEP will lead to behavioral disinhibition, particularly among persons who do not use condoms regularly. Such findings make it clear that greater effort is needed to provide PrEP for high-risk persons with multiple sex partners.

Presented by Dr Buchbinder in May 2017. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Buchbinder in March 2018.

Financial affiliations in the past 12 months: Dr Buchbinder has participated in research trials that have received provision of medicines from Gilead Sciences, Inc.

References


<table>
<thead>
<tr>
<th>Transmission Risk Group</th>
<th>With Indications for PrEP, %</th>
<th>Estimated No. (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1,232,000</td>
<td>(661,000-1,803,000)</td>
</tr>
<tr>
<td>Men who have sex with men, aged 18-59 yrs</td>
<td>24.7</td>
<td>542,000</td>
</tr>
<tr>
<td>Persons who inject drugs, aged ≥18 yrs</td>
<td>18.5</td>
<td>115,000</td>
</tr>
<tr>
<td>Heterosexually active adults, aged 18-59 yrs</td>
<td>0.4</td>
<td>624,000</td>
</tr>
<tr>
<td>Men</td>
<td>0.2</td>
<td>157,000</td>
</tr>
<tr>
<td>Women</td>
<td>0.6</td>
<td>468,000</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; PrEP, preexposure prophylaxis. Adapted from Smith et al.

should also be counseled about the possibility of start-up syndrome when initiating PrEP (gastrointestinal effects are most common) and informed that symptoms generally resolve within several weeks. They should also be informed that if they lose health insurance or change health providers there are resources available to help connect them with care without a lapse in PrEP services (eg, pleaseprepme.org).

In studies of MSM and heterosexual persons on PrEP with TDF/tenofovir disoproxil fumarate (TDF/emtricitabine), persons with lower estimated glomerular filtration rate (eGFR) (below 90mL/min), persons older than 50 years, and those weighing less than 55 kg were at increased risk for experiencing an apparent diminution of eGFR while on PrEP. Analysis of the Partners PrEP and Partners Demonstration Project studies indicated that more than 75% of increases in creatinine level were unconfirmed on repeat testing and that there was no difference in detecting true renal effects whether testing is done every 3 versus every 6 months. In the Thai study of PWID referenced above, recent injection drug use had no effect on creatinine levels, and renal effects were more likely with older age. Available data indicate that creatinine levels return to near normal after PrEP is discontinued.


**Perspective**

**Opioids and HIV Infection: From Pain Management to Addiction Treatment**

HIV-infected persons are more likely to have chronic pain, receive opioid analgesic treatment, receive higher doses of opioids, and to have substance use disorders and mental illness compared with the general population, putting them at increased risk for opioid use disorder. Management of opioid use in HIV-infected individuals can be complex, and the limited data on opioid treatment in this population are conflicting with regard to its effect on HIV outcomes. Buprenorphine treatment for opioid use disorder improves HIV outcomes and other outcomes. This article summarizes a presentation by Chinazo O. Cunningham, MD, MS at the IAS–USA continuing education program, Improving the Management of HIV Disease, held in Atlanta, Georgia, in March 2017.

**Keywords:** HIV, opioid analgesia, opioids, chronic pain, opioid use disorder, buprenorphine

The opioid epidemic in the United States is reflected in the increasing number of drug overdose deaths since 2000, with more recent dramatic increases in overdose deaths attributable to heroin and other synthetic opioids (Figure 1). Any illness with a high mortality rate should prompt decisive action. There is an enormous gap in treatment for opioid use disorder. National data from 2013 indicate that of an estimated 22.5 million people with substance use disorder, only 2.6 million (12%) have received any type of treatment.1

**Pain, Opioid Analgesics, and HIV**

Chronic pain is more common among HIV-infected versus -uninfected individuals, with estimates of its prevalence ranging from 25% to 90%.2-9 Pain among HIV-infected individuals has diverse etiologies, including HIV infection itself, aging, and the adverse effects of medications. Opioids are more commonly prescribed to HIV-infected individuals, and estimates of the proportion of infected individuals prescribed opioids range from 21% to 53%.4,10-12 HIV-infected persons also receive higher doses of opioids and are more likely to have substance use disorder and mental illness.4,9,10 Thus, risk of opioid misuse is elevated in the HIV-infected population.

