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Topics in Antiviral Medicine™

A publication of the IAS–USA

Perspectives CME

Topics in Antiviral Medicine™

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

- Discuss the control of HIV through natural immune responses, vaccine-mediated immunity, or passive immunotherapy with monoclonal antibodies, and implications for viral persistence and eradication
- Define barriers to and strategies for delivering preexposure prophylaxis to at-risk populations
- Identify common drug-drug interactions of direct-acting antiviral drugs for treatment of hepatitis C virus (HCV), especially in HIV/HCV-coinfected patients on antiretroviral therapy
- Describe the normal aging process and the epidemiologic and clinical characteristics of the older HIV-infected patient

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, and for those who are experienced in the principles of complex chemotherapy (eg, antiretroviral therapy) and are actively treating or will be treating patients with HCV infection.

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

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Friday, October 16, 2015
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Little Rock, Arkansas
Friday, September 11, 2015
Arkansas Department of Health
Registration: $50

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Tuesday, September 22, 2015
New York Marriott Marquis
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Philadelphia, Pennsylvania
Thursday, October 22, 2015
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Perspective

What Will It Take to Cure HIV?

Investigational strategies to attempt HIV cure or remission include very early initiation of antiretroviral therapy to limit the latent HIV reservoir and preinfection vaccination. In the setting of viral suppression, strategies include reactivation of latently infected cells (eg, through "shock" therapy with histone deacetylase inhibitors or other agents); use of broadly neutralizing antibodies, therapeutic vaccines, immunotoxins, or other immune-based therapies to kill latently infected cells; and gene editing to induce target cell resistance (eg, by eliminating the CC chemokine receptor 5 [CCR5] coreceptor). Improved ability to detect and quantify very low levels of virus is needed. This article summarizes a presentation by Jintanat Ananworanich, MD, PhD, at the IAS–USA continuing education program held in New York, New York, in October 2014.

Keywords: HIV, cure, remission, viral reservoir, latent infection

HIV cure research currently focuses on 2 goals: complete eradication of HIV from the body and HIV remission. During remission, virus can still be detected at low levels in cells or through ultrasensitive testing in plasma, but antiretroviral therapy is not necessary unless continued monitoring reveals increased viremia.

Cases of Remission and Effects of Antiretroviral Therapy in Infants With Early Acute HIV Infection

Timothy R. Brown, also referred to as the Berlin patient, remains the only known person in whom HIV appears to be eradicated. Brown stopped taking antiretroviral therapy approximately 7 years ago and has had no detectable virus capable of replicating since. The mechanism of the possible eradication in this case included bone marrow transplantation with cells lacking the CC chemokine receptor 5 (CCR5) coreceptor, rendering the cells resistant to HIV infection. Two other patients, referred to as the Boston patients, experienced HIV remission 3 months and 7 months, respectively, after receiving bone marrow transplantation with cells that included the CCR5 coreceptor. The HIV-infected Mississippi baby, born to an HIV-infected mother who did not receive antiretroviral therapy, began antiretroviral therapy at 30 hours after birth. HIV infection was confirmed and the infant achieved viral suppression 1 month after starting treatment. Treatment was stopped after 18 months because the child was lost to follow-up care, and no virus was detected for a subsequent 27 months. In mid-2014, the child's plasma HIV RNA level rebounded to 10,000 copies/mL to 16,000 copies/mL, and it was subsequently determined that HIV RNA level had increased to 9 copies/mL 2 weeks before the rebound.[1-4]

There have been several other cases of infants who received antiretroviral therapy during early acute HIV infection, resulting in the absence of detectable virus. An HIV-infected baby in California who received antiretroviral treatment at 4 hours after birth continued therapy for 14 months with no detectable cellular or plasma virus. Four HIV-infected Canadian babies who received antiretroviral treatment within their first 24 hours have remained on treatment for 2.5 years to 7 years with no detectable virus. Another Canadian baby who received antiretroviral treatment within 24 hours of birth had no detectable virus during 3 years of treatment but exhibited viral rebound 2 weeks to 3 weeks after stopping treatment. Similarly, an HIV-infected baby in Milan began antiretroviral treatment 12 hours after birth and had no detectable virus for 3 years while receiving treatment but exhibited viral rebound 2 weeks to 3 weeks after stopping treatment.[5-9]

In general, it is believed that earlier initiation of antiretroviral therapy and the longer it is maintained improve the chance of limiting the viral reservoir and achieving HIV remission. However, among the infants who eventually exhibited rebound after stopping antiretroviral therapy, time to viral rebound was longest for the Mississippi baby despite a later start of therapy (30 hours) than the Canadian baby (< 24 hours) or the Milan baby (12 hours) and a shorter duration of therapy (18 months, 3 years, and 3 years, respectively). The baseline HIV RNA level of the Mississippi baby (19,812 copies/mL) was between that of the Canadian baby (808 copies/mL) and the Milan baby (152,560 copies/mL). The Mississippi baby's longer remission period might be partially explained by the shorter duration of antiretroviral therapy before an HIV RNA level of less than 50 copies/mL was achieved (1 month of therapy for the Mississippi baby vs 6 months for the Canadian baby and 3 months for the Milan baby).

Testing performed while the Mississippi baby was in remission and was not taking antiretroviral therapy and the Milan baby and Canadian baby were taking antiretroviral therapy showed that whereas all 3 had negative test results for HIV DNA in peripheral blood, replication-competent virus, and anti-HIV antibody, the Canadian baby and the Milan baby displayed evidence suggestive of ongoing viral replication. The Milan baby had detectable HIV-specific T cells and a high percentage of activated T cells, and the Canadian baby had detectable cell-associated HIV RNA

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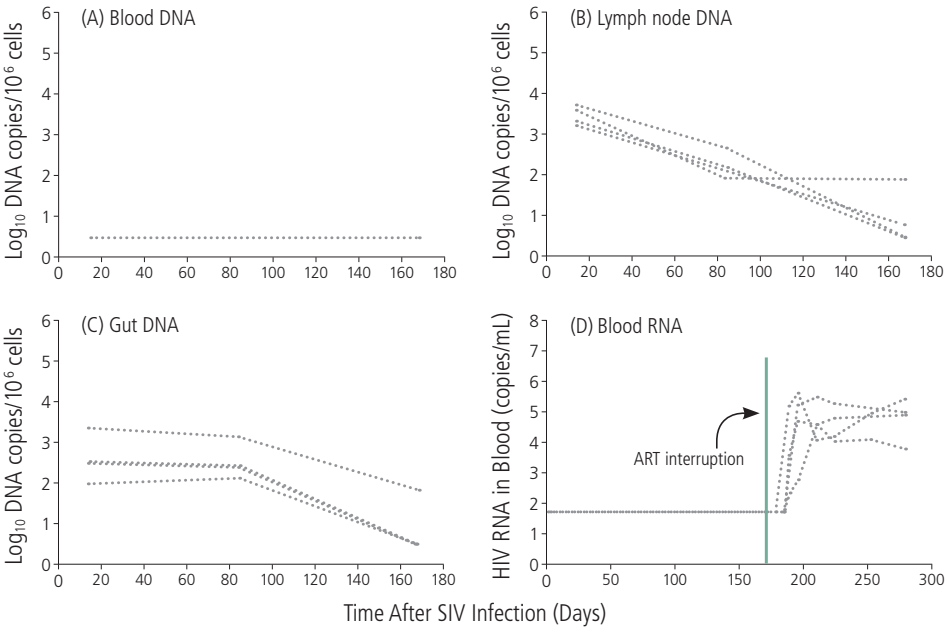

Figure 1. Simian immunodeficiency virus (SIV) proviral DNA was detected in the lymph nodes (B) and gut (C) but not in peripheral blood (A) after antiretroviral therapy (ART) was initiated in macaques 3 days after infection. All macaques had detectable blood HIV RNA after interruption of ART (D). Adapted from Whitney et al.[11]

levels; these findings were not present in the Mississippi baby.[2,5,8]

These cases of transient HIV remission also show how current tools are limited in their ability to detect low numbers of HIV-infected cells. Acute HIV infection is associated with low levels of HIV DNA, which are further reduced by antiretroviral therapy during early acute infection to levels that may be undetectable. Currently, whether virus is present or in what amount it is present cannot be determined below the detection limits of current assays. Potential methods for measuring ongoing viral replication in the reservoir include measurement of cell-associated HIV RNA, single-copy HIV RNA, and replication-competent virus using viral outgrowth assays. Recently, it has been shown that the replication-competent HIV reservoir may be 60 times greater than what is currently measured by viral outgrowth assay, as there are viruses that are intact but not induced by this method.[10] Investigators are examining the use of inducible HIV RNA assays to activate HIV-infected cells, in an attempt to measure reservoirs capable of replicating.

Is Early Antiretroviral Therapy Crucial to Limiting HIV Persistence?

