Volume **23** Issue **5** December **2015**/January **2016**

Topics in Antiviral Medicine™

A publication of the IAS–USA

Perspectives CME

Review CME

Topics in Antiviral Medicine™

Scan our QR code to access the IAS–USA website

IAS–USA
International Antiviral Society–USA

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. 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. Generous support for this activity has been received from the below contributors.

Independent educational grants for the 2015 *Improving the Management of HIV Disease* continuing medical education program:

PLATINUM SUPPORTERS
Gilead Sciences, Inc
ViiV Healthcare
Gold Supporters
Bristol-Myers Squibb
Janssen Therapeutics
Merck & Co, Inc

Additional support for select activity types in this national program is provided by:
AbbVie

Independent educational grants for the 2015 *Management of Hepatitis C Virus in the New Era: Small Molecules Bring Big Changes* continuing medical education program:

Gold Supporters
AbbVie
Bristol-Myers Squibb
Gilead Sciences, Inc
Silver Supporter
Merck & Co, Inc

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.

All authors and contributors provide disclosures of financial interests, and this information is available at the end of each article.

This journal 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 *Topics in Antiviral Medicine.*

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

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 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"at"iasusa.org
Mail: IAS–USA
425 California Street, Suite 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 2161-5861 (Print)
ISSN 2161-5853 (Online)

Printed in USA on acid-free paper

Volume 23 Issue 5 December 2015/January 2016

Topics in Antiviral Medicine™

A publication of the IAS–USA

Perspectives CME

Review CME

Announcements

ON LINE **Please visit our website at www.iasusa.org to complete the posttest and evaluation for this activity and claim CME credit. You can also subscribe or change your mailing address by updating your user profile online.**

Topics in Antiviral Medicine™

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 3.5 *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 January 31, 2016, to January 31, 2017. 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: 3.5 *AMA PRA Category 1 Credits*™
- Release date: January 31, 2016
- Expiration date: January 31, 2017

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. The posttest, evaluation, and CME claim form can be found online at www.iasusa.org.

Learning Objectives

On completion of this activity, participants will be able to:

- Describe methods for diagnosis and treatment of acute HIV infection, as well as the potential role of acutely HIV-infected persons in cure studies
- Identify appropriate initial antiretroviral therapy for individuals with HIV infection, as well as monitoring strategies for those taking therapy
- Describe current guidelines for managing cholesterol to reduce cardiovascular disease risk in HIV-infected individuals, and the potential use of statin therapy for these individuals
- Compare results from original research studies on advance care planning in HIV-infected adults in the era of antiretroviral therapy

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 infection.

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 Little has no relevant financial affiliations to disclose. Dr Johnson has served as a consultant to ViiV Healthcare and has received payment for development of educational presentations from Clinical Care Options. Dr Stein has served on data and safety monitoring boards for Lilly and received research grants awarded to his institution from Gilead Sciences, Inc. He has intellectual property rights licensed by the Wisconsin Alumni Research Foundation for carotid ultrasound and cardiovascular disease risk and receives royalties for a textbook chapter from UptoDate. Drs Sangarlangkarn, Merlin, and Tucker have no relevant financial affiliations to disclose. Dr Kelley receives support from the National Institute on Aging (1K23AG040774-01A1), the American Federation for Aging Research, and the National Palliative Care Research Center. Dr Richman has been a consultant to Bristol-Myers Squibb, Chimerix, Gilead Sciences, Inc, Hera Therapeutics, and Monogram Biosciences, Inc. Dr Benson serves on a data and safety monitoring board for GlaxoSmithKline/ViiV Healthcare. She has received research grants awarded to the University of California San Diego from Gilead Sciences, Inc, and ViiV Healthcare. Her spouse, Dr Robert T. Schooley, was awarded research grants, paid to his institution, from Boehringer Ingelheim Pharmaceuticals, Inc, and Bristol-Myers Squibb. His institution has received payment for his consultative advice or data monitoring committee service from GlobeImmune, Gilead Sciences, Inc, and Monogram Biosciences. He serves as a consultant to CytoDyn, Hera Therapeutics, and Farmak and has stock options from CytoDyn, Hera Therapeutics, and GlobeImmune. Dr Hirsch and Ms Jacobsen have no relevant financial affiliations to disclose.

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. Funds are pooled and distributed to activities at the sole discretion of IAS–USA. Grantors have no input into any activity, including its content, development, or selection of topics or speakers. Generous support for this activity has been received from the below contributors:

Independent educational grants for the 2015 *Improving the Management of HIV Disease*® CME program:

PLATINUM
Gilead Sciences, Inc
ViiV Healthcare

Gold
Bristol-Myers Squibb
Janssen Therapeutics
Merck & Co, Inc

Additional support for select activity types in this national program is provided by:

AbbVie

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.

Please visit our website at www.iasusa.org to complete the posttest and evaluation for this activity and claim CME credit.

UPCOMING EVENTS

IAS–USA Live Courses

Improving the Management of HIV Disease®: Full-Day Courses

Designed for HIV specialists who are actively involved in HIV disease management. Advanced-level presentations with balanced, timely, scientifically rigorous, and clinically relevant information. Early registration: $75

Spring 2016

New York, New York — Wednesday, March 23, 2016
Co-Chairs: Gerald H. Friedland, MD, Yale University; Paul A. Volberding, MD, University of California San Francisco

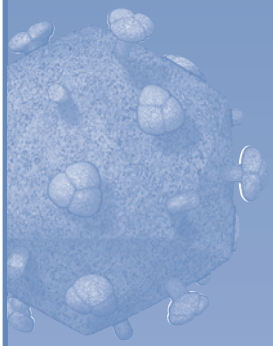
Atlanta, Georgia — Friday, April 8, 2016
Co-Chairs: Jeffrey L. Lennox, MD, Emory University; Michael S. Saag, MD, University of Alabama at Birmingham

Washington, DC — Friday, April 15, 2016
Co-Chairs: Henry Masur, MD, George Washington University; Michael S. Saag, MD, University of Alabama at Birmingham

Los Angeles, California — Monday, April 25, 2016
Co-Chairs: Constance A. Benson, MD, University of California San Diego; Ronald T. Mitsuyasu, MD, University of California Los Angeles

San Francisco, California — Friday, May 6, 2016
Co-Chairs: Stephen E. Follansbee, MD, Kaiser Permanente San Francisco (Retired); Robert T. Schooley, MD, University of California San Diego

Chicago, Illinois — Monday, May 9, 2016
Co-Chairs: John P. Phair, MD, Northwestern University (Emeritus); Paul A. Volberding, MD, University of California San Francisco



Evolving Strategies in Hepatitis C Management: Small-Group Workshops

Intensive, half-day workshops designed to improve the clinical care of people infected with hepatitis C virus. Small-group, interactive format limited to no more than 50 clinical decision makers (physicians, nurse practitioners, PharmDs, and physician assistants). Registration: $70

Atlanta, Georgia — Thursday, April 7, 2016
Washington, DC — Thursday, April 14, 2016
Los Angeles, California — Tuesday, April 26, 2016
San Francisco, California — Thursday, May 5, 2016

Interactive Webinars With IAS–USA Faculty

Live, interactive CME in the comfort of home or office, free of charge. Participants can ask questions and receive responses in real time. Visit the IAS–USA website for more on past an upcoming webinars.

February

Persistent Challenges of HIV Transmission Control in Injection Drug Use: Lessons From the Indiana Outbreak
Presenter: Diane M. Janowicz, MD, Indiana University School of Medicine — Tuesday, February 16, 2016

March

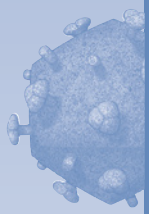
CROI 2016: A Summary of the Most Important Studies for Clinical Practice
Presenter: Paul E. Sax, MD, Harvard Medical School, Brigham and Women's Hospital — Tuesday, March 15, 2016

Cases on the Web

A series of web-based, case-driven continuing medical education activities (CME) sponsored by IAS–USA, created to offer convenient online access to top-quality education.

Coming Soon

Antiretroviral Therapy: Caring for HIV-Infected Patients and Preventing HIV Transmission
Author: Kenneth H. Mayer, MD, Harvard Medical School



Some 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. Early registration for live courses is strongly recommended. Food and beverages at live IAS–USA events are purchased with registration fees, not grant support money. These activities have been approved for *AMA PRA Category 1 Credit*™.

Perspective

Treatment of Acute HIV Infection and the Potential Role of Acutely HIV-Infected Persons in Cure Studies

Diagnosis of acute HIV infection is important for accurate estimation of HIV incidence, identifying persons who are unaware of their HIV infection, and offering immediate treatment and risk-reduction strategies. The higher viral loads associated with acute HIV infection are associated with an increased risk of transmission. Current treatment recommendations are the same for acute and established infections. Studies of acute HIV infection indicate that initiation of antiretroviral therapy during this period may allow greater recovery of CD4+ T-cell count and function and may result in a smaller latent viral reservoir and a skewing of infection away from central memory CD4+ T cells toward shorter-lived transitional memory CD4+ T cells. This article summarizes a presentation by Susan J. Little, MD, at the IAS–USA continuing education program, Improving the Management of HIV Disease*, held in Los Angeles, California, in April 2015.*

Keywords: HIV, acute infection, transmission risk, CD4+ cell recovery, latent viral reservoir, memory CD4+ T cells, HIV cure

Acute HIV infection is defined as the earliest phase of infection following acquisition of virus and before seroconversion (ie, the period in which the patient is HIV RNA positive and antibody negative). The duration of this phase varies depending on the diagnostic assays used to detect infection. Acute HIV infection is characterized by a markedly elevated peak viral load in blood and genital secretions. Screening for acute HIV infection is not routinely performed, primarily because of difficulties in case finding and cost of the diagnostic assays. Diagnosis of acute HIV infection is dependent on direct detection of virus through testing for the p24 antigen or increasingly through nucleic acid testing (or test; NAT), although there are currently no point-of-care HIV NATs approved by the US Food and Drug Administration (FDA) for HIV diagnosis, and the only FDA-approved diagnostic assay for detecting the p24 antigen has poor sensitivity for detecting acute HIV infection.[1]

Importance of Diagnosing Acute HIV Infection

Data vary regarding the influence of acute HIV infection on HIV transmission, but it has been estimated that 25% to 50% of HIV transmission is associated with sexual exposure to an individual with acute infection.[2-4] Plasma viral load is the greatest predictor of HIV transmission risk, with higher viral load associated with higher risk of transmission. However, the greater infectivity of persons with acute HIV infection may not be exclusively related to higher plasma viral load levels. Ma and colleagues demonstrated that plasma from macaques with acute simian immunodeficiency virus (SIV) infection was at least 750 times more infectious per virion than plasma from macaques with chronic SIV infection.[5] This difference may be related in part to the absence of neutralizing antibodies in the acutely infected animals; the addition of heat-inactivated plasma to plasma from acutely infected macaques blocked infection.

The laboratory screening algorithm to detect acute or chronic HIV infection published in 2014 recommends the use of a fourth-generation HIV-1/2 antigen/antibody combination assay to initiate HIV screening (Figure 1).[6] A negative result on an antigen/antibody test indicates an absence of HIV infection within approximately the last 17 days (ie, the window period for detection of HIV-1 p24 antigen, a structural protein product of the HIV-1 *gag* gene).[7] Because a positive result on an antigen/antibody test does not differentiate antibody from antigen (only 2 fourth-generation assays were FDA approved when the laboratory testing algorithm was being developed in 2011), the sample is then tested using an HIV-1/2 antibody differentiation immunoassay, which has replaced the Western blot from earlier testing algorithms, to differentiate HIV-1 antibodies from HIV-2 antibodies. If results are negative for antibody, an NAT is performed, with a positive result indicating acute infection.

In contrast to the laboratory HIV screening algorithm, field-based HIV screening methods rely primarily on point-of-care assays that do not typically detect acute HIV infection (the sensitivity of the HIV-1/2 antigen/antibody point-of-care combination assay approved by the FDA in 2013 does not support its use for detection of acute HIV infection[1]). For example, a positive rapid antibody test result could be confirmed using a fourth-generation immunoassay followed by an HIV-1/2 antibody differentiation immunoassay, but this algorithm would not detect acute HIV infection in persons who are HIV antibody negative. A challenge for field-based screening programs that wish to identify persons with acute HIV infection is the decision regarding use of alternative testing for those who are antibody negative. The decision depends somewhat on the risk level of a population, the cost of the diagnostic assays, and the prevalence of acute infection in the population (likely unknown in settings in which screening for acute infection has not been performed). Although there is 1 FDA-approved fourth-generation point-of-care assay, it is substantially less sensitive than the fourth-generation assays approved for use in the laboratory screening algorithm (Figure 1). The overall prevalence of HIV infection is not well correlated with the prevalence of acute infection, as

Dr Little is Professor of Medicine at the University of California San Diego.

suggested by the yield of acute HIV screening programs in many international settings.[8] Thus, a relatively low overall HIV prevalence does not indicate that screening for acute infection is unnecessary. There are many point-of-care NATs in development that may markedly simplify and improve point-of-care screening approaches for acute HIV infection.

Detection of acute HIV infection is crucially important for 1) accurate estimation of HIV incidence; 2) identifying persons who are unaware of their infection; 3) offering immediate treatment and risk-reduction strategies; 4) identifying HIV transmission hot spots (geographic regions with high HIV transmission rates); and 5) tailoring prevention services to individual behaviors and risks associated with acute infection.

Treatment of Acute HIV Infection

According to current guidelines on antiretroviral therapy from the US Department of Health and Human Services and the IAS–USA, antiretroviral therapy is recommended for all HIV-infected individuals to reduce the risk of disease progression and to prevent HIV transmission.[9,10] Persons initiating antiretroviral therapy should be willing and able to commit to treatment and should understand the benefits and risks of therapy and the importance of adherence.

Data on treatment as prevention demonstrate that earlier versus later initiation of antiretroviral therapy substantially reduces the risk of HIV transmission. Mathematical models of the impact of increasing use of antiretroviral therapy on population HIV incidence (new infections by country) further support treatment as prevention as a strategy to reduce HIV transmission. Preliminary estimates from 53 low- and middle-income countries demonstrate a correlation between antiretroviral therapy coverage (the percentage of all people living with HIV infection who are receiving antiretroviral therapy) and population HIV incidence.[11] Additionally, a South African study recently reported a 1.1% reduction in HIV incidence for every 1% increase in antiretroviral therapy coverage.[12]

Recommended antiretroviral regimens do not differ for treatment of acute and established HIV infections. Recommended initial regimens are the integrase strand transfer inhibitor–based regimens of 1) dolutegravir, abacavir, and lamivudine (only in individuals who are negative for the HLA-B*5701 allele); 2) dolutegravir plus tenofovir disoproxil fumarate and emtricitabine; 3) elvitegravir, cobicistat, tenofovir disoproxil fumarate, and emtricitabine (only if baseline creatinine clearance > 70 mL/min); 4) elvitegravir, cobicistat, tenofovir alafenamide, and emtricitabine (the fixed-dose combination of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide was approved for use in antiretroviral therapy–naive persons in November 2015); and 5) raltegravir plus tenofovir disoproxil fumarate and emtricitabine; and the protease inhibitor–based regimen of ritonavir-boosted darunavir plus tenofovir disoproxil fumarate and emtricitabine.[9] Genotypic drug-resistance testing is recommended regardless of whether antiretroviral therapy is initiated immediately or is deferred.[10]

In the SPARTAC (Short Pulse Antiretroviral Therapy at Seroconversion) study, which investigated when to initiate treatment for newly HIV-infected persons (< 6 months), 2 short-course antiretroviral regimens of 12 weeks and 48 weeks were compared with no immediate treatment, the standard of care at the time for this population.[13] The primary end point was the combined measure of time to a CD4+ cell count of less than 350/μL or initiation of long-term antiretroviral therapy. The 48-week regimen (hazard ratio [HR], 0.63; $P = .01$) but not the 12-week regimen (HR, 0.93; $P = .67$) was associated with a significant delay in time to the primary end point compared with no immediate treatment. However, the delay in progression with the 48-week regimen was roughly equivalent to the time spent on treatment, arguing against any benefit to be gained by interrupting treatment. There was no evidence of adverse outcomes in terms of drug resistance or impaired CD4+ cell recovery after initiation of long-term antiretroviral therapy.