**Current Guidelines for Opioid Treatment for Chronic Pain**

The Centers for Disease Control and Prevention (CDC) guidelines for prescribing opioids for non–cancer-related chronic pain are summarized in the Table.13 The guidelines cover 3 major areas: 1) when to initiate or continue opioid treatment for chronic pain; 2) which opioid to choose, dose and duration of treatment, and follow-up and discontinuation; and 3) assessing risks and harms. Practitioners should prescribe nonpharmacologic or nonopioid therapies when possible, establish goals of treatment, and discuss risks and benefits with patients. If an opioid is prescribed, it should be an immediate-release, short-acting agent at the lowest effective dose. The currently recommended dose for an opioid is below the range of 50 to 90 morphine milligram equivalents (MMEs). Risk of overdose increases as MMEs increase.

The CDC guidelines also specify that opioids should be prescribed in no greater quantity than needed (enough for ≤3-7 days). Concurrent use of opioids and benzodiazepines should be avoided. Naloxone should be considered for high-risk patients. The New York State Department of Health permits free naloxone kits to be dispensed, and practitioners have a standing order that patients may obtain naloxone kits from pharmacies. A prescription drug monitoring program (eg, Internet System for Tracking Over-Prescribing [I-Stop] in New York State) and urine drug tests should be used to monitor persons receiving opioid treatment.

**Figure 1.** Overdose deaths involving opioids in the United States, 2000 to 2015. Adapted from Centers for Disease Control and Prevention.24

---

Dr Cunningham is Professor of Medicine, Associate Chief of the Division of General Internal Medicine, Director of the General Internal Medicine Fellowship Program, and Director of Diversity Affairs in the Department of Medicine at Albert Einstein College of Medicine/Montefiore Medical Center in Bronx, New York.
Pharmacologic treatment of opioid use disorder consists of opioid antagonists and opioid agonists. Opioid antagonists, such as naltrexone, block the effects of opioids and can be used to precipitate opioid withdrawal in patients experiencing opioid overdose. Opioid agonists, such as methadone and buprenorphine, are used to treat opioid use disorder by providing substitution for illicit opioids. Both antagonists and agonists are used in the treatment of opioid use disorder, but differ in their mechanisms of action, side effects, and contraindications.

### Treatment of Opioid Use Disorder

Pharmacologic treatment of opioid use disorder consists of the opioid antagonist naltrexone and the opioid agonists methadone and buprenorphine. Naltrexone is a non-opioid antagonist that blocks the effects of opioids at the opioid receptor. Methadone is a full opioid agonist that binds to the opioid receptor and provides substitution for illicit opioids. Buprenorphine is a partial opioid agonist that binds to the opioid receptor at lower doses and provides substitution for illicit opioids. The use of these medications in the treatment of opioid use disorder is based on their ability to alleviate withdrawal symptoms, reduce the risk of overdose, and improve outcomes for individuals with opioid use disorder.