Initiation of antiretroviral therapy in macaques 3 days after establishment of simian immunodeficiency virus (SIV) infection resulted in undetectable proviral DNA levels in peripheral blood but not in the lymph nodes or gut, with DNA levels at these sites declining during 6 months of treatment (Figure 1).[11] Viral rebound was observed when antiretroviral treatment was stopped, suggesting that seeding of the viral reservoir begins very early and that initiation of treatment at 3 days in this animal model is not early enough to prevent it.

The size and composition of the latent HIV reservoir are affected by early antiretroviral therapy. In basic CD4+ cell differentiation, stimulation of naive CD4+ cells by antigens causes them to differentiate into memory CD4+ cells that consist of stem cell, central, transitional, and effector memory CD4+ cells. The shorter-lived transitional and effector memory cells are more likely to differentiate into terminally differentiated cells and then die, whereas central memory cells are longer lived and constitute a latently infected cellular reservoir during HIV infection. During chronic HIV infection, the latent reservoir is large and central memory CD4+ cell infections still constitute a major part of the latently infected cell pool even after years of antiretroviral therapy. The reservoir size is much smaller during acute HIV infection, with years of antiretroviral therapy resulting in a marked decrease in latently infected cells.

Levels of integrated HIV DNA were examined among HIV-infected patients in Thailand who started antiretroviral therapy within 2 weeks of infection, within 3 weeks to 4 weeks of infection, or during chronic infection, and had plasma viral loads below detection limits at 2 years.[12] Starting treatment within the first 2 weeks of infection resulted in much lower levels of integrated HIV DNA in all CD4+ cell subsets than when antiretroviral therapy was initiated during chronic HIV infection, and persistence of the viral reservoir was intermediate among patients starting antiretroviral therapy at 3 weeks to 4 weeks after infection.

Studies in the VISCONTI (Virological and Immunological Studies in Controllers After Treatment Interruption) cohort of posttreatment controllers—a group of 14 patients in France who started antiretroviral therapy early and exhibited control of viremia after interrupting treatment for 6 years or more—showed that early treatment could skew the distribution of latently HIV-infected cells to shorter-lived transitional memory cells that may be more rapidly cleared by the immune system (Figure 2).[13]

Strategies to Eliminate HIV Persistence

One HIV remission and cure strategy currently under investigation is pre-infection vaccination. In a study of 16 macaques, a cytomegalovirus (CMV)-vector SIV vaccine given prior to SIV infection did not prevent infection but did result in control of viremia in 9 macaques and in SIV eradication in 8 macaques, with no evidence of virus in

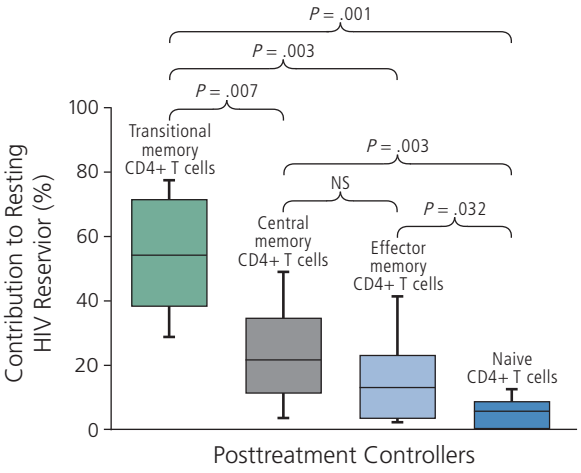

Figure 2. The HIV reservoir skewed to shorter-lived transitional memory cell subsets in the VISCONTI (Virological and Immunological Studies in Controllers After Treatment Interruption) cohort of posttreatment controllers. NS indicates not a statistically significant difference. Adapted from Saez-Cirion et al.[13]

organs or blood in the latter group.[14] This response likely reflects the ability of the replicating CMV vector to generate ongoing immune responses. In responding animals, the vaccine was able to generate a very rapid early mucosal immune response that contained the virus before drastic systemic spread of infection. Further, immune response was not limited to immune-dominant epitopes, with the broadness of response preventing viral escape.

A prime-boost adenovirus 26 and modified vaccinia virus Ankara (MVA) vaccine resulted in control of SIV viremia in 3 of 8 macaques. Control of viremia was associated with a broad CD8+ cell response and neutralizing antibody response.[15] This vaccine for HIV will be investigated in patients starting antiretroviral therapy during early acute HIV infection, to determine whether it may help them achieve HIV remission.

Another remission strategy, in the setting of suppressed HIV viral load, is the use of "shock" therapy to activate latently infected cells to produce virus. In a study using the histone deacetylase (HDAC) inhibitor romidepsin as shock therapy, reactivation of HIV was observed but was not accompanied by a reduction in HIV DNA level, indicating that few, if any, HIV-infected cells were killed after reactivation.[16]

Strategies to kill latently HIV-infected cells include use of broadly neutralizing antibodies and vaccines. Broadly neutralizing antibodies bind cell-free virus and might clear infected cells. In one study, administration of 1 or 2 doses of the broadly neutralizing monoclonal antibody PGT121 to macaques with low baseline chimeric SIV/HIV (SHIV) viral load resulted in remission of virus for more than 1 year, long after PGT121 was no longer detectable in the blood.[17] Numerous such monoclonal antibodies are being investigated for use in humans. A study of monoclonal antibody VRC01 administered during acute HIV infection is planned, and the AIDS Clinical Trials Group (ACTG) network is planning a study of this antibody in chronically HIV-infected patients.

Immunotoxins may also be used to kill HIV-infected cells, particularly in tissue. When this strategy was previously assessed as monotherapy it was ineffective, but it has since produced promising results when used in combination with antiretroviral therapy. A study in humanized mice showed a marked reduction in HIV RNA-positive cells in tissue when a combination of an immunotoxin with a pseudomonas endotoxin and antiretroviral therapy was used (Figure 3).[18]

Inducing resistance to HIV infection in cells has been examined by using gene therapy to eliminate CCR5 coreceptor. In one study, HIV-infected patients underwent leukapheresis and their cells underwent gene editing with zinc finger nucleases to remove CCR5 genes. Modified cells that no longer expressed CCR5 were then proliferated and reinfused into the same patient. HIV DNA levels were reduced but interruption of antiretroviral therapy resulted in viral rebound in all patients. However, viral rebound was followed by spontaneous control of virus in 1 patient who was heterozygous for the CCR5 gene and who exhibited the highest level of engraftment of the modified cells (see Tebas et al, 2014[19]). Studies are currently examining additional doses of the modified cells and use of chemotherapy preconditioning to improve engraftment.

Summary

HIV cure strategies currently being examined in human studies (Figure 4[20]) begin with minimizing the HIV reservoir through early antiretroviral therapy and use of broadly neutralizing antibodies. Once viral load is suppressed, latently infected cells can be reactivated (eg, with HDAC inhibitors or activation of toll-like receptors or protein kinase C) and immune-based

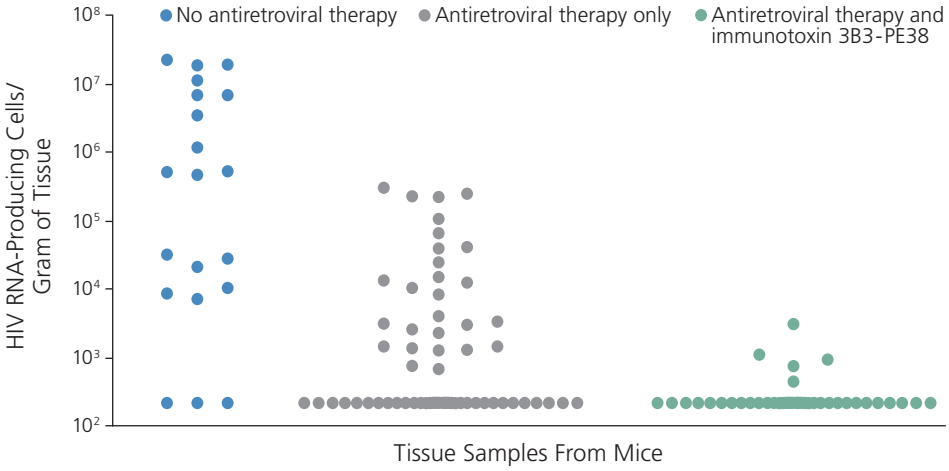

Figure 3. Effects of immunotoxin 3B3-PE38 combined with antiretroviral therapy on HIV RNA in tissue in mice. Adapted from Denton et al.[18]