Researchers in San Diego, California, performed a retrospective study to determine if there is a crucial period following acute HIV infection during which initiation of antiretroviral therapy can maximize the potential for restoration of normal immune function.[14] The study included 468 recently infected, antiretroviral therapy–naive individuals in whom CD4+ cell count trajectories were observed over 48 months during which some initiated therapy. An estimated date of infection was calculated for each participant using virologic and serologic data at time of presentation. A total of

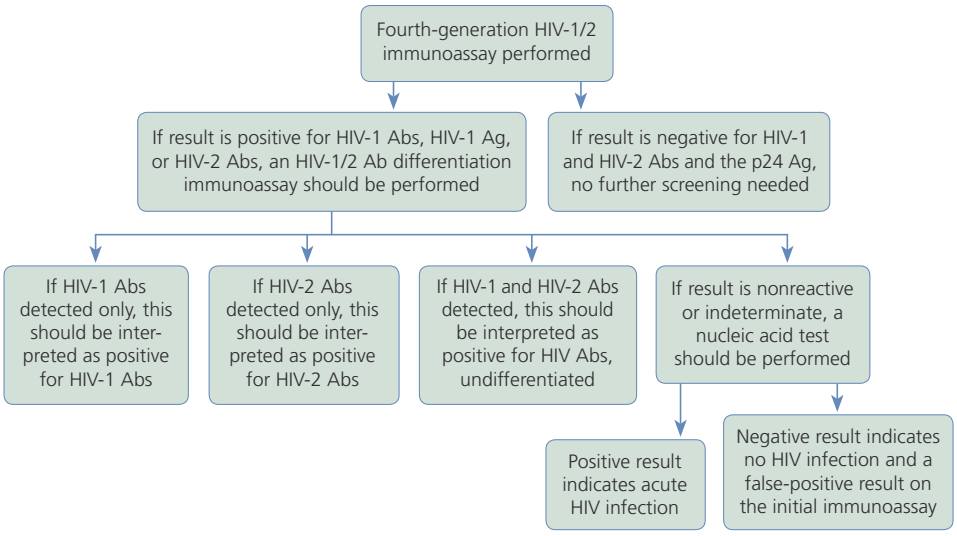


Figure 1. Laboratory screening algorithm for diagnosis of HIV infection. Ab indicates antibody; Ag, antigen. Adapted from Centers for Disease Control and Prevention.[6]

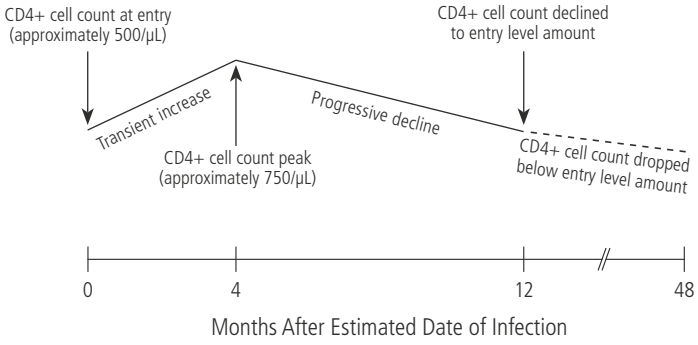


Figure 2. Changes in CD4+ cell count following estimated diagnosis of HIV infection in individuals who did not initiate antiretroviral therapy. Adapted from Le et al.[14]

136 remained antiretroviral therapy naive for the duration of the study, and the remainder initiated therapy. Among those who did not initiate immediate therapy, mean CD4+ cell count spontaneously increased from approximately 500/μL at baseline to approximately 750/μL in approximately 4 months (a period during which natural immunologic recovery appeared to be occurring) followed by a progressive decline (Figure 2). Outcomes were assessed in 6 groups, based on the timing of initiation of antiretroviral therapy and the CD4+ cell count at the time therapy was initiated. Individuals in groups 1 and 4 initiated therapy within 4 months of the estimated date of HIV infection, at CD4+ cell counts above 500/μL and below 500/μL, respectively; those in groups 2 and 5 initiated therapy between 4 months and 12 months after the estimated date of HIV infection, at CD4+ cell counts above 500/μL and below 500/μL, respectively; and those in groups 3 and 6 initiated therapy more than 12 months after the estimated date of HIV infection, at CD4+ cell counts above 500/μL and below 500/μL, respectively. A normal CD4+ cell count was defined as 900/μL or higher. Based on the hypothesis that initiation of antiretroviral therapy during this period might improve immunologic recovery, outcomes were compared among groups of individuals who exhibited durable viral suppression after initiation of therapy (Figure 3). Individuals who initiated therapy within 4 months of HIV infection at CD4+ cell counts above 500/μL exhibited a robust early CD4+ cell response, and individuals who initiated therapy within 12 months of HIV infection at CD4+ cell counts above 500/μL eventually achieved similar CD4+ cell counts of 900/μL or greater. The individuals who initiated therapy within 4 months of HIV infection, but at a starting CD4+ cell count below 500/μL, demonstrated a statistically significantly lower potential for achieving a normal CD4+ cell count within the study period.

Overall, the study showed that the probability of achieving a CD4+ cell count above 900/μL while taking antiretroviral therapy was greatest for those who initiated therapy within 4 months of the estimated date of HIV infection with a CD4+ cell count of greater than 500/μL. Each month that antiretroviral therapy was delayed reduced the probability of achieving a normal CD4+ cell count by approximately 10%; the probability of achieving a normal CD4+ cell count was reduced by 94% if CD4+ cell count was below 500/μL at the time of initiation of antiretroviral therapy, regardless of the estimated date of HIV infection. Overall, less than 25% of antiretroviral therapy–naive individuals maintained a CD4+ cell count of 500/μL or higher for more than 12 months after their estimated date of infection.

Treatment of Acute Infection and HIV Cure

An unanswered question related to the timing of antiretroviral therapy during acute HIV infection is whether earlier initiation of antiretroviral therapy might help limit the latent viral reservoir. Viral latency is established early and preferentially in nondividing and minimally activated cells. Only a small fraction of resting memory CD4+ T cells carry integrated viral genomes, and levels of latently infected cells remain relatively stable during antiretroviral treatment.[15,16] A subset of latently infected cells may persist indefinitely, even in individuals who initiate antiretroviral therapy during acute HIV infection.[17]

One case that initially raised hope of eradication or spontaneous control of the latent viral reservoir was that of the Mississippi baby.[18] The baby's mother was diagnosed with HIV infection during labor, and the newborn infant was found to be HIV infected at 30 hours of life. Antiretroviral treatment with zidovudine, lamivudine, and nevirapine was initiated at 30 hours of life and at 1 week of life was switched to zidovudine, lamivudine, and ritonavir-boosted lopinavir. The baby achieved an undetectable viral load at day 30 and maintained viral suppression during follow-up. The mother discontinued the child's therapy sometime between 15 months and 18 months, after which the infant continued to exhibit viral suppression. Unfortunately, the child's HIV RNA level rebounded to 16,000 copies/mL at 27 months. In retrospect, single-copy levels of HIV RNA were observed at months 24 and 26 and HIV DNA was detected at 24 weeks. Thus, although the virus was not eradicated, this case does suggest that sustained virologic control might be achieved by very early initiation of antiretroviral treatment in at least some individuals even after interruption of therapy.

The VISCONTI (Viro-Immunological Sustained Control after Treatment Interruption) cohort comprises participants from French studies who exhibited posttreatment virologic control.[19] To be considered posttreatment controllers, individuals had to be identified during acute HIV infection (before development of the immunoglobulin M antibody), had to initiate antiretroviral treatment within the first 3 months of infection, and had to continue treatment for at least 24 months. A total of 14 individuals who had initiated antiretroviral therapy early, achieved rapid and sustained virologic suppression, and maintained durable suppression of viremia for several years after stopping therapy were identified. Overall, these individuals had an undetectable viral load at a median of 3 months of antiretroviral therapy (0.5 months to < 8 months) and a median duration of therapy of 36.5 months. Most of these posttreatment controllers lacked the

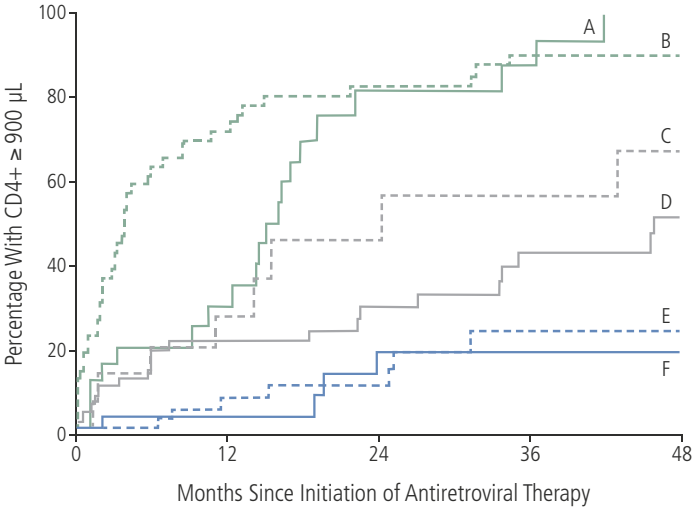


Figure 3. CD4+ cell count recovery in HIV-infected individuals who initiated antiretroviral therapy within 4 months of estimated date of infection (EDI) at CD4+ cell counts (A) above 500/µL or (D) below 500/µL; 4 months to 12 months after EDI at CD4+ cell counts (B) above 500/µL or (E) below 500/µL; or more than 12 months after EDI at CD4+ cell counts (C) above 500/µL or (F) below 500/µL. Adapted from Le et al.[14]

protective HLA-B*5701 allele overrepresented in individuals who spontaneously control HIV. The viral reservoirs in the posttreatment controllers had lower total levels of HIV DNA than those found in individuals who did not exhibit posttreatment control, with lower levels of integrated HIV in their naive CD4+ T-cell populations and a skewed distribution of infection toward shorter-lived transitional memory CD4+ T cells within the resting memory CD4+ cell population.

A similar finding regarding the potential skewing of infection to shorter-lived memory CD4+ T cells was observed in the RV254/SEARCH010 study (a collaboration of the US Military HIV Research Program and the South East Asia Research Collaboration with Hawaii [SEARCH]) in Thailand in which acutely HIV-infected participants initiate antiretroviral therapy at diagnosis of HIV infection.[20] Initiation of antiretroviral therapy within 2 weeks of infection was associated with undetectable HIV DNA in long-lived memory CD4+ T cells in 100% of participants, compared with 63% of participants who initiated therapy at 2 weeks to 4 weeks and 0% of participants who initiated therapy at 24 weeks or later. These findings suggest that earlier treatment limits persistence of virus in long-lived central memory CD4+ T cells.

Conclusion

It is unclear whether or to what degree antiretroviral treatment during acute HIV infection might lead to HIV cure. Most individuals are infected with a single viral variant or a few highly related variants, and ensuing viral genetic diversity in those who do not begin antiretroviral treatment makes attempts at immunologic interventions (eg, vaccines) and antiretroviral therapy more challenging. HIV-specific CD4+ cell responses may be preserved by early antiretroviral therapy, and early therapy may result in diminished levels of persistent immune activation. Although HIV reservoirs may become smaller with earlier antiretroviral treatment, infection generally persists in memory CD4+ T cells. However, antiretroviral therapy during acute HIV infection may protect central memory CD4+ T cells from infection and may skew the distribution of latently infected cells to shorter-lived memory CD4+ T cells.[17] Even if early antiretroviral treatment cannot effect a cure, individuals treated during acute infection should prove the best candidates for HIV cure interventions, because they have smaller viral reservoirs and better-preserved immune systems than individuals who initiate antiretroviral therapy later during infection.

Presented by Dr Little in April 2015. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Little in January 2016.

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

References

1. Rosenberg NE, Kamanga G, Phiri S, et al. Detection of acute HIV infection: a field evaluation of the determine® HIV-1/2 Ag/Ab combo test. *J Infect Dis*. 2012;205(4):528-534.
2. Volz EM, Ionides E, Romero-Severson EO, Brandt MG, Mokotoff E, Koopman JS. HIV-1 transmission during early infection in men who have sex with men: a phylodynamic analysis. *PLoS Med*. 2013; 10(12):e1001568.
3. Brenner BG, Roger M, Routy JP, et al. High rates of forward transmission events after acute/early HIV-1 infection. *J Infect Dis*. 2007; 195(7):951-959.
4. Lewis F, Hughes GJ, Rambaut A, Pozniak A, Leigh Brown AJ. Episodic sexual transmission of HIV revealed by molecular phylodynamics. *PLoS Med*. 2008;5(3):e50.
5. Ma ZM, Stone M, Piatak M, Jr., et al. High specific infectivity of plasma virus from the pre–ramp-up and ramp-up stages of acute simian immunodeficiency virus infection. *J Virol*. 2009;83(7):3288-3297.
6. Centers for Disease Control and Prevention and Association of Public Health Laboratories. Laboratory testing for the diagnosis of HIV infection: updated recommendations. http://www.cdc.gov/hiv/pdf/hivtestingalgorithmrecommendation-final.pdf. Accessed on January 14, 2016.
7. Fiebig EW, Wright DJ, Rawal BD, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary *HIV infection*. *AIDS*. 2003;17(13):1871-1879.
8. Cohen MS, Gay CL, Busch MP, Hecht FM. The detection of acute HIV infection. *J Infect Dis*. 2010;202 Suppl 2:S270-S277.
9. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed on January 14, 2016.
10. Gunthard HF, Aberg JA, Eron JJ, et al. Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society–USA panel. *JAMA*. 2014;312(4):410-425.
11. Hill AM, Pozniak A, Heath K, Raymond A, Mahy M, Ford N. Predicted impact of antiretroviral treatment on preventing new HIV infections in 53 low- and middle-income countries with large HIV epidemics [CROI Abstract 1118]. In Special Issue: Abstracts From the 2015 Conference on Retroviruses and Opportunistic Infections. *Top Antivir Med*. 2015;23(e-1):517.
12. Tanser F, Barnighausen T, Grapsa E, Zaidi J, Newell ML. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. *Science*. 2013;339(6122):966-971.
13. Fidler S, Porter K, Ewings F, et al. Short-course antiretroviral therapy in primary HIV infection. *N Engl J Med*. 2013;368(3):207-217.

14. Le T, Wright EJ, Smith DM, et al. Enhanced CD4+ T-cell recovery with earlier HIV-1 antiretroviral therapy. *N Engl J Med*. 2013;368(3): 218-230.

15. Finzi D, Blankson J, Siliciano JD, et al. Latent infection of CD4+ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. *Nat Med*. 1999;5(5): 512-517.

16. Siliciano JD, Kajdas J, Finzi D, et al. Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4+ T cells. *Nat Med*. 2003;9(6):727-728.

17. Ananworanich J, Dube K, Chomont N. How does the timing of antiretroviral therapy initiation in acute infection affect HIV reservoirs? *Curr Opin HIV AIDS*. 2015;10(1):18-28.