### Table. Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Non-Cancer-Related Chronic Pain

<table>
<thead>
<tr>
<th>Initiating Treatment With Opioids</th>
<th>Determining Opioid Selection, Dose, Duration, Follow-up, and Discontinuation</th>
<th>Assessing Risks and Harms of Treatment With Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nonpharmacologic and nonopioid therapies are preferred</td>
<td>• Prescribe immediate-release (not long-acting) formulations</td>
<td>• Evaluate and mitigate harms</td>
</tr>
<tr>
<td>• Establish treatment goals (pain and function levels)</td>
<td>• Prescribe lowest effective opioid dose (&lt;50-90 morphine milligram equivalent)</td>
<td>• Consider naloxone</td>
</tr>
<tr>
<td>• Discuss risks and benefits of opioid use and patient and practitioner responsibilities</td>
<td>• Prescribe no greater quantity than needed (enough for ≤3-7 days)</td>
<td>• Use a prescription drug monitoring program</td>
</tr>
<tr>
<td></td>
<td>• Reevaluate effectiveness. If risk or harms are substantial, taper or discontinue</td>
<td>• Order urine toxicology tests</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Avoid concurrent use of opioids and benzodiazepines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Offer buprenorphine or methadone to treat opioid use disorder</td>
</tr>
</tbody>
</table>

Data compiled from Dowell et al. 13

How use of opioids may affect HIV outcomes remains unclear. It may seem that when practitioners prescribe opioid analgesics to HIV-infected patients, HIV outcomes are better, perhaps because patients are more adherent to office visits and HIV medications. However, data from the few studies in this area are conflicting. In studies of any versus no opioid analgesic use, utilization of antiretroviral therapy was higher in 1 study, 4 no difference in utilization of antiretroviral therapy was observed in 3 studies, 10,12,14 and no difference in adherence to antiretroviral therapy was observed in another study. 11 Viral loads were higher among individuals taking opioids in 2 studies 4,14 and were no different in 2 other studies 10,12 In studies comparing misuse versus no misuse of opioids, adherence to antiretroviral therapy was worse among participants who misused opioids. 11,15

Interpretation of urine toxicology test results is more complex than is generally thought. 16 There are many causes of false-positive or -negative findings. Among the most common mistakes in interpretation of urine toxicology testing are those involving oxycodone—a frequently prescribed controlled substance—and fentanyl. A urine screening assay that specifically includes oxycodone should be used. If oxycodone is taken in high enough doses, “spillover” may occur resulting in positive findings for opiates. Similarly, a urine test result positive for opiates may be associated with use of morphine, codeine, hydrocodone, or heroin, as there is no way to distinguish among these in a screening assay. Metabolites of fentanyl are not detected in typical screening tests. With regard to use of benzodiazepines, individuals taking clonazepam typically have test results negative for benzodiazepines. Thus, to accurately interpret the results of urine testing, metabolic pathways and which metabolites are being tested in screening assays must be understood. If there is doubt about the results of a urine screening test, confirmatory testing using gas chromatography mass spectrometry should be ordered, as it provides levels of all metabolites and accurate identification of the cause of a positive test result for opiates.

### Figure 2. Conceptual representation of the opioid effects and log doses of the full opioid agonist methadone, the partial opioid agonist buprenorphine, and the opioid antagonist naloxone. Adapted from Substance Abuse and Mental Health Services Administration. 25
such as alcohol or benzodiazepines are used concomitantly with buprenorphine.

With regard to treatment delivery, methadone is highly regulated and buprenorphine is minimally regulated. For persons receiving treatment from methadone maintenance treatment programs, methadone must be delivered by a physician at that program and counseling visits, urine toxicology tests, dosing, dispensing, prescribing, and availability are regulated at the state and federal levels. Buprenorphine treatment can be administered in any clinic setting, including syringe-exchange programs. Physicians, nurse practitioners, and physician assistants may prescribe buprenorphine, which is particularly important in the context of HIV care, given the crucial role of nurse practitioners and physician assistants in this setting. To prescribe buprenorphine, physicians must complete 8 hours of training and nurse practitioners and physician assistants must complete 24 hours of training to receive a waiver and Drug Enforcement Administration “X” number. Buprenorphine is dispensed in community pharmacies and can be prescribed in a 30-day supply with refills. Practitioners may only prescribe buprenorphine for 30 patients during the first year but can apply to treat up to 100 and, in some situations, up to 275 patients thereafter.