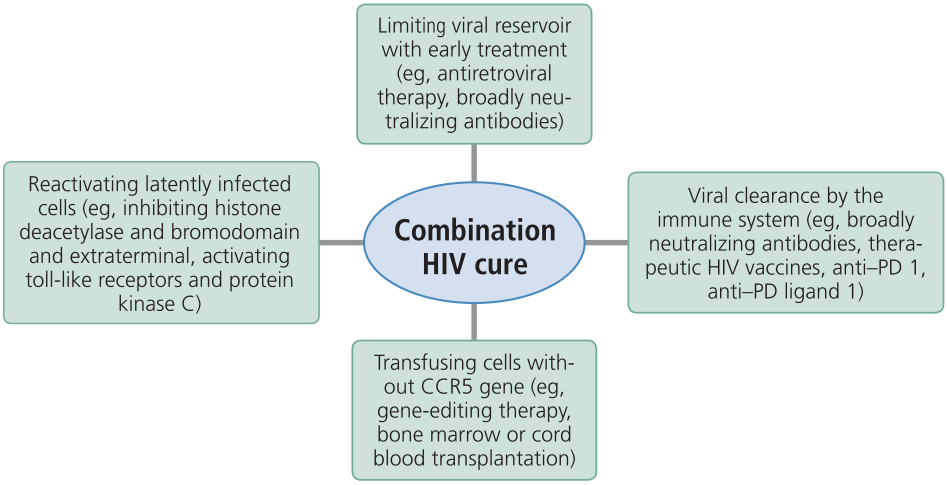

Figure 4. Different HIV cure strategies currently used in human studies that may need to be combined in order to achieve HIV remission. CCR5 incidates CC chemokine receptor 5; PD, programmed cell death.[20]

therapies (eg, broadly neutralizing antibodies, therapeutic vaccines, or anti–programmed cell death [PD] 1 and anti–PD ligand 1 agents) can be used to kill HIV-infected cells, or cells can be made resistant to HIV (eg, transfusion with CCR5-negative cells). Achieving meaningful HIV remission or cure will almost certainly require combined treatments rather than single approaches.

Testing to determine if HIV remission or cure has been achieved is challenging. Treatment cessation is the ultimate test of HIV remission, and ensuring safety requires frequent monitoring of viral load and a low threshold for restarting treatment.[21] In some planned studies, viral load will be measured every 3 days to 7 days and treatment will be restarted with viral recrudescence. Many of the drugs being tested for HIV cure are cancer drugs with potential toxic efftects and many require intravenous infusion. Studies of the various HIV cure strategies will be a major burden to patients, requiring frequent follow-up, blood draws, and tissue sampling. Because there are many proposed treatments in the pipeline and because combination treatments will be needed, novel study designs to quickly move from demonstrating safety of individual therapy to assessing combination therapy for efficacy will be crucial. It will also be crucial to optimize the tools used to measure the HIV reservoir in tissue and blood.

In conclusion, SIV and HIV eradication has thus far been achieved via a CMV vector vaccine that maintained an effector T–cell response against SIV and via bone marrow transplantation utilizing CCR5-negative cells (the Berlin patient[1]). Early antiretroviral therapy is currently the most effective strategy to limit establishment of the HIV reservoir. Complete eradication of HIV will be difficult or impossible to achieve in the near future. HIV remission is a more attainable goal that will require testing of combination therapies to reduce the size of the HIV reservoir and boost HIV-specific immunity. In this early stage of HIV cure research, there will be many disappointments, but it is important to iteratively learn from these and steadily move the field forward.

Presented by Dr Ananworanich in October 2014. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Ananworanich in March 2015. The views expressed are those of the authors and should not be construed to represent the positions of the US Army or the Department of Defense.

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www.HCVguidelines.org

- Developed by a panel of experts in the field.
- Provides practitioners with regularly updated, evidence-based, consensus recommendations for screening, treating, and managing patients with HCV.
- Assists practitioners in treating the estimated 3 to 4 million Americans infected with HCV by highlighting the latest information in improved diagnostics and new drug options as they meet FDA approval.
- Offers guidance to practitioners about how to best use the next generation of direct-acting antivirals and other treatment options in the care of their patients.

Recommendations for Testing, Managing, and Treating Hepatitis C

Recommendations for Testing, Managing, and Treating Hepatitis C is a website sponsored by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in collaboration with the International Antiviral Society–USA (IAS–USA) to provide the most current guidance for the treatment of hepatitis C virus (HCV) infection.

Sections of the AASLD/IDSA/IAS–USA HCV Guidance were recently updated based on new data presented at the 50th International Liver Congress of the European Association for the Study of the Liver (EASL). Visit www.HCVguidelines.org to review the latest updates.

Available Sections:

- HCV Testing and Linkage To Care
- When and in Whom to Initiate HCV Therapy
- Initial Treatment of HCV Infection
- Retreatment of Persons in Whom Prior Therapy Has Failed
- Monitoring Patients Who Are Starting Hepatitis C Treatment, Are on Treatment, or Have Completed Therapy
- Unique Patient Populations
  - Patients With HIV/HCV Coinfection
  - Patients With Decompensated Cirrhosis
  - Patients Who Develop Recurrent HCV Infection Post–Liver Transplantation
  - Patients With Renal Impairment
- Management of Acute HCV Infection

Perspective

Preexposure Prophylaxis For HIV Prevention: What We Know and What We Still Need to Know for Implementation

Preexposure prophylaxis (PrEP) with tenofovir and emtricitabine has been shown to be effective and cost-effective in preventing acquisition of HIV infection. However, PrEP has not yet been widely adopted in the clinical practice setting. Data thus far, although imperfect, do not indicate an increase in risk behaviors in the setting of PrEP, although potential risk compensation outside of the clinical trial setting should be further examined. Substantial work remains to implement and support PrEP use, including identification of optimal settings for providing and managing PrEP, identification of methods to ensure optimal adherence to treatment, and employment of strategies to deliver PrEP to populations at greatest risk. This article summarizes a presentation made by Raphael J. Landovitz, MD, MSc, at the 2015 Conference on Retroviruses and Opportunistic Infections held from February 23 to February 26 in Seattle, Washington.

Keywords: HIV, PrEP, preexposure prophylaxis, tenofovir, emtricitabine, adherence, risk compensation, PrEP uptake, resistance

Despite the availability of a robust portfolio of prevention tools, there are still approximately 6000 new HIV infections daily worldwide (Figure 1).[1] Preexposure prophylaxis (PrEP) is an important tool in the fight against HIV, but much work remains to increase PrEP uptake and optimize the preventive yield of this strategy.

PrEP With Tenofovir and Emtricitabine

Fixed-dose tenofovir and emtricitabine (tenofovir/emtricitabine) was approved by the US Food and Drug Administration (FDA) for use in HIV prevention in July 2012 and remains the only available FDA-approved regimen for PrEP.[2]

Tenofovir/emtricitabine possesses a number of advantageous characteristics for PrEP, including a relatively high barrier to resistance, rapid concentration in genital and rectal tissues, and a long intracellular half-life. Use in nonhuman primate models suggests that tenofovir/emtricitabine confers greater protection than tenofovir alone, that tenofovir-based PrEP confers protection against HIV exposure via various mechanisms of action, and that oral tenofovir concentrates less well in cervicovaginal tissues than in rectal tissues—a finding with important implications for forgiveness of nonadherence to PrEP in the context of vaginal HIV exposure.[3-5] These models also indicate that intermittent dosing might be protective, suggesting the feasibility of on-demand use for some populations.[6]

In addition to being potent inhibitors of viral reverse transcriptase, tenofovir/emtricitabine may reduce inflammation and immune activation. A study by Castillo-Mancilla and colleagues showed decreased HLA-DR and CD38 expression in CD8+ lymphocytes and decreased levels of soluble CD14 and soluble CD27 in uninfected volunteers who received tenofovir/emtricitabine daily for 30 days followed by a washout period of more than 30 days.[4]

PrEP was developed based on the observation that a crucial aspect of the efficacy of postexposure prophylaxis (PEP) is the time from HIV exposure to the first dose of antiretroviral medication. Efficacy is maximized as the time between exposure and PEP initiation approaches zero. The time sensitivity of PEP efficacy suggested that minimizing the time between exposure and PEP initiation could be achieved by having antiretroviral medication already present in relevant tissues by the time the HIV exposure occurred. This is similar to malaria prevention strategies, which may include use of a chemoprophylactic agent before, during, and after an unintended exposure to the infectious agent. Such preclinical and clinical observations led to human trials and, ultimately, to 5 phase III randomized controlled trials of oral PrEP.