18. Persaud D, Gay H, Ziemniak C, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. *N Engl J Med*. 2013; 369(19):1828-1835.

19. Saez-Cirion A, Bacchus C, Hocqueloux L, et al. Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study. *PLoS Pathog*. 2013;9(3):e1003211.

20. Ananworanich J, Vandergeeten C, Chomchey N, et al. Early ART intervention restricts the seeding of the HIV reservoir in long-lived central memory CD4 T cells [Abstract 47]. 20th Conference on Retroviruses and Opportunistic Infections (CROI). March 3-6, 2013; Atlanta, Georgia.

Top Antivir Med. 2016;23(5):156-160.

Perspective

Antiretroviral Therapy for HIV Infection: When to Initiate Therapy, Which Regimen to Use, and How to Monitor Patients on Therapy

Antiretroviral therapy is recommended for all patients with HIV infection. The benefit of immediate antiretroviral therapy was confirmed by results from the START (Strategic Timing of Antiretroviral Treatment) trial, which showed a 57% reduction in risk for the composite end point of AIDS-related events, serious non–AIDS-related events, or death from any cause with immediate treatment in antiretroviral therapy–naive participants with CD4+ cell counts above 500/µL. Other changes in HIV care include the widespread adoption of integrase strand transfer inhibitor–based regimens. Considerations regarding when to initiate antiretroviral therapy, which initial regimens to use, and appropriate monitoring of individuals taking antiretroviral therapy are discussed. This article summarizes an IAS–USA continuing education webinar presented by Steven C. Johnson, MD, in July 2015.

Keywords: HIV, antiretroviral therapy, START trial, HIV treatment guidelines, antiretroviral therapy recommendations, monitoring

When to Initiate Antiretroviral Therapy

Most current guidelines on antiretroviral therapy recommend antiretroviral therapy for all HIV-infected individuals to reduce the risk of disease progression and to prevent transmission of HIV.[1-3] Results from 2 recently reported randomized trials—START (Strategic Timing of Antiretroviral Treatment) and TEMPRANO (Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults)—provide definitive support for early initiation of antiretroviral therapy.[4,5]

From its inception, the START trial was somewhat controversial in terms of whether a large randomized trial of early antiretroviral therapy was necessary given other available clinical data and in light of the remarkable benefit of therapy in preventing HIV transmission. In the trial, antiretroviral therapy–naive participants from around the world who had CD4+ cell counts above 500/µL were randomly assigned to receive immediate (n = 2326) or deferred (n = 2359) treatment (deferred until CD4+ count declined to less than 350/µL or until the development of AIDS).[4] The study required use of an approved combination of antiretroviral medications from the US Department of Health and Human Services (DHHS) guidelines. The predominant regimen was a nucleos(t)ide analogue reverse transcriptase inhibitor (nRTI) backbone of tenofovir disoproxil fumarate (TDF) and emtricitabine plus efavirenz. Some protease inhibitors (PIs) were used, and relatively few integrase strand transfer inhibitors (InSTIs) were used. As announced in a National Institutes of Health press release in May 2015, the data and safety monitoring board for the trial recommended that participants in the deferred-initiation arm be offered antiretroviral therapy on the basis of superiority of immediate treatment.[6]

The primary end point of the START trial was a composite of AIDS-related events (plus Hodgkin disease), serious non–AIDS-related events (cardiovascular disease, end-stage renal disease, non–AIDS-related cancer), or death by any cause. Figure 1 shows time to first primary end point event in the immediate-treatment group and the deferred-treatment group (hazard ratio [HR], 0.43; $P < .001$); HRs for the various end point components were 0.28 ($P < .001$) for serious AIDS-related events, 0.61 ($P = .04$) for serious non–AIDS-related events, and 0.58 ($P = .13$) for death by any cause. Immediate treatment was associated with a significantly reduced risk for tuberculosis (HR, 0.29; $P = .008$) and Kaposi sarcoma (HR, 0.09; $P = .02$) and a numerically reduced risk for malignant lymphoma (HR, 0.30; $P = .07$), non–AIDS-defining cancers (HR, 0.50; $P = .09$), and cardiovascular disease (HR, 0.84, $P = .65$). Subgroup analyses showed that HRs for the primary end point always favored immediate

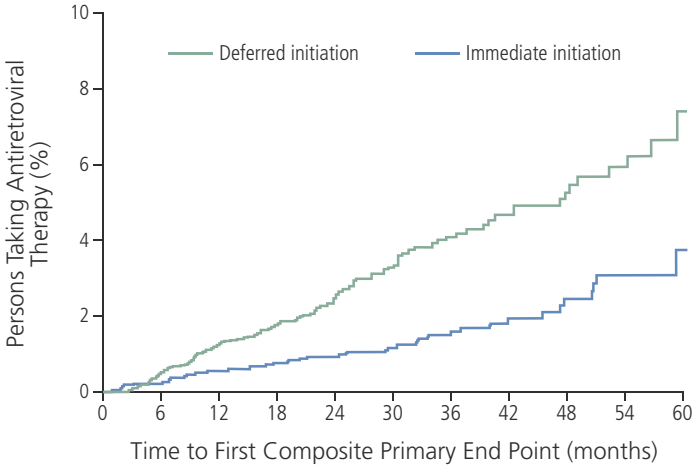


Figure 1. Time to first primary end point (serious AIDS-related or non–AIDS-related event, including death) in individuals who received immediate versus deferred antiretroviral therapy in the START (Strategic Timing of Antiretroviral Treatment) trial. Adapted from Lundgren et al.[4]

Dr Johnson is Director of the University of Colorado HIV/AIDS Clinical Program and Professor of Medicine at the University of Colorado School of Medicine in Aurora, Colorado.

Table 1. Subgroup Analysis for Primary End Point in the START Trial

Subgroup	Percentage in Group	Immediate Initiation of ART N (rate[a])	Deferred Initiation of ART N (rate[a])	Hazard Ratio	P Value
Age					0.98
≤35 y	48.8	15 (0.43)	31 (0.91)	0.47	
>35 y	51.2	27 (0.78)	65 (1.85)	0.42	
Sex					0.38
Male	73.2	35 (0.66)	74 (1.40)	0.47	
Female	26.8	7 (0.42)	22 (1.34)	0.31	
Race					0.65
Black	30.1	15 (0.82)	28 (1.52)	0.57	
White	44.5	21 (0.63)	53 (1.54)	0.40	
Other	25.4	6 (0.34)	15 (0.91)	0.37	
Region					0.55
High income	46.0	20 (0.56)	51 (1.42)	0.39	
Low or moderate income	54.0	22 (0.65)	45 (1.35)	0.48	
CD4+ cell count (baseline)					0.71
<600/μL	31.5	10 (0.44)	35 (1.54)	0.28	
600/μL-800/μL	48.6	24 (0.70)	46 (1.38)	0.50	
>800/μL	19.9	8 (0.63)	15 (1.14)	0.56	
HIV RNA level (baseline)					0.25
<5000 copies/mL	31.8	12 (0.56)	18 (0.83)	0.66	
5000-30,000 copies/mL	35.5	13 (0.53)	36 (1.41)	0.38	
>30,000 copies/mL	32.5	17 (0.72)	42 (1.92)	0.37	
Current smoker					0.93
Yes	31.9	18 (0.78)	43 (1.81)	0.43	
No	68.1	24 (0.52)	53 (1.16)	0.44	
10-year CVD risk score[b]					0.56
<0.8	32.7	8 (0.35)	17 (0.77)	0.46	
0.8-3.6	32.3	11 (0.48)	27 (1.23)	0.39	
>3.6	33.5	23 (1.00)	50 (2.05)	0.50	

Abbreviations: ART, antiretroviral therapy; CVD, cardiovascular disease; START, Strategic Timing of Antiretroviral Treatment. Adapted from Lundgren et al.[4]
[a]Rate per 100 person-years.
[b]Risk calculated using information from the Framingham Heart Study.

antiretroviral therapy, with the effect being statistically significant in nearly all subgroups examined (Table 1).

Safety has been an issue in the debate over when to initiate antiretroviral therapy. In START, immediate and deferred therapy had similar safety profiles: symptomatic grade 4 adverse events occurred in 73 participants each in the groups that received immediate therapy and deferred therapy, unscheduled hospitalizations occurred in 262 and 287 participants, respectively, and the rate of bacterial infections was lower in the group that received immediate therapy. Of note, the antiretroviral regimens used in the trial tended to be older regimens with relatively little use of integrase strand transfer inhibitors and may therefore have been associated with more frequent adverse events.

The TEMPRANO trial examined early antiretroviral therapy and isoniazid preventive treatment in African individuals with CD4+ counts below 800/μL who did not meet then-current World Health Organization guidelines for antiretroviral therapy.[5] A total of 2056 participants were randomly assigned to receive deferred or immediate antiretroviral treatment with or without isoniazid. Overall, 41% of participants had CD4+ cell counts of 500/μL or higher. As shown in Figure 2, risk of death or severe HIV-related illness, the primary end point, was reduced with early antiretroviral therapy with or without isoniazid preventive treatment among those with CD4+ cell counts of 500/μL or higher.

The benefits of immediate antiretroviral therapy have now been demonstrated in large, randomized, international trials. The data supporting a benefit to personal health are now as strong as the data supporting treatment as prevention. Country-specific and global guidelines on when to initiate antiretroviral therapy should soon be harmonized. It is sobering that only an estimated 41% of the world's 36.9 million persons with HIV infection are currently taking antiretroviral therapy.[7] A statement from the DHHS on July 28 indicated that in light of the findings of the START and TEMPRANO trials, the recommendation for initiating therapy in all patients regardless of pretreatment CD4+ cell count remains the same, with the strength of the recommendation upgraded to A1 for all HIV-infected persons.[8] Among individuals with acute HIV infection, potential benefits of immediate antiretroviral therapy include improved laboratory markers of

disease progression, reduced severity of acute infection, reduced viral replication and better preservation of immune function, reduced size of the latent viral reservoir, and reduced risk of HIV transmission with reduction in viral load. Individuals with elite control of HIV infection—those who have a high CD4+ cell count and a low or undetectable viral load without antiretroviral treatment—may also benefit from antiretroviral therapy, as they still have chronic inflammation caused by HIV infection that may increase their risk for comorbid conditions. In a recent study, after adjustment for demographic and clinical factors, individuals with elite control of HIV infection had higher rates of all-cause, cardiovascular, and psychiatric hospitalizations than persons with HIV infection controlled with antiretroviral therapy.[9]

Which Initial Antiretroviral Regimen to Use

Initial antiretroviral therapy typically consists of a 2-nRTI backbone with a third component of a nonnucleoside analogue reverse transcriptase inhibitor (NNRTI), a PI, or an InSTI. Options include once-daily therapy, and different combinations are available that can help with adherence issues or insurance copays.

A number of recent trials have compared standard regimens. One of these, the AIDS Clinical Trials Group (ACTG) 5257 trial, was an open-label trial that compared ritonavir-boosted atazanavir, ritonavir-boosted darunavir, and raltegravir, each with TDF and emtricitabine in approximately 1800 individuals who were naive to antiretroviral therapy.[9] At 96 weeks, the group receiving raltegravir had superior outcomes compared with the other 2 groups, based on composite virologic and tolerability end points. Virologic failure occurred in 9% of the group receiving raltegravir, 15% of the group receiving darunavir, and 13% of the group receiving atazanavir, and tolerability failure occurred in 1%, 5%, and 14%, respectively. Improved tolerability, as well as efficacy, has contributed to the wide adoption of InSTI-based regimens.

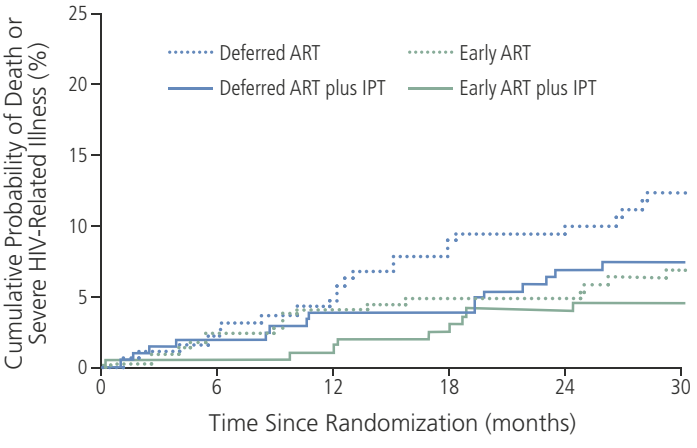


Figure 2. Risk for primary end point in individuals with a baseline CD4+ cell count of 500/μL or higher in the TEMPRANO (Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults) trial. ART indicates antiretroviral therapy; IPT, isoniazid preventive therapy. Adapted from Danel et al.[5]

Table 2. Recommended and Alternative Regimens for Initial Antiretroviral Therapy From the US Department of Health and Human Services

Recommended Regimens
InSTI-based regimens
– Dolutegravir, abacavir, and lamivudine[a] (only for individuals who test negative for the HLA-B*5701 allele)
– Dolutegravir plus TDF and emtricitabine[a]
– Cobicistat-boosted elvitegravir, TDF, and emtricitabine[a] (only for individuals with a pretreatment estimated CrCl ≥70 mL/min)
– Cobicistat-boosted elvitegravir, TAF, and emtricitabine[a]
– Raltegravir plus TDF and emtricitabine[a]
PI-based regimen
– Ritonavir-boosted darunavir plus TDF and emtricitabine[a]
Alternative Regimens
NNRTI-based regimens
– Efavirenz, TDF, and emtricitabine[a]
– Rilpivirine, TDF, and emtricitabine[a] (only for individuals with a pretreatment HIV RNA level <100,000 copies/mL and a CD4+ cell count >200 cells/μL)
PI-based regimens
– Cobicistat-boosted atazanavir plus TDF and emtricitabine[a] (only for individuals with a pretreatment estimated CrCl ≥70 mL/min)
– Ritonavir-boosted atazanavir plus TDF and emtricitabine[a]
– Cobicistat- or ritonavir-boosted darunavir plus abacavir and lamivudine[a] (only for individuals who test negative for the HLA-B*5701 allele)
– Efavirenz, TDF, and emtricitabine[a]

Abbreviations: CrCl, creatinine clearance; InSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate. Adapted from US Department of Health and Human Services.[1]

[a]Lamivudine and emtricitabine may be substituted for one another.

Current DHHS recommendations for initial antiretroviral therapy are shown in Table 2 and include 5 InSTI-based regimens. Although there are guidelines for initiation of antiretroviral therapy, choices should be tailored to the individual.

Table 3 shows some of the advantages and disadvantages of nRTIs, InSTIs, PIs, and NNRTIs in approved regimens. Of the 2 recommended nRTI backbones, TDF and emtricitabine have activity against hepatitis B virus, and some data indicate that this combination produces higher virologic response rates than abacavir and lamivudine when combined with ritonavir-boosted atazanavir or efavirenz in individuals with a baseline HIV RNA level of 100,000 copies/mL or higher. TDF and emtricitabine are available in a single-pill formulation with efavirenz, rilpivirine, or cobicistat-boosted elvitegravir, and abacavir and lamivudine are available in a single-pill formulation with dolutegravir. In 2015, a coformulation of a new form of tenofovir (tenofovir alafenamide [TAF]) with emtricitabine and cobicistat-boosted elvitegravir was approved by the US Food and Drug Administration (FDA).