Buprenorphine is primarily used in a coformulation with the opioid antagonist naloxone (buprenorphine/naloxone). When taken sublingually as directed, buprenorphine is absorbed and naloxone is not. When buprenorphine/naloxone is crushed and injected, the naloxone will cause immediate opioid withdrawal, making misuse of this coformulation unlikely.

Buprenorphine integrates well into HIV treatment. The multisite BHIVES (Buprenorphine HIV Evaluation and Support) Initiative was primarily a prospective cohort design that included 386 HIV-infected participants with opioid dependence who were eligible for buprenorphine treatment. Participants were followed up for 12 months, with outcomes obtained from interviews every 3 months and medical record review. Proportions of participants who initiated antiretroviral therapy and achieved viral suppression (HIV RNA level <400 copies/mL) were substantially higher among those taking buprenorphine/naloxone for at least 3 of 4 quarters than those taking it for less than 3 quarters during a year period (Figure 3). Retention in treatment with buprenorphine/naloxone was associated with reduced use of opioids and stimulants and no change in use of sedatives compared with baseline (Figure 4). Retention in treatment with buprenorphine/naloxone also led to improvements in physical and mental quality of life. Individuals with cocaine use had no difference in buprenorphine treatment outcomes than those without

---

**Figure 3.** HIV outcomes are improved with retention on buprenorphine treatment ($P \leq .05$ for all comparisons with baseline). Adapted from Allic et al.\(^18\)

**Figure 4.** Drug treatment outcomes are improved with retention on buprenorphine treatment. Adapted from Fiellin et al.\(^19\)
cocaïne use. No adverse effect on liver enzymes has been observed with buprenorphine/naloxone despite the fact that many HIV-infected individuals studied also had HCV infection.\textsuperscript{21-23}

**Summary**

The opioid epidemic in the United States continues to grow. Although there has been a plateau in opioid-analgesic–related deaths, overall, opioid-related deaths continue to increase. A large gap remains between the number of persons eligible for treatment for opioid use disorder and the number of those receiving treatment. There are many challenges to managing pain with opioids, including interpretation of urine toxicity test results. How use of opioid analgesics affects HIV outcomes remains unclear. However, available data indicate that integration of buprenorphine with HIV treatment is associated with many positive outcomes.

Presented by Dr Cunningham in February 2017. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Cunningham in October, 2017.

Financial affiliations in the past 12 months: Dr Cunningham holds stock and stock options for Quest Diagnostics. Her spouse is employed by and holds stock options for Quest Diagnostics.

**References**


Top Antivir Med. 2018;25(4):143-146. ©2018, IAS–USA. All rights reserved.
The IAS–USA publishes *Topics in Antiviral Medicine™* as a resource for physicians and other health care practitioners who are actively involved in the care of patients with HIV or other viral infections. This open-access journal is now available as an online resource only. It is indexed in Index Medicus/ME/DLINE and PubMed.

The following guidelines describe the types of articles and contributions published in the journal, outline its policies, and provide instructions for authors. For further information, contact *Topics in Antiviral Medicine™* at journal@iasusa.org.

**Categories of Articles**

**Perspectives.** Perspective articles are summaries of selected talks given at IAS–USA continuing medical education courses. An IAS–USA medical writer prepares a summary manuscript from a transcript of the talk. The manuscript is reviewed and edited by the presenter and the journal’s appointed peer reviewer(s).

**Reviews.** *Topics in Antiviral Medicine™* welcomes original review articles on current issues related to infection with HIV or other viruses. *Topics in Antiviral Medicine™* does not publish original research. Manuscripts should be 3000 to 6000 words (excluding references, tables, and figures) and should include numbered references and a brief introductory abstract of approximately 100 to 200 words. Original, adapted, or reprinted figures and tables may be included and should be cited in the text and accompanied by a brief title. Adapted and reprinted work requires proof of permission obtained from the original publisher and authors. Authors interested in submitting unsolicited manuscripts are encouraged to submit an outline or abstract of the proposed manuscript first; please contact the editor for further information.