The first such study, the iPrEx (Chemoprophylaxis for HIV Prevention in Men) study, enrolled a global population of men who have sex with men (MSM) and transgender women, randomly assigning participants to receive oral tenofovir/emtricitabine or a placebo daily and providing comprehensive HIV prevention services to each group. In 2010, the results from the iPrEX study were published, demonstrating a 42% reduction in incident HIV infections among individuals who were administered a daily oral regimen of tenofovir/emtricitabine.[7,8] Chronologically, the next milestone in PrEP development was the FEM-PrEP (Preexposure Prophylaxis Trial for HIV Prevention Among African Women) trial, which was designed similarly to the iPrEx study and showed a 6% effectiveness rate of PrEP among uninfected women in Kenya, South Africa, and Tanzania.[9]

The Centers for Disease Control and Prevention (CDC)-sponsored TDF2 trial evaluating tenofovir/emtricitabine in heterosexual men and women in Botswana showed a 62% overall protection rate, including 80% in men and 49% in women.[10] Importantly, the subset analysis in women did not show a statistically significant difference in PrEP effect compared with placebo in this study. The Partners PrEP trial conducted among HIV-serodiscordant heterosexual couples in Kenya and Uganda provided the first statistically

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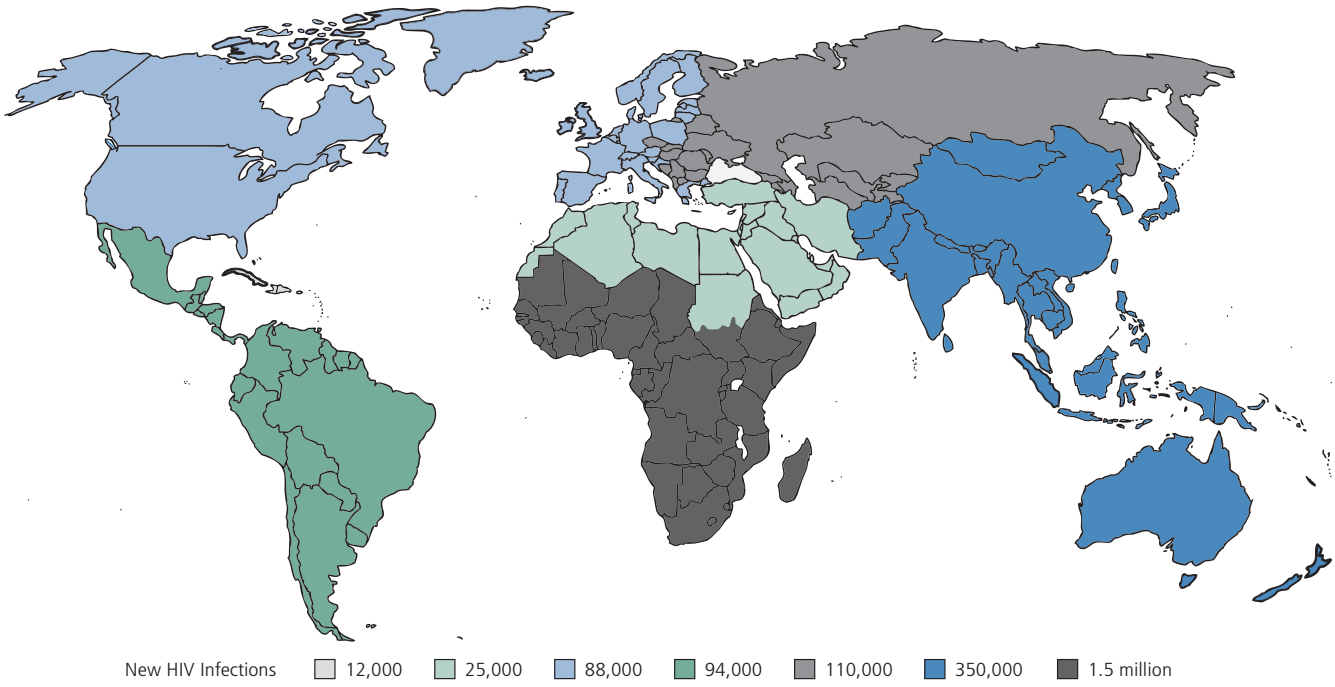

Figure 1. Annual new HIV infections in 2013. Adapted from the Joint United Nations Program on HIV/AIDS.[1]

significant demonstration of PrEP effectiveness for both men and women, with a protective efficacy rate of 63% in women and 71% in men with tenofovir alone, and 66% in women and 84% in men with tenofovir/emtricitabine.[11] The VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial evaluating oral and vaginal tenofovir gel and tenofovir/emtricitabine in women showed no preventive benefit of any of the oral or topical PrEP strategies.[12]

The discrepant results of the trials are at least partly explained by differences in adherence. There is a strong correlation between preventive effectiveness and levels of active drug detected in plasma and cellular samples from PrEP study participants (Figure 2). Studies of single-dose PrEP have shown that levels of tenofovir in rectal tissue are approximately 10 to 100 times higher than those in cervicovaginal tissue, which may help explain the difference in efficacy results between men and women even when adherence rates appear similar.[5] Understandably, the wide range of effectiveness estimates from phase III trials has resulted in confusion among practitioners and patients. Although subject to inherent limitations, models and subset analyses based on these data provide some clarity regarding the level of adherence needed to achieve high protective effectiveness. A modeled analysis of data from the iPrEx trial suggests that a 99% rate of preventive effectiveness (confidence interval [CI], 96%-99%) in cases of rectal exposure is achievable in men when PrEP with tenofovir/emtri-citabine is taken 7 days per week as prescribed.[13] An analysis of women in the Partners PrEP trial who had plasma tenofovir levels suggestive of steady state daily dosing indicated that 6 to 7 daily doses of tenofovir/emtricitabine per week could achieve a 94% rate of effectiveness (CI, -17% to 100%) in cases of vaginal exposure.[14,15]

PrEP Uptake

PrEP has not been widely adopted despite strong evidence of its preventive effectiveness. Some of the delay in uptake may be caused by competing priorities and limited resources. However, PrEP raises concerns that undoubtedly contribute to its slow uptake. There is concern that PrEP will lead to decreased condom use, increased numbers of sexual partners, and increased numbers of sexually transmitted infections (STIs), including HIV infections—so-called risk compensation. There are also concerns about emergence of resistant virus that could compromise subsequent dosing options, about how quickly protection is achieved and how durable it is after cessation of treatment, and about safety, particularly in diverse populations that are not well represented in phase III clinical trials. More data are needed to determine the best settings and contexts in which to administer PrEP, and the best ways to measure and maximize adherence to prescribed PrEP regimens; to assess if less than daily dosing of PrEP with tenofovir/emtricitabine can confer protection and to whom PrEP should be targeted; to determine if better options are coming; and, perhaps most importantly, to determine if PrEP can be made available to and be used by individuals at the greatest risk.

Risk Compensation

With risk compensation there is the concern that PrEP users will increase their risk behaviors in the setting of imperfect preventive effectiveness, thus increasing the risk of HIV infection at the individual and population levels. Modeling of the potential effects of risk

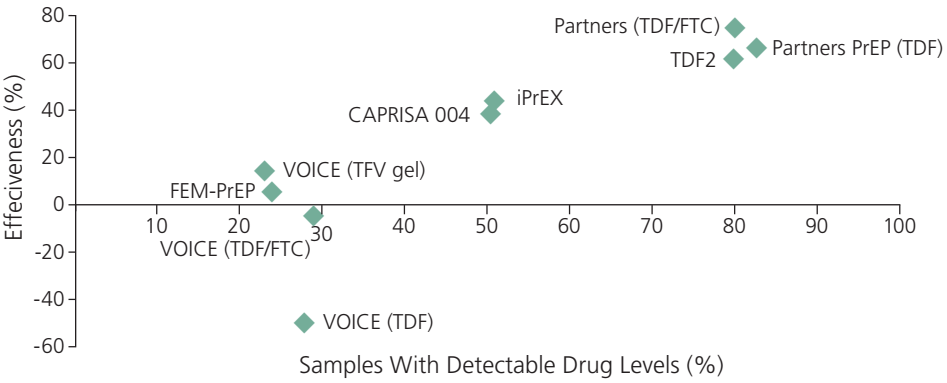

Figure 2. Relationship between effectiveness and adherence in preexposure prophylaxis (PrEP) and microbicide trials (Pearson correlation, 0.86; $P = .003$). CAPRISA indicates Centre for the AIDS Programme of Research in South Africa; FEM-PrEP, Preexposure Prophylaxis Trial for HIV Prevention Among African Women; FTC; emtricitabine; iPrEx, Chemoprophylaxis for HIV Prevention in Men; TDF, tenofovir disoproxil fumarate; TFV, tenofovir; VOICE, Vaginal and Oral Interventions to Control the Epidemic. Adapted from AIDS Vaccine Advocacy Coalition (AVAC).[36]

compensation in resource-limited settings showed that increases in risk behaviors at higher levels of preventive effectiveness of PrEP could maintain substantial reductions in numbers of new infections at the population level; however, an increase in risk behaviors would be expected to be associated with a population-level increase in new HIV infections at lower levels of preventive effectiveness.[16]

Primary analyses of data from phase III trials of PrEP did not show evidence of risk compensation, a finding that is likely attributable to the provision of combination HIV prevention interventions regardless of randomized medication assignment and to the use of placebos in the trials' designs. Studies of other prevention modalities (eg, antiretroviral therapy as prevention, vaccines, and voluntary male circumcision) have yielded inconsistent data on risk compensation, including increases in risk behaviors in some vaccine trials, trials of voluntary male circumcision, and studies of antiretroviral therapy as prevention.[17-19] In addition, the occurrence of risk compensation is suggested by increases in rates of STIs, particularly syphilis, among HIV-infected MSM since the widespread adoption of antiretroviral therapy. Although early data from open-label extensions of phase III trials of PrEP have generally supported decreases in risk behaviors when PrEP is used in the context of combination prevention services, a secondary analysis of the Partners PrEP study showed that an overall decrease in risk behaviors during the blinded phase of the trial was followed by an increased trajectory of risk behaviors—measured as number of nonprimary sexual partners—after determination of PrEP efficacy and unblinding of treatment assignment to study participants.[20] Further, it was reported at an October 2014 forum on PrEP sponsored by the San Francisco Department of Public Health that in a subset of a large PrEP cohort in Northern California, 45% of individuals reported reduced condom use in association with PrEP use.