Nephrotoxic effects are a concern with tenofovir use. In a recently reported retrospective analysis of the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) cohort, cumulative exposure to TDF as well as to ritonavir-boosted atazanavir or ritonavir-boosted lopinavir was associated with

Table 3. Advantages and Disadvantages of Antiretroviral Drugs

Drug Class/Name	Advantages	Disadvantages
nRTIs		
TDF and emtricitabine	Coformulated with efavirenz, rilpivirine, or cobicistat-boosted elvitegravir in single-tablet regimens Activity against hepatitis B virus Better virologic responses than abacavir and lamivudine with baseline HIV RNA level of ≥100,000 copies/mL when combined with ritonavir-boosted atazanavir or efavirenz	Nephrotoxic effects Decreases bone mineral density more than other regimens
TAF and emtricitabine	Rates of renal insufficiency and decreased bone mineral density seen with TAF are less than those observed with TDF	
Abacavir and lamivudine	Coformulated with dolutegravir in a single-tablet regimen	Cardiovascular risk in some studies Hypersensitivity in individuals who test positive for the HLA-B*5701 allele
InSTIs		
Dolutegravir	Once-daily dosing May have a higher barrier to resistance than elvitegravir or raltegravir Coformulated with abacavir and lamivudine No food requirement No interactions with cytochrome P450 3A4	Inhibits renal tubular secretion of creatinine and can increase serum creatinine without affecting glomerular function
Cobicistat-boosted elvitegravir	Coformulated as a single-tablet regimen with TDF or TAF and emtricitabine Once-daily dosing	Cobicistat inhibits active tubular secretion of creatinine and can increase serum creatinine without affecting glomerular function Drug-drug interactions
Raltegravir	Compared with other InSTIs, has longest postmarketing experience No food requirement No interactions with cytochrome P450 3A4	Twice-daily dosing May have a lower genetic barrier to resistance than regimens that contain boosted PIs or dolutegravir
PIs		
Ritonavir- or cobicistat-boosted atazanavir	Once-daily dosing Boosted PI with a higher barrier to resistance Atazanavir is coformulated with cobicistat	Indirect hyperbilirubinemia Food requirement Nephrolithiasis and cholelithiasis Drug-drug interactions
Ritonavir- or cobicistat-boosted darunavir	Once-daily dosing Boosted PI with a higher barrier to resistance Darunavir is coformulated with cobicistat	Food requirement Gastrointestinal adverse effects Drug-drug interactions
Ritonavir-boosted lopinavir	Only PI coformulated with ritonavir Once- or twice-daily dosing No food requirement	Requires 200 mg of ritonavir daily Possible increased risk of myocardial infarction Drug-drug interactions
NNRTIs		
Efavirenz	Once-daily dosing Coformulated with TDF and emtricitabine Long-term clinical experience Efavirenz-based regimens (except for efavirenz plus abacavir and lamivudine) have well-documented efficacy in individuals with high HIV RNA levels	Transmitted drug resistance more common than with PIs or InSTIs CNS-related adverse effects, including depression and suicidality (in some studies) Lower barrier to resistance than PIs or InSTIs Drug-drug interactions
Rilpivirine	Once-daily dosing Coformulated with TDF and emtricitabine Compared with efavirenz, fewer discontinuations for CNS-related adverse effects, fewer lipid-related effects, and fewer rashes	Not recommended for individuals with pretreatment HIV RNA levels >100,000 copies/mL or CD4+ cell counts <200/μL Transmitted drug resistance more common than with PIs or InSTIs Food requirement Drug-drug interactions

Abbreviations: CNS, central nervous system; InSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; nRTI, nucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate. Adapted from US Department of Health and Human Services.[1]

risk of chronic kidney disease, although risk decreased over time when TDF was stopped.[10] The new formulation of TAF has been associated with a lower rate of chronic kidney disease and loss of bone density when compared with TDF.[11]

Increased cardiovascular risk has been observed in some studies of abacavir and lamivudine. A recent report from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) showed an increased risk of myocardial infarction when abacavir had been recently used.[12] Individuals who test positive for the HLA-B*5701 allele have an approximately 50% risk of having a hypersensitivity reaction to abacavir.

Among InSTIs, now the most common class of drugs used with an NRTI backbone for initial antiretroviral therapy, dolutegravir and elvitegravir have the advantage of once-daily dosing, with raltegravir being dosed twice daily. Cobicistat, a boosting agent currently available in a single-tablet formulation with elvitegravir, and dolutegravir can inhibit renal tubular secretion of creatinine, resulting in elevation of serum creatinine without any effect on glomerular function. This effect should not be confused with the nephrotoxic effects observed with TDF use, for example.

PI-based regimens are now used less frequently, although cobicistat is available in coformulations with darunavir and atazanavir. NNRTI-based regimens are available in single-tablet formulations. However, efavirenz is associated with higher rates of transmitted drug resistance than PI- or InSTI-based regimens and is also associated with central nervous system–related adverse effects.

Risk of transmitted drug resistance should be considered when selecting initial antiretroviral therapy. A study sponsored by the Centers for Disease Control and Prevention assessed the prevalence of drug resistance in cases of newly diagnosed HIV infection from 2007 to 2010 in 10 surveillance areas: Chicago, Illinois; Colorado; Florida; Los Angeles, California; Louisiana; Michigan; New York; Seattle, Washington; South Carolina; and Texas.[13] Infections were classified as recent or established based on serologic techniques. Among 3904 recent cases, any transmitted drug resistance was found in 17.9%, NNRTI-associated resistance in 10.5%, nRTI-associated resistance in 7.0%, and PI-associated resistance in 4.5%. Among 11,963 established cases, any transmitted drug resistance was found in 15.5%, and NNRTI-, nRTI-, and PI-associated resistance were found in 7.3%, 6.5%, and 4.4%, respectively.

In a study that examined baseline clinical samples from studies of antiretroviral therapy–naive participants predominantly in the United States and Western Europe in 2000, 2003, and 2013, NNRTI-associated resistance increased from 1.9% to 7.8% and nRTI-associated resistance declined slightly from 2.7% to 2.2%.[14] Thus far, InSTI-associated resistance has been infrequent; in the samples from 2013, drug resistance–associated mutations were found in only 1 of 1617 samples.

Data from New York State indicate an increase in the rate of any transmitted drug resistance from 17% in 2006 to 24% in 2013.[15] Data from San Diego, California, for 1996 to 2013 indicate an overall prevalence of transmitted drug resistance of 16.2%, consisting of predominantly NNRTI-associated resistance (10.1%), with prevalence increasing over time.[16] Rates of resistance to PIs and nRTIs have remained relatively unchanged. Resistance to 2 and 3 drug classes has been seen in 4.8% and 0.9% of individuals, respectively.

Promising new antiretroviral drugs include TAF, a tenofovir prodrug associated with lower risk of bone loss and nephrotoxic effects than the current TDF formulation. As mentioned above, the first coformulation with TAF was recently approved by the FDA. Additional coformulations with TAF are likely to be approved in the near future. The investigational, once-daily, NNRTI doravirine is effective against virus with the K103N NNRTI resistance–associated mutation. A coformulation of the investigational InSTI cabotegravir and the NNRTI rilpivirine in long-acting parenteral form is currently being evaluated in clinical trials. Individuals initially receive a 3-drug combination that includes cabotegravir and rilpivirine in oral form, which is then simplified to only these 2 drugs for individuals with an undetectable viral load; those with maintained viral suppression are then randomly assigned to receive a monthly injection of these 2 drugs in parenteral form. Newer classes of antiretroviral drugs in development include the investigational attachment inhibitor fostemsavir and the investigational maturation inhibitor BMS-955176.

Monitoring of Individuals Taking Antiretroviral Therapy

DHHS recommendations for monitoring of viral load and CD4+ cell count are shown in Table 4. Viral load should be monitored at time of entry into care, 2 weeks to 4 weeks after initiation of antiretroviral therapy, and then every 4 weeks to 8 weeks until viral load is undetectable. Thereafter, monitoring is recommended every 3 months to 4 months during the first 2 years of antiretroviral therapy and then every 6 months if viral load remains consistently suppressed. However, monitoring should be conducted more frequently (ie, every 3 months) if there is a change in clinical status in individuals with maintained viral suppression (eg, new HIV clinical symptoms or treatment with systemic corticosteroids or antineoplastic therapy).

CD4+ cell count should be monitored at time of entry to care, 3 months after initiation of antiretroviral therapy, and every 3 months to 6 months during the first 2 years of therapy. In some cases, it may be helpful to measure CD4+ cell count 1 month after initiation of antiretroviral therapy, as the initial increase may be reassuring and may serve to support adherence to treatment. After the first 2 years, CD4+ cell count can be measured every 12 months in virologically suppressed individuals with counts of 300/μL to 500/μL. A relatively new recommendation is that measuring of CD4+ cell count is optional for individuals with consistent virologic suppression after 2 years of antiretroviral therapy and with CD4+ cell counts greater than 500/μL. With reassurance and education, patients have been generally accepting of this approach.

Table 4. Recommendations on the Frequency of Viral Load and CD4+ Cell Count Monitoring

Clinical Scenario	Viral Load Monitoring	CD4+ Cell Count Monitoring
Before initiation of antiretroviral therapy	At time of entry into care	At time of entry into care
After initiation of antiretroviral therapy	After 2-4 wk of therapy; every 4-8 wk until viral load is undetectable	3 mo after initiation of therapy
During the first 2 years of antiretroviral therapy	Every 3-4 mo	Every 3-6 mo
After 2 years of antiretroviral therapy, consistently virologically suppressed, with CD4+ cell count of 300/µL-500/µL	Every 6 mo	Every 12 mo
After 2 years of antiretroviral therapy, consistently virologically suppressed, CD4+ cell count of >500/µL	Every 6 mo	Optional
Change in clinical status (eg, new HIV clinical symptom or initiation of treatment with interferon alfa, chronic systemic corticosteroids, or antineoplastic therapy)	Every 3 mo	Perform CD4+ cell count and repeat as clinically indicated

Adapted from US Department of Health and Human Services.[1]

There are a number of important points to remember when monitoring viral load and CD4+ cell count. The DHHS guidelines use an HIV RNA of less than 200 copies/mL to indicate virologic response; virologic failure is a confirmed HIV RNA level greater than 200 copies/mL. The significance of low-level viremia (HIV RNA level <200 copies/mL but quantifiable) is unclear, with some studies demonstrating risk of virologic failure and others not finding such risk. From a practical standpoint, a detectable HIV RNA level of less than 200 copies/mL should not prompt a change in antiretroviral regimen. Blips under this threshold may represent transient viremia, and such increases can be used to discuss with individuals the importance of adherence to antiretroviral treatment without raising concern about clinical implications. Also, there is substantial laboratory variation in HIV RNA levels—the minimum fold change that should be considered clinically significant is 3 or 0.5 $\log_{10}$ (eg, a change in HIV RNA level from 40,000 copies/mL to 20,000 copies/mL is not clinically significant).

With regard to measurement of CD4+ cell count, counts vary by time of day. In one study, CD4+ cell count was 59/µL higher at 10:00 PM than at 8:00 AM. Variation in CD4+ cell count is also observed between and likely within laboratories. CD4+ cell count may increase by 2-fold after a splenectomy, with such an increase representing a lack of improvement in immune function. Lower CD4+ cell count despite viral suppression has been associated with older age and with lower counts at the time of initiation of antiretroviral therapy. Individuals taking suppressive antiretroviral therapy who do not develop high CD4+ cell counts can be reassured that disease progression is much less likely than for those with similar CD4+ cell counts who are not taking antiretroviral therapy. In addition, whereas HIV infection results in a reduced number and percentage of CD4+ cells, factors that cause a more global lymphocytopenia can result in a lower number of CD4+ cells without affecting percentage (eg, therapy with interferon alfa, chemotherapy, acute HIV infection).

In addition to monitoring of viral load and CD4+ cell count, primary care and comorbidity management should address the frequency and timing of patient follow-up. Factors that must also be taken into account include depression, bipolar disorder or other mental illness, alcohol use, tobacco use, recreational drug use, hepatitis B virus infection, hepatitis C virus infection, human papillomavirus infection, heart disease, hyperlipidemia, diabetes, hypertension, and aging.

Summary

Antiretroviral therapy is recommended for all persons living with HIV infection. Data from the START trial should remove any remaining doubt about the remarkable benefits of antiretroviral therapy for all HIV-infected individuals. The choice of antiretroviral regimen should be based on the results of these randomized clinical trials and on patient-specific factors. Recent guidelines suggest that monitoring may occur less frequently for individuals who respond well to treatment.

Presented by Dr Johnson in July 2015. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Johnson in January 2016.

Financial affiliations in the past 12 months: Dr Johnson has served as a consultant to ViiV Healthcare and has received payment for development of educational presentations from Clinical Care Options.

References

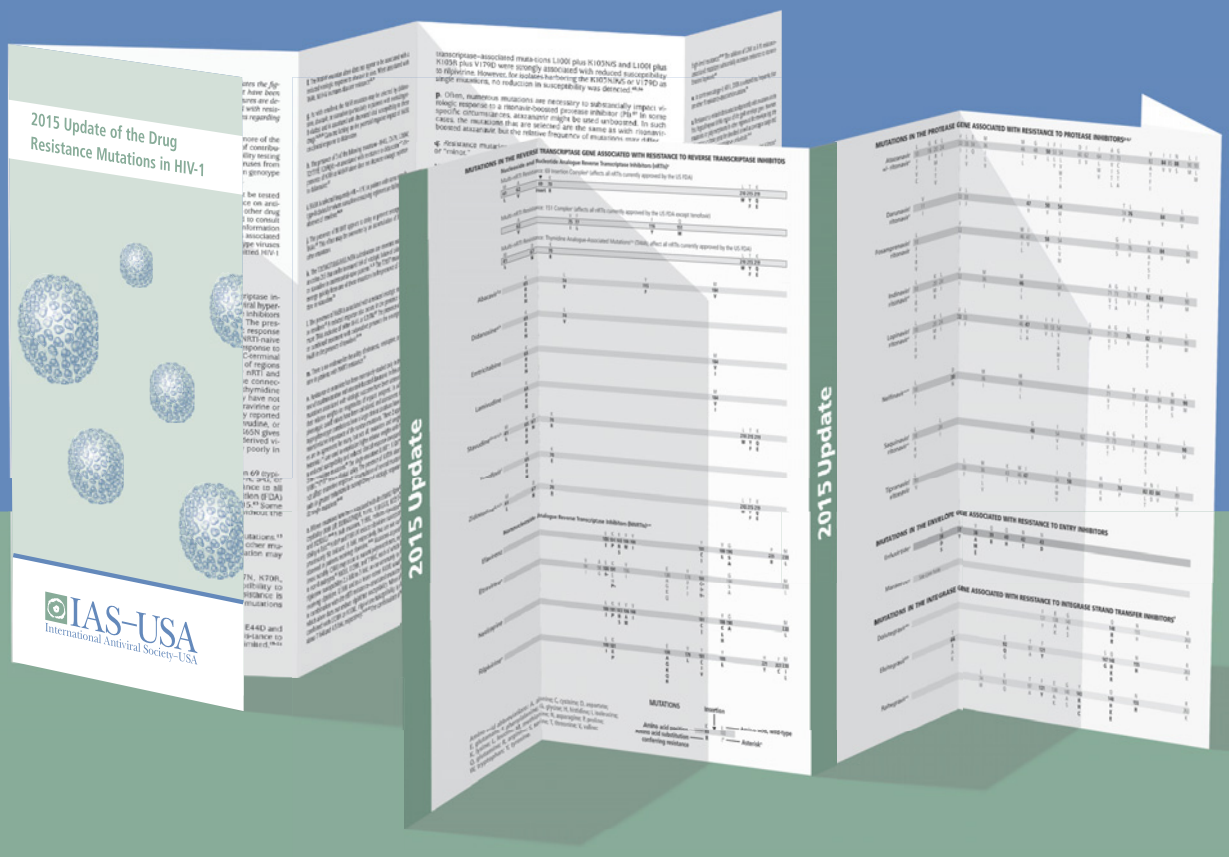
1. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed on January 21, 2016.
2. Gunthard HF, Aberg JA, Eron JJ, et al. Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society–USA panel. *JAMA*. 2014;312(4):410-425.
3. European AIDS Clinical Society. European guidelines for clinical management and treatment of HIV-infected adults in Europe. http://www.eacsociety.org/files/guidelines-7.1-english.pdf. Accessed on January 21, 2016.
4. Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV Infection. *N Engl J Med*. 2015;373(9):795-807.