**Editorials.** *Topics in Antiviral Medicine™* invites submission of editorials. Editorials should be approximately 500 to 1500 words (excluding references) and should include numbered references.

**Special Contributions.** A special contribution article often represents the unique contribution (such as a consensus statement) of an author or group of authors.

**Cases From the Field.** *Topics in Antiviral Medicine™* invites submission of case reports accompanied by a scholarly literature review of the topic. Each case report should be 1500 to 3000 words (excluding references, tables, and figures), include numbered references, and seek to teach an important lesson for HIV or viral hepatitis care practitioners.

**Stories.** Stories for the *Telling Stories* column share the experiences of those involved in the care of people infected with HIV or other viruses. Stories may be approximately 800 to 3500 words; submissions are welcome for consideration.

**Commentaries.** Discussion on a current issue in the management of viral diseases is welcome as a Commentary. Commentaries should be 500 to 1500 words and include numbered references as appropriate. Commentaries may be invited by the editors; unsolicited submissions are also welcome for consideration.

**Letters to the Editor.** Letters to the editor are welcome and should be sent to the address listed below. Please limit letters to 300 words.

**Special Issues.** *Topics in Antiviral Medicine™* often publishes issues with a special focus, such as summaries of IAS–USA continuing medical education courses and reports from scientific meetings.

**Reprints.** Reprints of articles by expert panels convened by the IAS–USA are included periodically in *Topics in Antiviral Medicine™*.

**Submission of Manuscripts**

Manuscripts should be submitted via mail or e-mail to the address below. Each author should complete an Authorship Form, which is available online at www.iasusa.org/pub or may be obtained by contacting the editor at the address below. Outlines or abstracts of proposed manuscripts are welcome and may be sent via mail or e-mail.

**Editor.** *Topics in Antiviral Medicine™* IAS–USA
425 California St, Ste 1450
San Francisco, CA 94104-2120
E-mail: journal@iasusa.org

Receipt of submitted manuscripts will be acknowledged by editorial staff, and submissions will be reviewed by peer reviewers. Acceptance for publication is based on the quality and relevance of the work.

**Copyright**

Copyright to all manuscripts and graphics published in *Topics in Antiviral Medicine™* is owned by the IAS–USA unless noted otherwise. All authors and contributors of manuscripts accepted for publication, with the exception of US federal government employees, must sign a copyright transfer form as a condition of publication.

**Authorship Requirements**

*Topics in Antiviral Medicine™* uses the definition of authorship formulated by the International Committee of Medical Journal Editors and published in its *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*. This definition states that authorship “should be based on the following 4 criteria: (1) Substantial contributions to the concept or design of the work; or the acquisition, analysis, or interpretation of data for the work; (2) drafting the work or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work ensuring that questions related to the accuracy of integrity of any part of the work are appropriately investigated and resolved. . .”

**Financial Disclosure**

It is the policy of the IAS–USA to ensure balance, independence, objectivity, and scientific rigor in all of its educational programs. To that end, all authors and contributors of articles published in *Topics in Antiviral Medicine™* are required to disclose to readers any significant financial interest or other relationship with any organization having financial interest in the content of the manuscript. Financial interests include employment, consultancy, honorarium, grant/research support, major stock ownership, or membership in a speakers bureau and directly paid lectures, or other contributions. The complete financial disclosure statements for all authors and contributors are published with the articles.

---

The 2018 Clinical Conference at the National Ryan White Conference on HIV Care and Treatment will take place at the Gaylord National Hotel and Convention Center from December 9 to December 11.

The Clinical Conference starts 2 days before the National Conference (which runs December 11-14), and attendance cap has been raised from 400 to 600 HIV physicians, nurse practitioners, and physician assistants in Ryan White HIV/AIDS Program–Funded clinics and programs.

Registration is now open.