Viral Resistance

Perhaps the most contentious issue in the field of PrEP is the potential for emergence of viral resistance when HIV seroconversion occurs in the context of PrEP use. Various models have yielded conflicting predictions, ranging from doubling of or greater rates of transmitted resistance to an extremely limited impact on circulating resistant species.[21,22]

Data from phase III trials suggest that HIV seroconversion with resistant virus is quite rare. PrEP use, in the context of the monthly HIV testing performed in the studies, conferred sufficient protection to prevent HIV acquisition or was used sufficiently infrequently such as to be permissive of HIV acquisition without maintaining sufficient drug levels to select for resistant quasispecies of virus. Analyses of trial populations indicated the presence of the tenofovir-resistant mutation K65R or K70E or the emtricitabine-resistant mutation M184V/I in 0 of 36 participants who seroconverted in the active arm of the iPrEx study, in 4 of 51 participants in the active arm of the Partners PrEP study, in 0 of 10 participants in the active arm of the TDF2 study, in 4 of 33 participants in the active arm of the FEM-PrEP study, and in 1 of 113 participants in the active arm of the VOICE study. In these trials, there was a total of 9 (3.7%) cases of resistance among 243 serocoverters, or 5 (2.0%) cases when transmitted resistance was excluded; this total is equivalent to seroconversion with resistant quasispecies in 0.06% of persons exposed to tenofovir-based PrEP.[7,9-12,23-25] The M184V/I mutation was the most common and was associated with resistance to emtricitabine and lamivudine.

However, now that clinical protocols will allow for greater intervals between HIV tests, it will be important to monitor rates of occult HIV acquisition in the absence of PrEP use followed by resumption of PrEP use prior to occult infection diagnosis. Data suggest that administration of PrEP with tenofovir/emtricitabine in the setting of occult primary (acute) HIV infection carries an extremely high risk of generating resistance—more than 25% in aggregate across randomized studies. For this reason, clinical exoneration of acute or primary HIV infection, or use of viral load screening prior to PrEP initiation in high-risk patients is prudent.

Onset and Offset of Effect

Modeling using pharmacokinetic data that correlate tenofovir levels in peripheral blood mononuclear cells (PBMCs) with risk reduction observed in iPrEx study participants with similar levels

of tenofovir in PBMCs estimates that a 99% risk reduction is achieved after approximately 5 daily doses of tenofovir/emtricitabine and that a greater than 90% risk reduction persists up to 7 days after stopping drug from steady state.[26] After 7 days, protection would be expected to drop off precipitously. These estimates are based on daily dosing and apply to rectal HIV exposures only. Vaginal exposures have not been similarly modeled, although levels thought to be protective in cervicovaginal tissues, if in fact such levels are the crucial parameter for protection, are not achieved until after approximately 3 weeks of daily dosing with tenofovir/emtricitabine.

Safety

In general, tenofovir/emtricitabine is well tolerated in uninfected individuals. Three broad categories of adverse events are notable. A gastrointestinal "start-up syndrome" was observed in up to 18% of participants in 3 of the 5 phase III PrEP trials mentioned above but was usually self-limited and did not commonly result in PrEP discontinuation. Nephrotoxicity, an expected complication based on experience with tenofovir-based antiretroviral regimens in HIV-infected populations, was observed at grade 2 or higher in only 0.2% of nearly 5500 participants (no observed cases of Fanconi syndrome) randomly assigned to receive tenofovir/emtricitabine; all cases resolved after withdrawal of tenofovir/emtricitabine. Loss of up to 1.5% of bone mineral density (BMD) was observed during PrEP with tenofovir/emtricitabine, with some reversal of the trend observed after withdrawal of the drug. The observed changes in BMD were not associated with increased fracture risk.

These data represent adverse event rates in the setting of imperfect adherence to PrEP and relatively short follow-up periods. Optimal adherence could result in a greater frequency of adverse events. Evaluation of adverse event profiles of PrEP in diverse populations, some of which may already have a disposition toward renal or bone complications, will be important.

Supporting Adherence

Given that maximal protection is provided by daily dosing of tenofovir/emtricitabine, support for adherence is an important component of PrEP services. The most common approach to adherence support has been next-step counseling, which is a brief, theory-based intervention that uses a manualized intervention derived from motivational interviewing.[27] In 2014, the CDC distilled adherence support down to 3 topics for ease of clinician delivery: asking how patients have remembered to take past medications, asking if patients have had any difficulty taking their pills, and asking about what has been most helpful for reminding patients to take their medications.[28]

Investigational techniques to promote adherence include customized text messaging, such as a platform currently being evaluated by the California Collaborative Treatment Group (CCTG), and smart devices, such as an electronic pill case that provides an opportunity for real-time monitoring of dose taking and for interventions when doses are missed. Additional technologies, such as "smart" pill bottles that have a variety of adherence support strategies built in to them are in development.

A research group in Los Angeles, California, is currently completing enrollment of a demonstration project that will use real-time measurement of plasma tenofovir levels to support adherence among 375 MSM and transgender women at 2 community-based sites. Undetectable plasma levels will be used as a trigger for escalation of adherence support. This study will include a substudy of vitamin D and calcium supplementation in an attempt to mitigate loss of BMD.

Implementation and Scale-Up

Cost-effectiveness models of PrEP in a variety of populations emphasize that cost-effectiveness is greatest when PrEP is targeted to those with the highest risk of HIV acquisition. Buchbinder and colleagues showed that optimal targeting of PrEP—defined as targeting of populations with the lowest number needed to treat per HIV infection averted—for MSM and transgender women in the iPrEx study, was aimed toward those who reported engaging in condomless receptive anal intercourse in the past 3 months, having an STI in the past 6 months, or using cocaine in the past month.[29] In the iPrEx Open-Label Extension (OLE) study, 76% of the participants opted to take open-label PrEP at some point during follow-up, and higher-risk individuals were more likely to opt to take PrEP, suggesting good intervention targeting.[30] Participants whose tenofovir levels suggested adherence at an average of 4 or more doses per week had no seroconversions, with adherence again being higher in higher-risk individuals. Consistent with the comprehensive package of prevention services provided as part of the iPrEx OLE study, risk behavior decreased over time for all participants, whether or not they were taking tenofovir/emtricitabine as PrEP.

In the 3-city US PrEP Demonstration Project study, which evaluated individuals who were self-referred or referred by a practitioner for PrEP in community settings in San Francisco, California, Washington, DC, and Miami, Florida, 60% of referred individuals were interested in enrolling in the study and taking tenofovir/emtricitabine-based PrEP.[31,32] Of these individuals, between 80% and 100% maintained maximally protective mean adherence levels of at least 4 doses per week over 48 weeks of observation.

With regard to PrEP uptake outside the clinical trial setting, modeling performed by Grant and colleagues at the San Francisco AIDS Foundation has shown that based on known rates of HIV diagnoses, viral suppression, serosorting behavior, and uptake and persistence of PrEP among MSM and transgender women in San Francisco, uptake of PrEP is approximately one-third of that needed to achieve a 70% reduction in annual HIV infections.[33]

At present, there is no consensus among practitioners and policymakers regarding the optimal setting for

deploying PrEP in clinical practice. Krakower and colleagues refer to "the purview paradox" to describe the differing perspectives of HIV and primary care practitioners regarding the responsibility of PrEP prescribing.[34] Primary care practitioners are more likely to encounter at-risk individuals before HIV acquisition and often have the best longitudinal relationships with patients, but they may be less comfortable with the management of antiretroviral medications and their adverse effects and with the testing necessary to evaluate acute and chronic HIV disease. There may also be competing priorities in primary, acute, and preventive care that make a complex and possibly uncomfortable discussion with patients regarding sexual practices seem impractical. HIV practitioners, on the other hand, are familiar with antiretroviral drugs and their management, but may be less likely to encounter patients before seroconversion. In addition, HIV practitioners often have overburdened practices and often see patients in locations identified and stigmatized as catering to individuals already living with HIV or AIDS.