5. Danel C, Moh R, Gabillard D, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med.* 2015; 373(9):808-822.
6. National Institutes of Health. Starting antiretroviral treatment early improves outcomes for HIV-infected individuals. http://www.nih.gov/news-events/news-releases/starting-antiretroviral-treatment-early-improves-outcomes-hiv-infected-individuals. Accessed on January 21, 2016.
7. UNAIDS. Fact sheet 2015. http://www.unaids.org/en/resources/campaigns/HowAIDSchangedeverything/factsheet. Accessed on January 28, 2016.
8. Department of Health and Human Services. Statement by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents regarding results from the START and TEMPRANO trials. https://aidsinfo.nih.gov/news/1592/statement-from-adult-arv-guideline-panel-start-and-temprano-trials. Accessed on January 21, 2016.
9. Lennox JL, Landovitz RJ, Ribaudo HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naive volunteers infected with HIV-1: a randomized, controlled equivalence trial. *Ann Intern Med.* 2014;161(7):461-471.
10. Mocroft A, Lundberg GD, Ross M, et al. Exposure to antiretrovirals and development of chronic kidney disease-D:A:D Study Group [Abstract 142]. Conference on Retroviruses and Opportunistic Infections. February 23-26, 2015; Seattle, Washington.
11. Sax PE, Saag MS, Yin MT, et al. Renal and bone safety of tenofovir alafenamide vs tenofovir disoproxil fumarate [CROI Abstract 143LB]. In Special Issue: Abstracts From the 2015 Conference on Retroviruses and Opportunistic Infections. *Top Antivir Med.* 2015; 23(e-1):58.
12. Palella FJ, Althoff KN, Moore R, et al. Abacavir use and risk for myocardial infarction in the NA-ACCORD [Abstract 749LB]. Conference on Retroviruses and Opportunistic Infections. February 23-26, 2015; Seattle, Washington.
13. Kim D, Ziebell R, Saduvala KR, et al. Trend in transmitted HIV-1 antiretroviral drug resistance-associated mutations, 10 HIV surveillance areas, United States, 2007-2010. [Abstract 149]. Conference on Retroviruses and Opportunistic Infections. March 3-6, 2013; Atlanta, Georgia.
14. Margot NA, Martin R, Miller MD, Callebaut C. Drug resistance mutations in treatment-naive HIV-infected patients 2000-2013. [Abstract 578]. Conference on Retroviruses and Opportunistic Infections. March 3-6, 2014; Boston, Massachusetts.
15. Wang Z, Walits E, Gordon DE, et al. Transmitted drug resistance and time of HIV infection, New York State, 2006-2013. [Abstract 599]. Conference on Retroviruses and Opportunistic Infections. February 23-26, 2015; Seattle, Washington.
16. Panichsillapakit T, Smith DM, Wertheim J et al. Transmitted HIV drug resistance among early infected persons in San Diego, California. [Abstract 600]. Conference on Retroviruses and Opportunistic Infections. February 23-26, 2015; Seattle, Washington.

Top Antivir Med. 2016;23(5):161-167.

Drug Resistance Mutations in HIV-1: Pocket Cards

The latest IAS–USA *Drug Resistance Mutations in HIV-1* pocket cards are now available. This double-sided resource card contains a current (as of November 2015) list of the mutations associated with clinical resistance to HIV and the accompanying user notes, which are regularly revised and disseminated by the IAS–USA Drug Resistance Mutations Group. An independent volunteer panel of experts focused on identifying key HIV-1 drug resistance mutations, the Drug Resistance Mutations Group strives to provide current, accurate, and unbiased information on these mutations for HIV practitioners.



The pocket cards may be purchased through the IAS–USA website. Visit http://www.iasusa.org/content/drug-resistance-mutations-in-HIV for more information or to access the online order form.

Perspective

Management of Lipid Levels and Cardiovascular Disease in HIV-Infected Individuals: Just Give Them a Statin?

Current guidelines for managing cholesterol to reduce cardiovascular disease (CVD) risk focus on providing the appropriate intensity of statin therapy to reduce low-density lipoprotein cholesterol (LDL-C) level. There is very little evidence supporting the use of treatments aimed at raising high-density lipoprotein cholesterol level or reducing triglyceride levels. HIV-infected persons have excess risk of CVD compared with the general population. Statins are less effective at reducing LDL-C levels in HIV-infected persons who are also at greater risk for adverse effects from statin treatment. When selecting a statin to achieve desired lowering of LDL-C level, the potential for drug interactions with antiretroviral therapy must be considered. Information from ongoing research is expected to help identify optimal strategies for use of statin treatment in this population. This article summarizes a presentation by James H. Stein, MD, at the IAS–USA continuing education program, Improving the Management of HIV Disease*, held in Chicago, Illinois, in May 2015.*

Keywords: HIV, cardiovascular disease, lipids, statins, LDL cholesterol, low-density lipoprotein cholesterol, statin intensity, REPRIEVE trial

Current Guidelines From the American College of Cardiology and the American Heart Association

In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) released guidelines for the treatment of blood cholesterol to reduce the risk of atherosclerotic cardiovascular disease (ASCVD).[1] These guidelines differ from previous versions in several respects: 1) they are heavily evidence based, relying almost exclusively on data from randomized clinical trials; 2) their focus is on reduction of low-density lipoprotein cholesterol (LDL-C) with therapy guided by ASCVD risk plus statin dose intensity; 3) treatment is not based on LDL-C level, and there are no LDL-C targets; 4) there are new ASCVD risk-assessment tools that provide better risk estimates for women and minority populations than previous versions; 5) and the new ASCVD risk calculator determines what dose of a statin an individual should be taking.

There is considerable evidence that statin therapy reduces adverse cardiovascular disease outcomes. A meta-analysis reported by the Cholesterol Treatment Trialists' Collaboration in 2010 included 129,526 participants in statin or control trials and 39,612 participants in 5 trials of more intensive or less intensive statin therapy.[2] Median follow-up was 5.1 years. In the meta-analysis, each 39 mg/dL reduction in LDL-C level was associated with a 10% reduction in all-cause mortality, a 20% reduction in coronary-related mortality, and a 20% reduction in major ASCVD-related events, including a 26% reduction in death caused by myocardial infarction (MI) or coronary heart disease, a 24% reduction in percutaneous coronary intervention and coronary artery bypass grafting, and a 15% reduction in incidence of stroke (all $P < .0001$). Benefits of statin therapy were observed in nearly all subgroups, including persons with or without heart disease or diabetes mellitus, men and women, and across age groups.

The ACC/AHA guidelines classify statin doses by 3 levels of intensity based on their ability to lower LDL-C levels in the general population (Table 1): high-intensity doses (atorvastatin 40-80 mg per day or rosuvastatin 20-40 mg) are expected to reduce LDL-C by 50% or more; moderate-intensity doses (atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg, pravastatin 40-80 mg, lovastatin 40 mg, fluvastatin 80 mg, or pitavastatin 2-4 mg) are expected to reduce LDL-C by 30% to 50%; and low-intensity doses (simvastatin 10 mg, pravastatin 10-20 mg, lovastatin 20 mg, fluvastatin 20-40 mg, or pitavastatin 1 mg) are expected to reduce LDL-C by 30% or less. Individual LDL-C responses to statin therapy are expected to vary in clinical practice. Simvastatin 80 mg is not recommended for use, owing to increased risk of myopathy and rhabdomyolysis.[1] Some clinicians avoid high-intensity doses of statins, particularly for individuals who might be at higher risk for developing muscle problems, and may instead choose lower-intensity doses of statins in

Table 1. Recommended Statin Doses for Achieving Desired Intensity of Treatment[a]

	High Intensity (≥50% decrease in LDL-C)	Moderate Intensity (30%-50% decrease in LDL-C)	Low Intensity (≤30% decrease in LDL-C)
Daily dose	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin 80 mg Pitavastatin 2-4 mg	Simvastatin[b] 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg

Abbreviations: LDL-C, low-density lipoprotein cholesterol. Adapted from Stone et al.[1]

[a]Individual responses to statin therapy varied in randomized controlled trials and are expected to vary in clinical practice.

[b]Simvastatin 80 mg is not recommended by the US Food and Drug Administration owing to the risk of myopathy and rhabdomyolysis.

Dr Stein is the Robert Turell Professor in Cardiovascular Research at the University of Wisconsin School of Medicine and Public Health in Madison, Wisconsin.

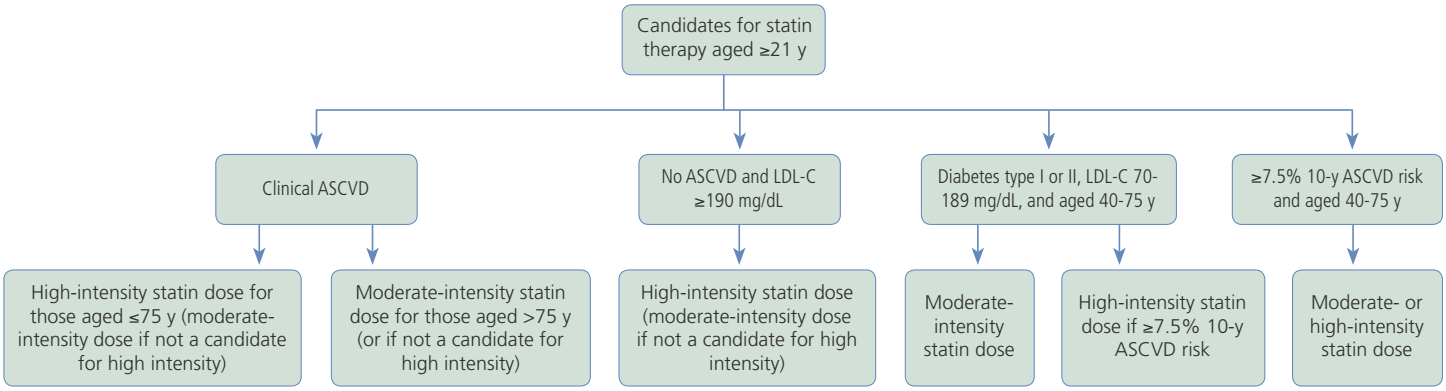


Figure. Individuals who may benefit from statin therapy and the recommended intensity of their treatment, by group. ASCVD indicates atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol. Adapted from Stone et al.[1]

conjunction with nonstatin interventions that have less evidence of reduction of cardiovascular events but also have less risk of causing muscle problems (eg, ezetimibe or bile acid–binding resins) (see Table 2 for recommended statin doses and their intensities in individuals taking antiretroviral therapy).

The Figure shows 4 groups of individuals who may benefit from statin therapy and the recommended intensity of their treatment: 1) individuals with clinical ASCVD, including acute coronary syndrome, MI, angina, revascularization, transient ischemic attack, stroke, and peripheral arterial disease; 2) individuals without ASCVD who have LDL-C levels of 190 mg/dL or higher, likely caused by familial hypercholesterolemia; 3) individuals aged 40 years to 75 years with type I or type II diabetes mellitus; and 4) individuals with a 10-year ASCVD risk of 7.5% or higher, calculated using newer risk-assessment tools. Other considerations when deciding about statin therapy include diabetes mellitus in individuals who are younger than 40 years or older than 75 years, a family history of premature ASCVD, an elevated lifetime risk of ASCVD, an LDL-C level of 160 mg/dL or higher, a high-sensitivity C-reactive protein (hs-CRP) level of 2.0 mg/L or higher, and subclinical atherosclerosis indicated by a coronary artery calcium score of 300 or higher or an ankle-brachial index number below 0.9.

Considerations in HIV Infection

The ACC/AHA guidelines acknowledge areas, including HIV infection, in which there are insufficient data from randomized clinical trials to provide high-level, evidence-based recommendations. Individuals with HIV infection are at increased risk of ASCVD. Most ASCVD risk in HIV-infected persons is attributable to traditional risk factors, including increasing age, male sex, smoking, diabetes mellitus, family history, hypertension, and dyslipidemia. Some excess risk is related to HIV infection, but how well ASCVD risk predictors work in HIV-infected individuals or how the excess risk associated with HIV infection can be captured with risk-assessment tools has not been established.

Perhaps the best data on excess CVD risk in HIV infection comes from the Veterans Aging Study Virtual Cohort.[3] In the study, which included 27,350 HIV-infected persons and 55,109 uninfected persons, higher rates of acute MI per 1000 person-years were observed among HIV-infected persons than uninfected persons aged 40 years to 49 years (2.0/1000 person-years vs 1.5/1000 person-years), 50 years to 59 years (3.9/1000 person-years vs 2.2/1000 person-years), and 60 years to 69 years (5.0/1000 person-years vs 3.3/1000 person-years). On multivariate analysis, the adjusted hazard ratio for MI in HIV-infected persons versus uninfected persons was 1.48 (95% confidence interval, 1.27-1.72). Some practitioners translate this 40% to 50% increased risk into a lower threshold for initiation of statin therapy. For example, a 5% 10-year risk for ASCVD might be used as the threshold for initiating treatment in HIV-infected persons who otherwise have no history of ASCVD, diabetes mellitus, or very high LDL-C levels.

Statins effectively reduce total cholesterol and LDL-C levels in persons with HIV infection, although their efficacy is somewhat reduced compared with the general population. They improve endothelial function and reduce progression of carotid intima-media thickness, although it is unclear whether statins reduce coronary calcium in the context of HIV infection. HIV-infected persons exhibit more frequent adverse effects during statin therapy, including more frequent elevation of creatine kinase and abnormal liver function test results, and are at risk for drug interactions between antiretroviral and lipid-lowering drugs.[4-6] In the absence of sufficient data from clinical trials regarding lipid lowering in HIV-infected persons, Table 2 provides some guidance on the use of high-, moderate-, or low-intensity statin treatment for individuals taking antiretroviral therapy, based on pharmacokinetic data and safety considerations.[1]

The REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) trial will evaluate the effects of pitavastatin 4 mg daily or a placebo in approximately 6500 HIV-infected persons aged 40 years or older who are not candidates for statin therapy based on current guidelines (see also Grinspoon et al[7]). The primary end point is composite major

adverse cardiac events, which include ASCVD-related death, MI, unstable angina, transient ischemic attack, stroke, or arterial revascularization. Secondary end points include individual major adverse cardiac events, overall mortality, LDL-C level, immune function, AIDS-related or non–AIDS-related events unrelated to CVD, and safety. Ascertaining the effects of statin therapy on inflammatory markers and immune activation in the context of HIV infection will be of particular interest in helping to determine if the excess CVD risk and the benefits associated with statin treatment are reflected by such markers.

Beyond the Guidelines: Do High-Density Lipoprotein Cholesterol and Triglyceride Levels Matter?

The ACC/AHA guidelines do not review evidence for treatment based on low high-density lipoprotein cholesterol (HDL-C) level, high triglyceride level, or combined dyslipidemia. Further, they contain only limited information and recommendations on the use of biomarkers or atherosclerosis imaging, because of a relative paucity of data from clinical trials. Available data indicate that attempts to increase HDL-C levels in persons receiving statin therapy do not result in risk reduction beyond that already achieved with statin therapy.

In the TNT (Treating to New Targets) trial, participants with heart disease had a reduced risk for CVD-related events while taking atorvastatin 80 mg versus atorvastatin 10 mg. In a post hoc analysis reported in 2007, risk for a CVD-related event was inversely associated with HDL-C quintile (P = .04); among persons whose LDL-C levels were reduced to below 70 mg/dL while taking statin therapy, HDL-C level was an independent predictor of CVD-related events (P = .03).[8] Based on these and other findings, trials of niacin therapy added to statin therapy to raise HDL-C level and to determine if additional preventive benefit could be achieved were conducted. In the AIM-HIGH trial, 3414 participants with ASCVD who had LDL-C levels of 180 mg/dL or lower, triglyceride levels of 150 mg/dL to 400 mg/dL, and HDL-C levels of 40 mg/dL or lower in men and 50 mg/dL or lower in women received statin therapy and were randomly assigned to receive extended-release niacin or a placebo. After 4 years of follow-up, there was no difference in CVD-related events between the 2 groups (P = .79).[9]

In the larger HPS2-THRIVE trial, 25,673 patients with ASCVD had higher HDL-C levels and lower triglyceride levels when niacin and laropiprant (a drug that prevents niacin-related flushing) were added to statin treatment, although there was no significant difference in prevalence of CVD-related events over 4 years (P = .29).[10] Niacin treatment was associated with an absolute 3.7% increase in incidence of serious adverse effects, including diabetes mellitus, infection, gastrointestinal effects, and myalgia; the relative risk for such effects was 5.2 among persons in China compared with 1.5 among persons in Europe.

In the absence of demonstrated reductions in ASCVD risk associated with pharmacologically induced increases in HDL-C levels in persons taking statins, it is worthwhile to consider the activity of HDL-C. It was once believed that HDL was mainly involved in reverse cholesterol transport. However, as atherosclerotic disease appears to have emerged as a dominant cause of death only in the last approximately 150 years, it is unlikely that HDL-C evolved solely to transport excess cholesterol back to the liver. Indeed, HDL-C also acts as an antiinflammatory particle with powerful antioxidant effects that is involved in host defense and immunity. Published data indicate a role for HDL in protection from endotoxins and trypanosomiasis. Data from Mendelian randomization studies do not strongly support the role of HDL-C in protecting against ASCVD. It appears that HDL-C is a marker rather than a mediator of disease and is not a suitable target of treatment.[11,12]

Table 2. Suggested Doses for Achieving Desired Intensity of Statin Treatment in HIV-Infected Individuals Taking Antiretroviral Therapy

High Intensity	Moderate Intensity	Low Intensity
With PI- or cobicistat-based regimens:		
Atorvastatin 20 mg Rosuvastatin 20 mg	Atorvastatin 10 mg Rosuvastatin 10 mg Pravastatin 40-80 mg Pitavastatin 2-4 mg	Pravastatin 10-20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg
With NNRTI-, raltegravir-, or dolutegravir-based regimens:		
Atorvastatin 40-80 mg Rosuvastatin 20 mg	Atorvastatin 10-20 mg Rosuvastatin 10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin 40 mg BID Pitavastatin 2-4 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg

Abbreviations: BID, twice daily. NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor. Courtesy of Michael P. Dube, MD. Adapted from Stone et al.[1]

Triglyceride levels have been a controversial CVD risk factor because they are associated with other risk factors such as obesity, diabetes mellitus, adverse lifestyle habits, inflammation, low HDL-C levels, small LDL particles, and excess LDL particles. However, Mendelian randomization studies have indicated that triglycerides play a potential causal role in ASCVD, albeit not as strong a role as LDL-C.[12-14] Nevertheless, there is little evidence to suggest that adding triglyceride-lowering medications to statin therapy provides additional risk reduction.

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) study evaluated the addition of fenofibrate or placebo to simvastatin in more than 5000 participants with diabetes mellitus, an average triglyceride level of 162 mg/dL, an average HDL-C level of 38 mg/dL, and an average LDL-C level of 100 mg/dL. After up to 7 years of follow-up, there were no differences between the fenofibrate group and the placebo group with regard to the composite end point of ASCVD-related death, nonfatal MI, or nonfatal stroke, a combined

end point of revascularization and congestive heart failure, or death from any cause.[15] Subgroup analysis suggested a possible benefit of fibrate therapy in reducing the risk of ASCVD-related outcomes in individuals with triglyceride levels above 204 mg/dL and HDL-C levels below 34 mg/dL ($P = .06$). A similar potential benefit was observed with niacin in a subgroup of the AIM-HIGH study who had high triglyceride levels (≥198 mg/dL) and low HDL-C levels (< 33 mg/dL; $P = 07$).[16] Thus, fibrates or niacin may add some benefit to statin treatment in individuals with high triglyceride levels and low HDL-C levels, although these treatments are associated with adverse effects.

Fish oil has been used to lower triglyceride levels, but there is little evidence that it is of benefit when added to statin therapy. The benefit of an eicosapentaenoic acid (EPA) formulation was shown in a Japanese study reported in 2007 in which the addition of EPA to pravastatin or simvastatin was assessed in more than 18,000 participants whose total cholesterol level was above 253 mg/dL; average baseline LDL-C level was 183 mg/dL, average HDL-C level was 59 mg/dL, and average triglyceride level was 154 mg/dL. In the context of a 25% reduction in LDL-C level in both groups and a 9% and 4% reduction ($P < .001$) in LDL-C level in the groups taking EPA or statins only, respectively, there was a significant absolute reduction of 0.7% ($P = .011$) in risk of major coronary events among all individuals taking EPA. Risk reduction was significant in secondary prevention (absolute reduction of 2%; $P = .048$) but not in primary prevention.[17]

Use of Nonstatin Drugs

In individuals with triglyceride levels above 500 mg/dL, fibrates (or niacin or fish oil) should be added to statin treatment to reduce the risk of pancreatitis. In all individuals receiving statin therapy, the addition of nonstatin treatments can be considered in cases of statin intolerance or persistent suboptimal response to statin treatment (eg, < 50% decrease in LDL-C level, LDL-C level remaining > 100 mg/dL in those receiving high-intensity treatment, or < 30% decrease in LDL-C level in those receiving moderate-intensity treatment). Ezetimibe is a likely choice for nonstatin treatment in such cases, as it has been shown to reduce the risk of CVD-related events.

In the IMPROVE-IT trial conducted in more than 18,000 persons diagnosed with acute coronary syndrome within 10 days of entry into the study, the addition of ezetimibe to simvastatin 40 mg resulted in a 10% reduction ($P = .003$) in risk for the composite end point of CVD-related death, MI, or stroke over 7 years.[18] The rate of ASCVD events in the group that received simvastatin alone was 22.2% in the context of an achieved LDL-C level of 70 mg/dL; the rate of ASCVD events in the group that received ezetimibe and simvastatin was 20.4% in the context of an achieved LDL-C level of 53 mg/dL. The number needed to treat with ezetimibe to prevent 1 additional adverse event was 56. The correlation between a reduction in ASCVD events and a reduction in LDL-C level in the trial was consistent with that observed in other lipid-lowering trials,[19] indicating that preventive benefit is largely caused by a lowering of LDL-C level. Although statins have antiinflammatory properties and some immunomodulatory effects, treatment should be directed at lipid lowering.

Summary

Reduction of CVD risk through lipid lowering is guided by determination of the appropriate dose intensity of statin treatment. Nonstatin therapies are less effective and can be considered additional therapy if statins are not well tolerated or if individuals show persistent suboptimal response to statin therapy. HIV-infected persons are at increased risk for CVD, although statins are less effective for lowering LDL-C level in such persons and are associated with more adverse effects. It is essential to consider potential drug interactions when selecting a statin for patients taking antiretroviral therapy. Information from the REPRIEVE trial will help define optimal approaches to statin treatment in this population. Further, practitioners should remember that smoking is a more powerful predictor of ASCVD risk in individuals with HIV infection. Helping patients to stop smoking and other adverse lifestyle habits may do more to reduce ASCVD risk in patients with HIV infection than titrating doses of lipid medications or combining such medications.

Presented by Dr Stein in April 2015. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Stein in January 2016.

Financial affiliations in the past 12 months: Dr Stein has served on data and safety monitoring boards for Lilly and received research grants awarded to his institution from Gilead Sciences, Inc. He has intellectual property rights licensed by the Wisconsin Alumni Research Foundation for carotid ultrasound and CVD risk and receives royalties for a textbook chapter from UptoDate.

References

1. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129(5 Suppl 2):S1-S45.
2. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670-1681.
3. Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med.* 2013;173(8):614-622.
4. Boccara F, Lang S, Meuleman C, et al. HIV and coronary heart disease: time for a better understanding. *J Am Coll Cardiol.* 2013;61(5):511-523.
5. Stein JH, Merwood MA, Bellehumeur JL, et al. Effects of pravastatin on lipoproteins and endothelial function in patients receiving human immunodeficiency virus protease inhibitors. *Am Heart J*. 2004;147(4):E18.
6. Silverberg MJ, Leyden W, Hurley L, et al. Response to newly prescribed lipid-lowering therapy in patients with and without HIV infection. *Ann Intern Med.* 2009;150(5):301-313.
7. Gilbert JM, Fitch KV, Grinspoon SK. HIV-related cardiovascular disease, statins, and the REPRIEVE trial. *Top Antivir Med.* 2015;23(4):146-149.

8. Barter P, Gotto AM, LaRosa JC, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med.* 2007; 357(13):1301-1310.
9. Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011;365(24):2255-2267.
10. Landray MJ, Haynes R, Hopewell JC, et al. Effects of extended- release niacin with laropiprant in high-risk patients. *N Engl J Med.* 2014; 371(3):203-212.
11. Voight BF, Peloso GM, Orho-Melander M, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet*. 2012;380(9841):572-580.
12. Holmes MV, Asselbergs FW, Palmer TM, et al. Mendelian randomization of blood lipids for coronary heart disease. *Eur Heart J*. 2014; 36(9):539-550.
13. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2011;123(20):2292-2333.
14. Do R, Willer CJ, Schmidt EM, et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat Genet*. 2013;45(11):1345-1352.
15. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med.* 2010;362(17): 1563-1574.
16. Guyton JR, Slee AE, Anderson T, et al. Relationship of lipoproteins to cardiovascular events: the AIM-HIGH Trial (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes). *J Am Coll Cardiol.* 2013;62(17):1580-1584.
17. Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet*. 2007;369(9567):1090-1098.
18. Cannon CP, Brindis RG, Chaitman BR, et al. 2013 ACCF/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes and coronary artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Acute Coronary Syndromes and Coronary Artery Disease Clinical Data Standards). *Circulation.* 2013;127(9):1052-1089.
19. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015; 372(25):2387-2397.

Top Antivir Med. 2016;23(5):167-171.

Review

Advance Care Planning and HIV Infection in the Era of Antiretroviral Therapy: A Review

Aroonsiri Sangarlangkarn, MD, MPH; Jessica S. Merlin, MD, MBA; Rodney O. Tucker, MD, MMM; Amy S. Kelley, MD, MSHS

In the era of antiretroviral therapy, HIV infection has become a chronic illness with associated multimorbidity, and practitioners are faced with an emerging population of HIV-infected patients with evolving needs for advance care planning (ACP), defined as communication between individuals and their proxies to plan for future health care decisions. This article provides a review of original research studies on ACP in HIV-infected adults in the era of antiretroviral therapy (1996-present) from PubMed, EMBASE, and PsycINFO. Eleven studies conducted between 1996 and 2015 met the selection criteria, with study sizes ranging from 9 to 2864 participants. Most studies consisted of white men in outpatient settings and had poorly defined definitions of ACP. Prevalence of ACP was variable (36%-54% had end-of-life communication, 8%-47% had advance directives). Lack of ACP was most commonly associated with low income, followed by lower severity of illness, low education level, black or Hispanic race, female sex, younger age, injection drug use, and social isolation. Practitioners reported limited time or energy and inadequate preparation or training as barriers to ACP. Existing literature on ACP in the era of antiretroviral therapy is limited, but shows that ACP prevalence in HIV-infected individuals is variable depending on socioeconomic factors, severity of illness, and practitioner resources and training. More research is needed to increase ACP among HIV-infected individuals.

Keywords: HIV, AIDS, advance care planning, advance directive, end-of-life care

Since the advent of effective antiretroviral therapy in 1996,[1,2] HIV-related mortality has declined substantially, and HIV has transitioned from a rapidly fatal illness to a chronic, manageable disease. The gain in life expectancy from antiretroviral therapy has resulted in an increasing proportion of older HIV-infected adults. By 2020, more than 50% of HIV-infected individuals in the United States will be older than 50 years.[3]

As HIV-infected individuals grow older, they are at increased risk of multimorbidity, defined as the development of multiple chronic conditions that interact to worsen mortality and functional outcomes.[4,5] As life expectancy among HIV-infected individuals becomes more influenced by multimorbid conditions instead of HIV infection in the era of antiretroviral therapy, multimorbidity has important ramifications on end-of-life experiences and advance care planning (ACP) in HIV-infected individuals.[6]

ACP is defined as a process of communication between individuals and their health care agents to understand, reflect on, discuss, and plan for a time when they may not be able to make their own health care decisions, in order to help maximize patient autonomy.[7] ACP may take many written forms, including advance directive, designation of health care proxies, living will, physician orders for life-sustaining treatment (POLST),[8] and documentation in electronic palliative care coordination systems,[9] among others.

As HIV evolved from a rapidly fatal illness to a chronic disease with early multimorbidity, the content and scope of ACP for HIV-infected individuals has also changed. The focus has shifted from living wills designed to address the circumstances of HIV-related, imminent death to more comprehensive ACP that includes treatment preferences for a range of possible clinical scenarios in the setting of chronic multimorbidity. On the other hand, certain ACP challenges unique to HIV-infected individuals remain the same despite improvements in HIV treatment. For example, HIV-infected individuals may experience HIV-related stigma, resulting in limited social support or isolation. They may receive help only from HIV-infected partners and friends and may lose this support network to HIV-related death or debility.[10] Without appropriate documentation of surrogate medical decision makers or effective ACP, decisions regarding end-of-life or emergent care for HIV-infected individuals may be legally deferred to estranged family members who may be unaware of the individual's HIV serostatus or treatment wishes.[11] Other challenges include a rapidly evolving knowledge base and the advent of new therapies that further complicate accurate prognostication, as well as disproportionate HIV infection in vulnerable populations who may have low health literacy or a limited understanding of ACP, including those of black or Hispanic race, those with mental illness, injection drug users, and prisoners.[12]

As more HIV-infected individuals survive into older age and new generations are protected from experiencing HIV infection as a life-limiting illness, it should be remembered that longevity does not obliterate the need for ACP. On the

Dr Sangarlangkarn is a geriatric fellow at the Icahn School of Medicine at Mount Sinai, in New York, New York. Dr Merlin is Assistant Professor of Medicine at the University of Alabama at Birmingham in Birmingham, Alabama. Dr Tucker is Associate Professor of Medicine at the University of Alabama at Birmingham in Birmingham, Alabama. Dr Kelley is Associate Professor at the Icahn School of Medicine at Mount Sinai, in New York, New York, and the James J. Peters Veterans Affairs Medical Center in Bronx, New York. Send correspondence to Aroonsiri Sangarlangkarn, MD, MPH, 24928 Gov Stockley Rd, Georgetown, DE 19947, or e-mail junest@post.harvard.edu.

contrary, practitioners must look ahead and prepare for the changing end-of-life needs of this uniquely vulnerable population. Currently, the US Department of Health and Human Services (DHHS) recommends ACP for all individuals with chronic, life-limiting illness or those aged 55 years and older, regardless of health status.[13] It is suggested that practitioners identify surrogate decision makers for their patients if possible, and that they document goals of care and preferences using POLST. However, the issue of ACP was not addressed in Infectious Diseases Society of America (IDSA) or DHHS HIV/AIDS practice guidelines.[14,15] There are currently no evidence-based recommendations on when or how HIV practitioners should discuss ACP with HIV-infected patients, especially those whose prognosis is driven by non–HIV-related multimorbidity in the era of antiretroviral therapy. Consequently, the available body of literature was examined to determine what is known about ACP in HIV-infected adults in the era of antiretroviral therapy. Based on existing knowledge, areas of crucial need for future research were also identified.