Although the optimal setting for PrEP delivery remains to be defined, there is considerable progress in attempts to create suitable infrastructure. Local jurisdictions are developing lists of practitioners who prescribe PrEP, such as that solicited by the Commissioner of Health in New York City. Consumers and practitioners are using the Internet to crowdsource practitioner referrals, troubleshoot operational impasses, and share novel science: a moderated "PrEP Facts" Facebook page has been created to serve as a trusted mechanism for such innovation. Community-based organizations have developed informational materials for PrEP users, including tips and strategies for educating practitioners on PrEP use and monitoring. The University of California San Francisco Clinicians Consultation Center has expanded its scope from PEP and prevention of mother-to-child transmission to include PrEP, and the Mississippi Department of Public Health has debuted a PrEP information hotline. The CDC and the World Health Organization have issued formal clinical guidance for practitioners regarding PrEP.[28,35] Some community-based organizations have created user-friendly materials to further streamline clinical processes for practitioners who may find formal guidelines overwhelming. New York City has developed academic detailing methods and has already detailed 900 clinical practices to educate providers, and has also developed implementation seminars to educate clinics on the operational details of providing PrEP services.

Despite evidence of cost-effectiveness when PrEP is appropriately targeted, PrEP users in the United States still struggle to piece together coverage of medication costs and associated testing and services. Private insurance will often provide coverage for PrEP in name; however, some plans carry large deductibles or very high copays. A number of resources exist to help with these problems (eg, patient assistance and copay support programs), but substantial self-efficacy and consumer ownership are still required to corral the required documentation and navigate processes. Some clinics are beginning to provide navigation assistance for PrEP use. For example, Washington state has implemented the first drug assistance program for PrEP in the United States. Although the program covers drug costs, it does not cover care, instead linking users to the Affordable Care Act and other insurance options for longitudinal care. New York state has instituted a different model, developing a care support program for PrEP but leveraging existing mechanisms to fund drug costs.

Expanding PrEP Options

With regard to therapeutic options, the field of PrEP is still in its infancy. Options being investigated include the use of maraviroc alone or in combination with the individual components of tenofovir/emtricitabine, which is currently in phase II safety evaluation in men and women. Long-acting injectable formulations would be an exciting advance in the field of PrEP. Long-acting rilpivirine, currently in phase II evaluation in the HIV Prevention Trials Network (HPTN) 076 study in women, is administered every 8 weeks, and cabotegravir, an investigational integrase strand transfer inhibitor that can be administered quarterly, is also in phase II safety evaluation in the HPTN 077 and ECLAIR studies. Monoclonal antibodies such as VRC01 have additional promise for HIV prevention and are moving into proof-of-concept trials.

Conclusion

PrEP is highly effective when taken as prescribed, and the most at-risk populations should be targeted. More data are needed regarding PrEP use in vulnerable and at-risk populations, including transgender individuals and at-risk women. Additional data and guidance on the use of PrEP for pericontraception coverage are also needed. PrEP should be implemented in close partnership with communities. No single intervention is likely to end the HIV epidemic, and PrEP scale-up is a global health imperative as part of combined prevention efforts.

The 1930s saw a burgeoning syphilis epidemic, fueled by public stigma surrounding syphilis testing and treatment and by concerns that syphilis treatment would increase sexual risk behaviors. The Works Progress Administration commissioned a "living newspaper," a public service message produced as a work of theater called *Spirochete*, the aim of which was to draw attention to and normalize the need for routine syphilis testing and treatment. As hormonal treatments for amenorrhea and dysmenorrhea became used for family planning in the 1950s, such was the stigma surrounding individuals seeking hormonal contraception that the *New York Times* only acknowledged its FDA approval with a 136-word article buried on page 75 of the May 10, 1960, issue, which included a caveat on the morality of such an indication for use.

Practitioners should not be on the wrong side of history by allowing individuals to be stigmatized by seeking to

use PrEP to avoid HIV infection and its attendant lifelong treatment. Placing control in the hands of uninfected individuals is a crucial advance, the power of which should not be overestimated.

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Francine Cournos, MD; Milton L. Wainberg, MD
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Perspective

Hepatitis C Virus Direct-Acting Antiviral Drug Interactions and Use in Renal and Hepatic Impairment

Direct-acting antiviral (DAA) drugs exhibit considerable variability in mechanisms of metabolism and the extent to which they are substrates, inhibitors, or inducers of cytochrome P450 enzymes or P-glycoprotein and other drug transporters. Thus, potential drug-drug interactions with other commonly used therapies also vary, as do the effects of renal and hepatic impairment on DAA drug exposure. Drug-drug interaction profiles and use in cases of renal or hepatic impairment are reviewed for the DAAs simeprevir; sofosbuvir; ledipasvir; the fixed-dose combination regimen of paritaprevir, ritonavir, and ombitasvir plus dasabuvir; and the investigational drugs daclatasvir and asunaprevir. This article summarizes a presentation by Lucas Hill, PharmD, at the IAS–USA continuing education program held in Chicago, Illinois, in October 2014.

Keywords: HCV, hepatitis C virus, direct-acting antiviral drugs, DAAs, drug-drug interactions, renal impairment, hepatic impairment, drug exposure

There are numerous potential drug-drug interactions that must be considered when using direct-acting antiviral (DAA) drugs for treatment of hepatitis C virus (HCV) infection. The following summarizes characteristics of interactions between newer DAAs and cytochrome P450 (CYP450) enzymes and drug transporters that affect the exposure to these and other commonly used drugs, as well as the effects of renal or hepatic impairment on DAA drug exposure.

Simeprevir

Exposure to the HCV protease inhibitor simeprevir is increased by approximately 60% when the drug is taken with food. Simeprevir is a substrate of the intestinal uptake transporter P-glycoprotein (P-gp). It is distributed to the liver by organic anion-transporting polypeptide (OATP), is metabolized primarily by hepatic CYP450 3A (CYP3A), and is an inhibitor of both OATP and P-gp as well as a mild inhibitor of intestinal (nonhepatic) CYP3A and CYP1A2.

Drugs that are CYP3A or P-gp substrates, particularly those with a narrow therapeutic index, are of special concern when coadministered with simeprevir. Table 1 shows the known drugs that can decrease simeprevir concentrations through induction of CYP3A4 and P-gp (eg, anticonvulsants, antimycobacterials, and HIV nonnucleoside reverse transcriptase inhibitors), and drugs that increase simeprevir concentrations through inhibition of CYP3A4 (eg, macrolides, antifungals, boosted HIV protease inhibitors, and cobicistat). Diltiazem and verapamil, also potent CYP3A4 inhibitors, are not mentioned in the simeprevir prescribing information, and caution should be used when these drugs are coadministered with simeprevir.

Also shown in Table 1 are drugs that exhibit increased concentrations when coadministered with simeprevir (eg, antiarrhythmics, calcium channel blockers, and statins). Phosphodiesterase type 5 inhibitors can be used without dose adjustment for erectile dysfunction but should be started at the lowest dose possible when used for pulmonary hypertension. For calcium channel blockers, monitoring blood pressure before making dose changes is generally sufficient. Statins are CYP3A4 substrates, and dosing recommendations with concomitant simeprevir are a maximum of 10 mg daily of rosuvastatin (an OATP substrate) and 40 mg daily of atorvastatin (a P-gp and OATP substrate). For other statins, the dose can be halved during simeprevir administration. Levels of digoxin (a P-gp substrate) should be monitored when coadministered with simeprevir.

Potential interactions between simeprevir and immunosuppressants are an important consideration for post–liver transplant patients. Cyclosporine is a potent CYP3A4 and P-gp inhibitor, and coadministration results in an approximately 6-fold increase in simeprevir exposure; therefore, coadministration of cyclosporine and imeprevir is not recommended. Coadministration of simeprevir and tacrolimus results in a small increase in simeprevir exposure and a small decrease in tacrolimus exposure. It is recommended that tacrolimus levels be monitored, with dose adjustment as needed. The pharmacokinetics of concomitant simeprevir and sirolimus have not been formally studied, and patients taking concomitant simeprevir and sirolimus should be monitored to determine if a dose adjustment is necessary.

Simeprevir is generally considered safe for patients with any degree of renal impairment. The drug is primarily hepatically metabolized and cleared, with less than 1% of it recovered in the urine. With severe renal impairment, there is a slight (62%) increase in the simeprevir area under the concentration-time curve (AUC) that is not considered clinically significant. The drug is also highly protein bound and thus unlikely to be removed by dialysis. In practice, simeprevir has been used to achieve cure in patients on dialysis.