Methods

Overview

This review describes original research studies on ACP for HIV-infected adults in the era of antiretroviral therapy. Because existing research on this topic is limited and heterogeneous, precluding a systematic review, this article provides a narrative review describing what is known about the topic. This research received no grant funding from any agency.

Search Strategy

This review utilized 2 groups of search terms: 1) those related to ACP; and 2) those related to HIV. Various search terms within the same group were combined using "OR," then the 2 groups of search terms (related to ACP or HIV) were combined using "AND."

Search terms within the ACP-related group that were combined using "OR" included advance care planning; advance health care planning, advance medical planning; advance directive; advance directives; resuscitation order; resuscitation orders; withholding resuscitation; resuscitation policy; resuscitation policies; do-not-resuscitate order; do-not-resuscitate orders; do not resuscitate order; do not resuscitate orders; resuscitation decision; resuscitation decisions; medical power of attorney; health care power of attorney; healthcare power of attorney; psychiatric will; end-of-life; and end-of-life communication. Search terms within the HIV-related group that were combined using "OR" included HIV and AIDS.

Afterward, ACP-related search terms were combined with HIV-related search terms using "AND." They were then used to search PubMed, EMBASE, and PsycINFO databases on September 4, 2015. The search was conducted by a professional librarian skilled and experienced in article searches. In PubMed, each of the above search terms was used as an official medical subject heading (MeSH) term and keyword. Related entry terms within each MeSH heading were also included in keyword searches.

Selection Criteria

Because of the focus on ACP in HIV-infected adults in the era of antiretroviral therapy, this review excluded articles on children or adolescents, studies conducted before 1996 (before effective antiretroviral therapy was available), articles in languages other than English, nonmedical articles (eg, legal articles), and nonoriginal research articles (eg, case reports, review articles, editorials, book chapters, and newspaper articles).

Procedure

In the first round of searches, web-based commercial reference management software (RefWorks, Bethesda, MD) was used to exclude duplicates. In the second round, article titles of all publications identified by the search strategy described above were reviewed to exclude results that did not focus on ACP in HIV-infected adults. If it was unclear based on the title whether an article should be included, a full review of the article's abstract was conducted to make the decision. During the third round, the above selection criteria were applied to the remaining articles to arrive at the studies included in this review. Common elements were extracted from each of the articles, including study design, types and numbers of subjects, demographic characteristics, severity of HIV disease, study definitions of ACP, rates of ACP reported, and factors associated with lack of ACP. To determine the level of significance of each factor despite the heterogeneous nature of available studies, this review also calculated the percentage of the number of times each factor was statistically significantly associated with lack of ACP per the number of times it was evaluated in the existing literature. During the review, common findings were also identified to establish themes that may be generalizable across populations.

Results

Of 716 publications identified using the search strategy described above, 11 articles met the selection criteria and were included in this review (Figure). Key features of the studies are summarized in Table 1. All studies were conducted in outpatient settings between 1996 and 2015, except for the study by de Caprariis and colleagues, which was conducted in an inpatient setting.[16] The number of participants ranged from 9 to 2864. Across studies, most participants were white men with education below the college level, except for the study by Mosack and colleagues in which most participants were black men.[17] The definitions of ACP were often broad, variable, and poorly defined, described as any form of end-of-life communication, any form of advance directive, or any discussion about the kind of care an individual would want if they were to become ill.

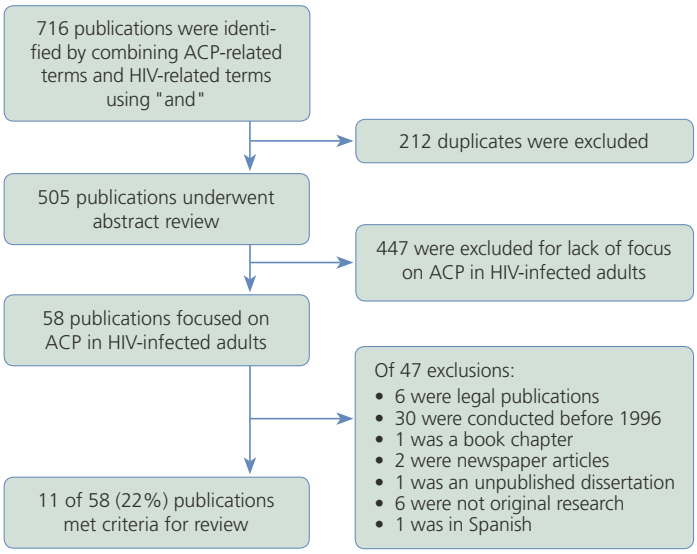


Figure. Article review flow chart.

Prevalence of Advance Care Planning Among HIV-Infected Individuals

Four of the studies reviewed examined the prevalence of advance directives. The completion rate of advance directives among the 4 studies ranged between 8% and 47%.[11,16,18,19] The majority of advance directives were completed in inpatient or presurgical settings,[18] and few HIV-infected patients completed advance directives in outpatient settings prior to hospital admission (7.6%).[16]

Of the 8 studies that investigated end-of-life communication, 3 described patient-reported prevalence rates of end-of-life communication, which ranged from 36% to 54%.[19-21] However, there were discrepancies between patient and physician reports of the occurrence of end-of-life communication. Curtis and colleagues found that 15 of 57 (26%) physician-patient pairs disagreed on whether end-of-life communication had taken place, with physicians overestimating its occurrence.[20] In 5 of the 15 discordant pairs, patients reported that end-of-life communication had taken place whereas physicians did not; in the remaining 10 discordant pairs, physicians reported that end-of-life communication had taken place whereas patients did not. The researchers did not comment on possible reasons for the discrepancies between patient and physician reports of end-of-life communication. However, a later study by Mosack and colleagues may shed some light on this discordance.[17] Based on data from qualitative interviews, they found a notable difference in how physicians and patients defined end-of-life communication. Practitioners tended to focus on the desired medical interventions at the end of life, while patients generally referenced the paperwork that results from end-of-life communication (eg, a living will or a power of attorney) instead of the process of ACP itself or the types of medical interventions enacted when there is a decline in health.

Factors Associated With Lack of ACP

Eight studies reported patient characteristics that are associated with a lack of an advance directive or end-of-life communication (Table 2). The most commonly reported factor per the number of times evaluated was low income. This was followed by lower severity of illness, described as a lack of current or prior history of AIDS, higher CD4+ cell count, fewer symptoms, or a lack of recent hospitalizations within the past 6 months. In 2 studies, rates of completion of advance directives were higher among HIV-infected individuals with certain comorbid conditions, such as cardiovascular disease (adjusted odds ratio [aOR], 2.3; 95% confidence interval [CI], 1.1-4.6),[11,18] neurologic disorders (aOR, 5.0; 95% CI, 2.2-12.1), chronic kidney disease (aOR, 3.3; 95% CI, 1.3-8.3), or malignancy (aOR, 2.8; 95% CI, 1.3-6.0).[18] Other factors included low education, black or Hispanic race, female sex, younger age, injection drug use, and social isolation (reported as living alone, having limited social support, or experiencing HIV-related stigma).

Three other themes also emerged as patient-related factors associated with advance directives and end-of-life communication. First, 3 studies reported that the prevalence of advance directives and end-of-life communication increased when individuals possessed positive psychosocial characteristics, such as less denial of illness, positive coping skills, a desire to be involved in medical decision making, a lack of discomfort discussing death, more social support, and living with family members (especially children).[11,19,22] Second, 1 study reported that certain misconceptions negatively correlated with rates of ACP, including the belief that discussing ACP will cause harm or death, or that having a living will makes it unnecessary to discuss ACP further.[23] Third, 4 studies reported how patients' relationships with their practitioners affected rates of ACP. For example, ACP was less likely to occur if patients had short relationships with or less trust in their clinicians.[19] ACP was also less likely if patients were cared for by physician assistants or nurse practitioners instead of physicians, despite no difference in disease conditions or overall satisfaction with care.[20] Researchers postulated that this may be due to some patients' beliefs that mid-level practitioners will not be the ones caring for them in the hospital, or the possibility that mid-level practitioners may have less education or experience conducting discussions about end-of-life care. Additionally, both physicians and patients reported waiting for the other to bring up the topic of ACP: patients expressed a desire to protect physicians from uncomfortable discussions, while physicians thought that discussing ACP might undermine a patient's hope.[17,23] Ultimately, a lack of discussions of ACP by clinicians was an important predictor of fewer completions of advance directives (aOR, 5.82; 95% CI, 4.50-7.52).[19]

Three additional studies described barriers to end-of-life communication reported by physicians. Barriers included limited time, energy, or preparation; uncertainty regarding prognosis; cultural discordance between practitioner and patient; potential change of physician at the end of life if

Table 1. Characteristics of Studies of Advance Care Planning

Source	Study Design	Type of Participants	N	Characteristics		Definition of ACP
				Demographics	Study Inclusion Criteria	
Erlandson et al,[11] 2012	Cross-sectional survey/interview	Patients	369	70% aged >55 y; 84% men; 76% white; 72% without college-level education; 20% were admitted to the hospital in the prior year	Aged 45-65 y; taking antiretroviral therapy; plasma HIV RNA level <200 copies/mL in the prior 6 mo	"Do you have an advance directive, living will, or durable power of attorney of health care decisions?"
de Caprariis et al,[16] 2013	Retrospective chart review	Patients	182	Median age, 47 y; 70% men; median time from HIV diagnosis, 9.5 y	Admitted to the hospital between 2004 and 2011	Any living will, health care proxy, or do-not-resuscitate order
Mosack et al,[17] 2015	Cross-sectional survey/interview	Practitioners and patients	11 and 42, respectively	65% men; 91% black; 25% had been diagnosed with AIDS at the time of the study	HIV specialists in a midsized Midwestern city and HIV-seropositive persons from the same clinics	The medical care one would want to receive should they become ill
Barocas et al,[18] 2015	Retrospective chart review	Patients	588	Mean age, 47 y; 81% men; 72% white; 41% had private insurance; mean CD4+ cell count, 634/μL	Aged >18 y; not in a prison or mental health facility; no legal guardian	An advance directive that allows patients to communicate health care preferences in the event that they are no longer able to make decisions
Wenger et al,[19] 2001	Cross-sectional survey/interview	Patients	2864	89% aged >50 y; 77% men; 49% white; 52% without high school–level education; 59% had AIDS	Aged >18 y with 1 visit to a nonmilitary, nonprison medical practitioner	Any end-of-life communication
Curtis et al,[20] 1999	Prospective cohort	Practitioners and patients	38 and 57, respectively	Median age, 39 y; 52% men; 65% white; 79% without college-level education; 63% with >24 mo since AIDS diagnosis	Prior AIDS-defining illness and CD4+ cell count <100/μL	Communications about end-of-life care
Mouton et al,[21] 1997	Cross-sectional survey/interview	Patients	861	Mean age, 35 y; 90% men; 66% white; 70% MSM; 47% without college-level education; 88% with AIDS	Aged >18 y	"Have you told your physicians that this is the approach you want taken in your treatment?"
Hutson,[22] 2015	Cross-sectional survey/interview	Patients	9	77% aged >50 y; 55% men; 66% white; 66% without college-level education; average time since HIV diagnosis, 16 y	Aged >21 y, residing in an Appalachian county in Tennessee	Not defined
Curtis et al,[23] 1997	Cross-sectional survey/interview	Practitioners and patients	19 and 47, respectively	Median age, 38 y; 66% men; 64% white	AIDS-defining illness and CD4+ cell count <200/μL	The kind of care one would want if they became too ill to speak for themselves
Karasz et al,[24] 2003	Cross-sectional survey/interview	Practitioners	16	Mean time in field, 16 y; 75% men	Caring for late-stage HIV-infected patients	Not defined
Curtis et al,[25] 2000	Prospective cohort	Practitioners and patients	38 and 57, respectively	Mean age, 39 y; 91% men; 65% white, 64% with CD4+ cell count <200/μL	AIDS-defining illness and CD4+ cell count <100/μL	The kind of care one would want if they became too ill to speak for themselves

Abbreviations: ACP, advance care planning; MSM, men who have sex with men.

Table 2. Patient Characteristics Associated With Lack of Advance Care Planning[a,b]

Source	Rate of ACP[c]	Characteristics							
		Low Income	Lower Illness Severity	Low Education Level	Nonwhite Race[d]	Female Sex	Younger Age	Injection Drug Use	Social Isolation
Erlandson et al,[11] 2012	47%	AD	AD	AD	0	AD	AD	…	AD
de Caprariis et al,[16] 2013	8%	…	…	…	…	…	…	…	…
Mosack et al,[17] 2015	…	…	…	…	…	…	…	…	…
Barocas et al,[18] 2015	23% AD	…	AD	…	0	0	AD	0	0
Wenger et al,[19] 2001	38% AD, 50% EOL	…	AD and EOL	EOL	AD and EOL	EOL	0	AD and EOL	EOL
Curtis et al,[20] 1999	54% EOL	EOL	0	0	EOL	EOL	0	EOL	…
Mouton et al,[21] 1997	36% EOL	EOL	EOL	EOL	EOL	0	…	0	0
Hutson,[22] 2015	…	…	…	…	…	…	…	…	EOL
Curtis et al,[23] 1997	…	EOL	EOL	EOL	EOL	EOL	EOL	EOL	0
Karasz et al,[24] 2003	…	…	…	…	…	…	…	…	…
Curtis et al,[25] 2000	…	…	EOL	…	…	…	…	…	…
Times reported per times evaluated	…	100%	86%	80%	67%	67%	60%	60%	50%

Abbreviations: ACP, advance care planning; AD, advance directive; EOL, end-of-life communication.