With regard to use in cases of hepatic impairment, 2.4- and 5.2-fold increases in simeprevir AUC have been reported in patients with Child-Turcotte-Pugh (CTP) class B and C disease, respectively. Simeprevir maximum concentration (C_{max}) is generally twice as high among HCV-infected patients as among

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Table 1. Drugs That Affect Simeprevir Concentrations or Whose Concentrations Are Affected by Simeprevir

Drugs That Decrease Simeprevir Concentrations	Drugs That Increase Simeprevir Concentrations	Drugs With Concentrations Increased by Simeprevir	
• Anticonvulsants - Carbamazepine - Oxcarbazepine - Phenobarbital - Phenytoin • Antimycobacterials - Rifabutin - Rifampin - Rifapentine • Dexamethasone (systemic) • Nonnucleoside reverse transcriptase inhibitors - Efavirenz - Etravirine - Nevirapine • St John's wort • Tipranavir	• Antifungals - Fluconazole - Itraconazole - Ketoconazole - Posaconazole - Voriconazole • Boosted protease inhibitors • Calcium channel blockers - Diltiazem - Verapamil • Cobicistat • Macrolides - Clarithromycin - Erythromycin - Telithromycin • Milk thistle	• Antiarrhythmics - Amiodarone - Disopyramide - Flecainide - Mexiletine - Propafenone - Quinidine • Calcium channel blockers - Amlodipine - Diltiazem - Felodipine - Nicardipine - Nifedipine - Nisoldipine - Verapamil • Cisapride • Digoxin	• Erythromycin • Phosphodiesterase type 5 inhibitors - Sildenafil - Tadalafil - Vardenafil • Sedative anxiolytics - Midazolam (oral) - Triazolam (oral) • Statins - Atorvastatin (40 mg) - Lovastatin - Pitavastatin - Pravastatin - Rosuvastatin (10 mg) - Simvastatin

uninfected controls. Moderate and severe hepatic impairment increased AUCs among HCV-infected patients by 1.3- and 2.8-fold for those with CTP class B and C disease, respectively, indicating that sizable increases in simeprevir exposure can be expected among HCV-infected patients with severe hepatic impairment.[1]

Potential adverse effects related to increased simeprevir exposure include rash, pruritus, photosensitivity, and increased bilirubin level. Strategies for reducing simeprevir exposure include avoiding substantial drug-drug interactions and taking the drug on an empty stomach.

Sofosbuvir

Sofosbuvir is a nucleotide analogue that prodrug is diphosphorylated in the liver to generate a nucleoside triphosphate analogue, and does not undergo traditional hepatic metabolism. Its primary (inactive) metabolite (GS-331007) undergoes renal elimination via glomerular filtration and active tubular secretion. Sofosbuvir is a substrate of P-gp and breast cancer resistance protein (BCRP). It has no appreciable inhibitory or induction effects on drug transporters or CYP450 enzymes. As shown in Table 2, drugs that reduce sofosbuvir levels by inducing P-gp include anticonvulsants, antimycobacte-rials, ritonavir-boosted tipranavir, and St John's wort. Increases of 5-fold or greater in the AUC of the primary circulating metabolite are observed in patients with severe renal impairment or end-stage renal disease (ESRD).[2] Thus, sofosbuvir is not recommended for patients with ESRD or a glomerular filtration rate (GFR) of less than 30 mL/min/1.73m^2. An ongoing study is evaluating lower doses of sofosbuvir (200 mg or 400 mg) in patients with severe renal impairment or ESRD.

Ledipasvir

The nonstructural protein 5A (NS5A) inhibitor ledipasvir is primarily eliminated in the feces as unchanged parent drug, with approximately 1% eliminated in the urine. It has little to no effect on CYP450 enzymes and is a substrate and weak inhibitor of P-gp and BCRP. As with sofosbuvir, coadministration of ledipasvir with P-gp inducers (eg, anticonvulsants, antimycobacterials, and St John's wort) should be avoided. There is potential for ledipasvir to interact with P-gp and BCRP substrates (Table 3). For example, ledipasvir increases levels of rosuvastatin (a BCRP substrate), and concurrent administration should be avoided. Because digoxin is a P-gp substrate, digoxin levels should be monitored. There are no substantial interactions between ledipasvir and the immunosuppressants cyclosporine and tacrolimus, making ledipasvir suitable for use in post–liver transplant patients.

Ledipasvir exhibits decreased solubility as gastric pH increases. Thus, ledipasvir should not be administered within 4 hours of antacids. Histamine 2 receptor antagonists should be administered simultaneously with ledipasvir or administration should be separated by 12 hours, with daily dose not exceeding the equivalent of famotidine 40 mg twice daily. Proton pump inhibitors should be administered simultaneously

Table 2. Drugs That Decrease Sofosbuvir Concentrations

- Anticonvulsants
  - Carbamazepine
  - Oxcarbazepine
  - Phenobarbital
  - Phenytoin
- Antimycobacterials
  - Rifabutin
  - Rifampin
  - Rifapentine
- Ritonavir-boosted tipranavir
- St John's wort

Table 3. P-gp and BCRP Substrates That Have Potential Interactions With Ledipasvir

P-gp Substrates	BCRP Substrates

• Antineoplastics
• Colchicine
• Digoxin
• Calcium channel blockers
  - Diltiazem
  - Verapamil
• Immunosuppressants
  - Cyclosporine
  - Tacrolimus
• Methotrexate
• Rivaroxaban
• Statins
  - Atorvastatin - Pravastatin
  - Lovastatin - Simvastatin
	• Antineoplastics
	• Ciprofloxacin
	• Methotrexate
	• Nucleoside analogue reverse transcriptase inhibitors
	  - Lamivudine
	  - Zidovudine
	• Statins
	  - Pravastatin
	  - Rosuvastatin

Abbreviations: BCRP, breast cancer resistance protein; P-gp, p-glycoprotein.

with ledipasvir, with daily dose not exceeding the equivalent of omeprazole 20 mg.

Ledipasvir undergoes little metabolism, and only a slight reduction in ledipasvir C_{max} has been observed as degree of hepatic impairment increases. Thus, ledipasvir is considered safe for patients with varying degrees of hepatic impairment.

Paritaprevir, Ritonavir, and Ombitasvir Plus Dasabuvir

The fixed-dose combination of ritonavir-boosted paritaprevir (an HCV protease inhibitor) with ombitasvir (an NS5A inhibitor) and dasabuvir (a nonnucleoside polymerase inhibitor) was recently approved by the US Food and Drug Administration. This fixed-dose combination of paritaprevir, ritonavir, and ombitasvir plus dasabuvir (PrOD) slightly increased digoxin C_{max} and AUC, suggesting a minimal effect on drugs that are P-gp substrates.

In a study of pravastatin used as an OATP substrate, pravastatin exposure was increased by approximately 2-fold when coadministered with PrOD, indicating that pravastatin dose should be halved when used with this combination. Levels of rosuvastatin, a substrate of both OATP and BCRP, showed increases of 2.6-fold in AUC and 7-fold in C_{max} when coadministered with PrOD; therefore, rosuvastatin dosage should likely be limited to 10 mg daily. The greatest effect of cyclosporine (an inhibitor of P-gp, BCRP, and OATP) on PrOD was a 2-fold increase in paritaprevir AUC, which is not considered clinically significant. However, this regimen substantially increases cyclosporine exposure (see below). Similarly, the greatest effect of ketoconazole (a CYP3A4 and P-gp inhibitor) on PrOD was a 2-fold increase in paritaprevir AUC. Increased ketoconazole exposure with coadministration of this regimen requires that the ketoconazole dose be limited to 200 mg. Caution should be used when administering PrOD with azoles, as increased paritaprevir levels can be expected.

When considering drug-drug interactions with PrOD, an important factor is the inclusion of ritonavir (a substrate of P-gp, CYP3A, and CYPD6; an inducer of CYP1A2, CYP2C8, CYP2C9, and CYP2C19; and an inhibitor of P-gp, CYP3A, CYP2D6, multirug resistance protein 1 [MRP1], OATP, and BCRP). Table 4 lists drugs that should be avoided or used with caution in patients receiving ritonavir. Based on other studies of PrOD pharmacokinetics, no dose adjustments are likely to be recommended for digoxin, duloxetine, fixed-dose emtricitabine and tenofovir disoproxil fumarate, escitalopram, methadone, progestin-only contraceptives, or raltegravir.[3] It is recommended that coadministration of carbamazepine (or other CYP450 inducing anticonvulsants) and gemfibrozil (which increases dasabuvir exposure) be avoided with this regimen. Dose adjustments for amlodipine and other calcium channel blockers are also likely to be recommended when coadministered with this regimen.

With regard to the effect of PrOD on immunosuppressants, substantial increases in cyclosporine and tacrolimus exposure levels can be expected. These increases primarily reflect the effects of ritonavir inhibition of CYP3A4 and P-gp. In a phase II study in which the cyclosporine dose was reduced to 20% of the usual daily dose and tacrolimus was dosed at 0.5 mg per week or 0.2 mg every 3 days, cyclosporine levels were maintained within the desired range, and tacrolimus doses of 0.5 mg to 1 mg every 1 week or 2 weeks maintained adequate blood levels in most patients.[4] Thus, concomitant use of these agents requires close monitoring of drug levels.

Among patients with moderate he patic impairment, ombitasvir, dasabuvir, and ritonavir drug exposure levels were comparable to those seen in controls, and paritaprevir AUC was increased by 62% . Among patients with severe hepatic impairment, ombitasvir AUC was reduced by 55%, ritonavir AUC was comparable to that seen in controls, paritaprevir AUC was increased by 920%, and dasabuvir AUC was increased by 320%.[5] PrOD is safe for use in patients with mild hepatic impairment, is not recommended for patients with moderate hepatic impairment, and is contraindicated for patients with severe hepatic impairment.