[a]Zeroes indicate no associations reported.
[b]Ellipses indicate not evaluated by the study.
[c]Data show rate of overall ACP when unspecified.
[d]Black or Hispanic race.

enrolled in hospice; and the belief that the physician themselves or the patient was not ready to discuss end-of-life care.[23-25]

Discussion

Research on ACP among HIV-infected individuals in the era of antiretroviral therapy is limited. Based on review of the existing literature, the reported rates of ACP among HIV-infected individuals are highly variable. Additionally, these rates were drawn from a small group of heterogeneous research studies, none of which were true prevalence studies. In the existing literature, the reported rate of end-of-life communication ranged between 36% and 54%, and the rate of completion of advance directives ranged between 8% and 47%, with most advance directives completed in acute care settings (in hospitals or prior to surgery). In comparison, the rate of completion of advance directives in the general US population ranged between 15% and 25%,[26] with only 18% completed prior to admittance to a hospital.[27]

This review identified multiple patient-related factors that correlated with a lack of ACP. Although heterogeneity across studies prevents statistical comparison among these factors, the frequency of statistical significance for each factor aggregated across studies may imply a level of importance. For example, low income may be an important contributor to lack of ACP, as it was most commonly reported as statistically significant when evaluated in the existing literature (4/4 studies) (Table 2). Akin to prior research in the uninfected population,[28,29] higher rates of ACP were found among HIV-infected individuals who were older or experienced a higher severity of illness, described as advanced HIV infection or comorbid conditions associated with increased morbidity and mortality, such as cardiovascular disease, neurologic disorders, chronic kidney disease, or malignancy. Additionally, similar to the general population, ACP in HIV-infected individuals was less common among vulnerable subgroups (those of black or Hispanic race, injection drug users, those of lower socioeconomic status, and those who were socially isolated).[29-38] The prevalence of ACP may be lower among such

individuals because of less trust in practitioners, cultural discordance, the misconception that discussing ACP will cause harm, a lack of available health care proxies,[22] or a lack of incentive to ensure the well-being of survivors, especially a lack of children in the household.[11,19]

From practitioners' perspectives, 2 types of factors limited ACP. First, logistic reasons may inhibit practitioners from discussing ACP, including limited time or energy and the loss of long-term relationships with patients owing to a change of physician after hospice enrollment. Second, some practitioners also reported feeling prohibited by inadequate preparation and training, described as not feeling ready to discuss ACP or having insufficient knowledge for the process (insufficient understanding of a patient's culture or discomfort with prognostication). Similar barriers were found in the general population, with lower rates of end-of-life communication and completion of advance directives if physicians lacked time or knowledge about how to engage in ACP.[39]

Despite substantial changes in the clinical course and treatment of HIV infection, as well as progress in the realm of ACP, many issues regarding ACP for HIV-infected individuals remained consistent from 1996 to recent years. Regardless of when they were conducted, most studies recommended that more efforts were needed to increase the quantity and quality of ACP among HIV-infected individuals.[11,16-25] Many barriers to ACP remained statistically significant over the past 2 decades, such as low education, low income, and lower severity of illness. Issues of discordance in end-of-life communication between patients and practitioners also persisted, such as discrepancies in reported occurrences of end-of-life communication or differences in how patients and practitioners define end-of-life communication.[17,20]

This research was limited by the small number of available studies. Because only a few of these studies were conducted in recent years, findings in the existing literature may not represent the current issues surrounding ACP and end-of-life communication among HIV-infected individuals. Moreover, there was a large amount of heterogeneity among the studies, limiting the opportunity for analysis of pooled data or statistical comparisons among risk factors related to the lack of ACP.

This review revealed several important gaps in the existing literature on ACP in the era of antiretroviral therapy. First, further investigation focusing on vulnerable subgroups is needed. Current evidence suggests that rates of ACP are lower in these populations and that some are particularly at risk for legal or familial conflicts if ACP is not completed. For example, with the rapidly shifting legal and political climates surrounding the issue of same-sex marriage, the hierarchy of surrogate decision makers for HIV-infected individuals with same-sex partners may change, creating a potential for confusion if ACP is not in place.[40-44]

Second, methods for increasing the rate of effective ACP among HIV-infected individuals should be developed, and future research should leverage factors associated with increased rates of ACP, such as targeting patients with higher severity of illness, building a trusting relationship between patient and practitioner, or encouraging ACP to promote the well-being of survivors. To increase rates and quality of ACP in the outpatient setting prior to a medical crisis, effective interventions are needed to equip practitioners with practical, time-saving tools that can help elicit patient-centered goals of care and accurate prognostication in the setting of multimorbidity. Although some tools are available for the general population, they have not yet been studied in HIV-infected individuals.[45,46]

Third, HIV service networks should develop strategies to translate research on ACP among HIV-infected individuals into policy and practice. Future efforts should employ multipronged approaches that remove barriers to ACP for both patients and practitioners, such as raising patient awareness regarding misconceptions around ACP and providing practitioners with recommendations on ACP and end-of-life communication in evidence-based practice guidelines, such as those from the IDSA or DHHS.

Last, as HIV-infected individuals survive longer with increased multimorbidity, their ACP needs may become similar to those of their uninfected counterparts who may be cared for by geriatricians and palliative care practitioners. As a result, collaborations between HIV and geriatrics or palliative care service networks may increase the prevalence and quality of ACP among HIV-infected individuals, possibly through direct contact with patients or through professional education. However, more research is needed to determine the most effective ways for such collaborations to take place.

Conclusion

Research on ACP in the era of antiretroviral therapy is limited but does reveal a highly variable prevalence of ACP among HIV-infected individuals. Rates of ACP are particularly low in vulnerable subgroups, possibly because of distrust, misconceptions, cultural discordance, or social isolation. In contrast, rates of ACP are higher among individuals who are older, have higher severity of illness, or suffer from certain comorbid conditions as part of multimorbidity, an entity that necessitates a new paradigm for ACP in the era of antiretroviral therapy. Practitioners reported clinical logistics and inadequate preparation as barriers to ACP. More research is needed to inform policy and create guidelines for HIV practitioners on when and how to discuss ACP with patients. Collaborations with geriatrics and palliative care service networks may help increase the prevalence and quality of ACP among HIV-infected patients, as these networks also care for patients with complex ACP needs. However, more research is needed to further define the ideal involvement of these networks in the care of this emerging population.

Financial affiliations in the past 12 months: Drs Sangarlangkarn, Merlin, and Tucker have no relevant financial affiliations to disclose. Dr Kelley receives support from the National Institute on Aging (1K23AG040774-01A1), the American Federation for Aging Research, and the National Palliative Care Research Center. This funding had no role in the research or manuscript preparation. No commercial or government funding was used to support this research.

References

1. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200/µL or less. *N Engl J Med.* 1997;337:725-733.
2. Gulick RM, Mellors JW, Havlir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. *N Engl J Med.* 1997;337(11):734-739.
3. Brooks JT, Buchacz K, Gebo KA, Mermin J. HIV infection and older Americans: the public health perspective. *Am J Public Health.* 2012; 102(8):1516-1526.
4. Pathai S, Bajillan H, Landay AL, High KP. Is HIV a model of accelerated or accentuated aging? *J Gerontol A Biol Sci Med Sci.* 2014; 69(7):833-842.
5. High KP, Brennan-Ing M, Clifford DB, et al. HIV and aging: state of knowledge and areas of critical need for research. A report to the NIH Office of AIDS Research by the HIV and Aging Working Group. *JAIDS.* 2012;60(Suppl 1):S1-18.
6. Kim DJ, Westfall AO, Chamot E, et al. Multimorbidity patterns in HIV-infected patients: the role of obesity in chronic disease clustering. *JAIDS.* 2012;61(5):600-605.
7. International Society of Advance Care Planning and End of Life Care. The definition of advance care planning. http://acpelsociety.com/index.php. Accessed on January 18, 2016.
8. Physician Orders for Life-Sustaining Treatment Paradigm (POLST). The national POLST paradigm. http://www.polst.org/. Accessed on January 18, 2016.
9. Mullick A, Martin J, Sallnow L. An introduction to advance care planning in practice. *BMJ.* 2013;347:f6064.
10. Poindexter C, Shippy RA. Networks of older New Yorkers with HIV: fragility, resilience, and transformation. *AIDS Patient Care STDs.* 2008;22(9):723-733.
11. Erlandson KM, Allshouse AA, Duong S, Mawhinney S, Kohrt WM, Campbell TB. HIV, aging, and advance care planning: are we successfully planning for the future? *J Palliat Med.* 2012;15(10): 1124-1129..
12. Kutzen HS. Integration of palliative care into primary care for human immunodeficiency virus-infected patients. *Am J Med Sci.* 2004; 328(1):37-47.
13. Agency for Health Research and Quality. National guideline clearinghouse. http://www.guideline.gov/content.aspx?id = 47803. Accessed on January 18, 2016.
14. Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV medicine association of the Infectious Diseases Society of America. *Clin Infect Dis.* 2014; 58(1):1-10.
15. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1–infected adults and adolescents. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed on January 18, 2016.
16. de Caprariis PJ, Carballo-Dieguez A, Thompson S, Lyon C. Advance directives and HIV: a current trend in the inner city. *J Community Health.* 2013;38(3):409-413.
17. Mosack KE, Wandrey RL. Discordance in HIV-positive patient and health care provider perspectives on death, dying, and end-of-life care. *Am J Hosp Palliat Care.* 2015;32(2):161-167.
18. Barocas JA, Erlandson KM, Belzer BK, Hess T, Sosman J. Advance directives among people living with HIV: room for improvement. *AIDS Care.* 2015;27(3):370-377.
19. Wenger NS, Kanouse DE, Collins RL, et al. End-of-life discussions and preferences among persons with HIV. *JAMA.* 2001;285(22): 2880-2887.
20. Curtis JR, Patrick DL, Caldwell E, Greenlee H, Collier AC. The quality of patient-doctor communication about end-of-life care: a study of patients with advanced AIDS and their primary care clinicians. *AIDS.* 1999;13(9):1123-1131.
21. Mouton C, Teno JM, Mor V, Piette J. Communication of preferences for care among human immunodeficiency virus-infected patients. Barriers to informed decisions? *Arch Fam Med.* 1997;6(4):342-347.
22. Hutson SP. Climbing back up the mountain: reflections from an exploration of end-of-life needs of persons living with HIV/AIDS in Appalachian Tennessee. *Am J Hosp Palliat Care.* 2015;[Epub ahead of print].
23. Curtis JR, Patrick DL. Barriers to communication about end-of-life care in AIDS patients. *J Gen Intern Med.* 1997;12(12):736-741.
24. Karasz A, Dyche L, Selwyn P. Physicians' experiences of caring for late-stage HIV patients in the post-HAART era: challenges and adaptations. *Soc Sci Med.* 2003;57(9):1609-1620.
25. Curtis JR, Patrick DL, Caldwell ES, Collier AC. Why don't patients and physicians talk about end-of-life care? Barriers to communication for patients with acquired immunodeficiency syndrome and their primary care clinicians. *Arch Intern Med.* 2000;160(11):1690-1696.
26. Miles SH, Koepp R, Weber EP. Advance end-of-life treatment planning. A research review. *Arch Intern Med.* 1996;156(10):1062-1068.
27. Salmond SW, David E. Attitudes toward advance directives and advance directive completion rates. *Orthop Nurs.* 2005;24(2):117-127.
28. Rao JK, Anderson LA, Lin FC, Laux JP. Completion of advance directives among U.S. consumers. *Am J Prev Med.* 2014;46(1):65-70.
29. Dobalian A. Advance care planning documents in nursing facilities: results from a nationally representative survey. *Arch Gerontol Geriatr.* 2006;43(2):193-212.
30. Beck A, Brown J, Boles M, Barrett P. Completion of advance directives by older health maintenance organization members: the role of attitudes and beliefs regarding life-sustaining treatment. *J Am Geriatr Soc.* 2002;50(2):300-306.
31. Kiely DK, Mitchell SL, Marlow A, Murphy KM, Morris JN. Racial and state differences in the designation of advance directives in nursing home residents. *J Am Geriatr Soc.* 2001;49(10):1346-1352.
32. Colenda C, Jensen M, Foster J, Kendrick B, Mewhinny K, Messick C. Variables predicting the completion of an advance directive by older adults. *Ann Longterm Care.* 1998;6(3).
33. Gordon NP, Shade SB. Advance directives are more likely among seniors asked about end-of-life care preferences. *Arch Intern Med.* 1999;159(7):701-704.
34. Carrese JA, Rhodes LA. Western bioethics on the Navajo reservation. Benefit or harm? *JAMA.* 1995;274(10):826-829.
35. Caralis PV, Davis B, Wright K, Marcial E. The influence of ethnicity and race on attitudes toward advance directives, life-prolonging treatments, and euthanasia. *J Clin Ethics.* 1993;4(2):155-165.
36. Buckle JM, Horn SD, Oates VM, Abbey H. Severity of illness and resource use differences among white and black hospitalized elderly. *Arch Intern Med.* 1992;152(8):1596-1603.
37. Blackhall LJ, Murphy ST, Frank G, Michel V, Azen S. Ethnicity and attitudes toward patient autonomy. *JAMA.* 1995;274(10):820-825.
38. Eleazer GP, Hornung CA, Egbert CB, et al. The relationship between ethnicity and advance directives in a frail older population. *J Am Geriatr Soc.* 1996;44(8):938-943.
39. Morrison RS, Morrison EW, Glickman DF. Physician reluctance to discuss advance directives. An empiric investigation of potential barriers. *Arch Intern Med.* 1994;154(20):2311-2318.
40. Loue S. Living wills, durable powers of attorney for health care, and HIV infection. The need for statutory reform. *J Leg Med.* 1995; 16(4):461-480.
41. New York State Department of Health. Fact sheet: family health care decisions act and HIV/AIDS. https://www.health.ny.gov/diseases/aids/providers/regulations/fhcda/ai_fact_sheet.htm. Accessed on January 18, 2016.
42. The White House. Respecting the rights of hospital patients to receive visitors and to designate surrogate decision makers for medical emergencies. https://www.whitehouse.gov/the-press-office/presidential-memorandum-hospital-visitation. Accessed on January 18, 2016.
43. Riou, G. Hospital visitation and medical decision making for same-sex couples. https://www.americanprogress.org/issues/lgbt/news/2014/04/15/88015/hospital-visitation-and-medical-decision-making-for-same-sex-couples/. Accessed on January 18, 2016.
44. Liptak, A. Supreme court asked to look abroad for guidance on same-sex marriage. http://www.nytimes.com/2015/04/07/us/supreme-court-asked-to-look-abroad-for-guidance-on-same-sex-marriage.html?_r = 0. Accessed on January 18, 2016.
45. University of California San Francisco. ePrognosis: estimating prognosis for elders. http://eprognosis.ucsf.edu/. Accessed on January 18, 2016.
46. Sudore RL, Knight SJ, McMahan RD, et al. A novel website to prepare diverse older adults for decision making and advance care planning: a pilot study. *J Pain Symptom Manage.* 2014;47(4):674-686.

Top Antivir Med. 2016;23(5):174-180.

Guidelines for Authors and Contributors

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. The journal is indexed in Index Medicus/MEDLINE and is distributed to approximately 13,000 national and international subscribers.

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"at"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 publishers 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™* publishes 1 or 2 issues each year with a special focus, for example, summaries of IAS–USA continuing medical education courses and reports from scientific meetings. For example, the special issues on the Conference on Retroviruses and Opportunistic Infections (CROI), held annually, include one issue that summarizes coverage of major topics relating to HIV, HCV, and other viral infections and another that publishes all of the abstracts presented at the conference.

Online Articles. Occasionally articles are online only. They are distinguished from printed articles by pagination beginning with "e."

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 Street, Suite 1450
San Francisco, CA 94104-2120
E-mail: journal"at"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

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.*[1] This definition states: "Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.... Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship." *Topics in Antiviral Medicine™* will not consider ghostwritten articles for publication.

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 contribution. The complete financial disclosure statements for all authors and contributors are published with the articles.

1. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Updated December 2014. Available at http://www.icmje.org. Accessed January 31, 2016.

IAS–USA
425 California Street, Suite 1450
San Francisco, CA 94104-2120

IAS–USA Spring 2016 Courses

- Improving the Management of HIV Disease®: Full-Day Courses
  - New York, New York — Wednesday, March 23, 2016
  - Atlanta, Georgia — Friday, April 8, 2016
  - Washington, DC — Friday, April 15, 2016
  - Los Angeles, California — Monday, April 25, 2016
  - San Francisco, California — Friday, May 6, 2016
  - Chicago, Illinois — Monday, May 9, 2016
- Evolving Strategies in Hepatitis C Management: Small-Group Workshops
  - Atlanta, Georgia — Thursday, April 7, 2016
  - Washington, DC — Thursday, April 14, 2016
  - Los Angeles, California — Tuesday, April 26, 2016
  - San Francisco, California — Thursday, May 5, 2016

Some dates above may be subject to change. For detailed course information, agendas, and online registration, visit www.iasusa.org.