Daclatasvir

The investigational NS5A inhibitor daclatasvir exhibits minimal renal clearance (5%) and is highly protein bound. It is metabolized by CYP3A4 and is a P-gp substrate and a moderate inhibitor of OATP1B1 and P-gp.

Daclatasvir is expected to be compatible with immunosuppressants. Coadministration of daclatasvir and cyclosporine resulted in no change in cyclosporine levels and an increase in daclatasvir levels (40% increase in AUC) that is likely clinically insignificant, and

Table 4. Drugs That Should Be Avoided or Used With Caution in Patients Receiving Ritonavir

Drugs That Should Not Be Used With Ritonavir		Drugs That Should Be Used With Caution With Ritonavir	
• Alfuzosin	• Salmeterol	• Atorvastatin	• Oral contraceptives
• Alprazolam	• Simvastatin	• Budesonide	• Phosphodiesterase type 5 inhibitors
• Amiodarone	• Triazolam	• Carbamazepine	• Pravastatin
• Cisapride	• Voriconazole	• Clarithromycin	• Quetiapine
• Diazepam	• Rifampin	• Colchicine	• Rifabutin
• Ergotamine	• Rivaroxaban	• Cyclosporine	• Rosuvastatin
• Flecainide		• Digoxin	• Sirolimus
• Lovastatin		• Fentanyl	• Tacrolimus
• Phenytoin		• Fluticasone	• Trazodone
• Pimozide		• Methadone (monitor)	

no clinically significant changes were observed with coadministration of daclatasvir and tacrolimus.[6]

Daclatasvir dose adjustments will be necessary when administered with potent CYP3A inhibitors or inducers. For example, the daclatasvir dose should be decreased to 30 mg daily for patients also receiving ritonavir-boosted atazanavir (a CYP3A inhibitor) and increased to 90 mg daily for patients also receiving efavirenz (a CYP3A inducer).[7]

Increases of up to 2-fold in daclatasvir AUC were observed among patients with moderate or severe renal impairment. The increased exposure is considered to be within the safety range for the drug, suggesting it can be used for patients with any degree of renal impairment.[8]

Among patients with hepatic impairment, although total daclatasvir levels increased with more severe impairment, the unbound levels of drug remained adequate and similar to levels in healthy controls, with clearance of the unbound fraction also remaining relatively unchanged.[9] Thus, daclatasvir use should be suitable for patients with any degree of hepatic impairment.

Asunaprevir

The investigational NS3 protease inhibitor asunaprevir, originally intended to be coformulated with daclatasvir, is metabolized by CYP3A4 and is a substrate of P-gp and OATP1B1, a weak inducer of CYP3A4, a weak inhibitor of P-gp, and a moderate inhibitor of CYP2D6.[10,11]

Ketoconazole substantially increased asunaprevir levels, indicating that caution will be needed when coadministering asunaprevir with CYP3A4 or P-gp inhibitors. Caution may also be necessary when coadministering asunaprevir with CYP2D6 substrates, including antidepressants, antipsychotics, codeine, and dextromethorphan.[12]

Asunaprevir is suitable for patients with ESRD. However, studies of hepatic impairment showed AUC increases of 10-fold with CTP class B disease and of 32-fold with CTP class C disease, indicating that the drug should not be used for patients with moderate or severe hepatic impairment.[10]

Summary

Table 5 provides a summary of inhibition, induction, and substrate profiles of the DAAs discussed here and recommendations for their use and dose adjustments as needed for patients with renal or hepatic impairment.[13] Prior to initiating treatment with HCV DAAs, patients' current medications must be reviewed for potential drug interactions

Table 5. Characteristics of Direct-Acting Antiviral Drugs and Dose Adjustments for Renal or Hepatic Impairment

Drug	Inhibition	Induction	Substrate	Renal Impairment	Hepatic Impairment
Asunaprevir[a]	Moderate inhibitor of CYP2D6	Weak inhibitor of CYP3A4 and P-gp	Substrate of CYP3A4, P-gp, and OATP1B1	No adjustment needed	Should likely be avoided in patients with CTP class B or C disease
Daclatasvir[a]	Moderate inhibitor of P-gp and OATP	NA	Substrate of CYP3A and P-gp	No adjustment needed	No adjustment needed
Ledipasvir	Mild inhibitor of P-gp, BCRP	NA	Substrate of P-gp	No adjustment needed	No adjustment needed
Paritaprevir, ritonavir, and ombitasvir plus dasabuvir	Inhibitor of CYP3A4, CYP2D6, P-gp, OATP, and BCRP	Inhibitor of CYP1A2, CYP2C8, CYP2C9, and CYP2C19 (based on ritonavir pharmacokinetics)	Substrate of CYP3A4, CYP2C8, and CYP2D6	Likely no adjustment needed	Not recommended in patients with CTP class B disease, and contraindicated in patients with CTP class C disease
Simeprevir	Mild inhibitor of intestinal CYP3A and CYP1A2; mild inhibitor of OATP and P-gp	NA	Substrate of CYP3A	No adjustment needed	Should be used with caution in patients with CTP class B or C disease
Sofosbuvir	NA	NA	Substrate of P-gp	Not recommended if GFR <30 mL/min/1.73m^2	No adjustment needed

Abbreviations: BCRP, breast cancer resistance protein; CTP, Child-Turcotte-Pugh; CYP, cytochrome P450; GFR, glomerular filtration rate; NA, not available; OATP, organic anion-transporting polypeptide; P-gp, P-glycoprotein. Adapted from Kiser et al.[13]
[a]Investigational drug.

and adjusted if needed. When selecting the ideal regimen for a patient, other comorbidities such as renal impairment or degree of liver disease are important considerations.

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Perspective

Will You Still Treat Me When I'm 64? Care of the Older Adult With HIV Infection

HIV infection is associated with chronic immune activation that is superimposed on immunologic senescence in older adults, resulting in the acquisition of age-related diseases at younger ages. The incidence of coronary artery disease is higher among HIV-infected persons than uninfected individuals matched for age and sex. HIV infection and its treatment have been associated with premature bone loss. Lung, hepatic, and anal cancers occur at younger ages in persons with HIV infection. HIV-infected patients are living longer, and proper attention to the management of comorbidities in this population is essential. This article summarizes an IAS–USA continuing education webinar presented by Howard Libman, MD, in January 2015.

Keywords: HIV, aging, age-related diseases, coronary artery disease, bone loss, cancer, mortality

Aging is characterized by progressive physiologic changes associated with increased susceptibility to many diseases. It is influenced by genetic factors, lifestyle, and environmental exposures. In general, aging is associated with loss of the physiologic reserves needed to cope with challenges to homeostasis, and all organ systems are affected to some degree. With regard to specific systems, it is difficult to determine the impact of age alone on the cardiovascular system, as there is an increased risk of hypertension, diabetes mellitus, obesity, and sedentary behavior with aging. Aging is also associated with a greater probability of fracture related to decreased bone mass and an increased risk of falling, and there is slowing of repair once fracture occurs. Bone mass declines by approximately 0.5% per year in older adults not infected with HIV.

Aging is accompanied by decrements in immune function, contributing to increased risk of infections, malignancies, and autoimmune disorders. The ability of B- and T-cell lymphocytes to generate responses to new antigens and vaccinations is diminished, there is decreased production of interleukin (IL)-2 and IL-2 receptors, thymic involution occurs, and the cytokine profile is consistent with a chronic, low-level inflammatory state.

The molecular basis of aging reflects the fact that natural selection does not play a role in preserving beneficial genes in later life, and some genes that provide benefit in early life may be detrimental with aging. There has been a variable effect of caloric restriction in prolonging life in laboratory animals. However, shortening of telomeres (the nucleoprotein end caps of chromosomes) increases the vulnerability of aging cells to DNA damage and dysregulation.

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HIV and Aging

HIV infection, even when controlled, in older adults is associated with chronic immune activation superimposed on immunologic senescence. In the setting of IL-2 downregulation and thymic dysfunction, older HIV-infected individuals may have delayed immune reconstitution. Chronic immune activation has been shown to result in accelerated aging of T cells, and it is unclear if these changes are reversed by antiretroviral therapy.[1]

Since the 1980s, an increasing percentage of HIV-infected patients are living longer, with approximately 30% now aged 50 years or older.[2] In 2012, 17.1% of newly diagnosed cases of HIV infection and 25.6% of newly diagnosed cases of AIDS were in adults aged 50 years or older.[2] Sexual contact among men who have sex with men is the most common mode of HIV transmission among older men, and heterosexual sexual contact is the most common mode of transition among older women.[2] Older persons may have acquired HIV infection later in life, may have more advanced HIV infection at the time of diagnosis, and may be at increased risk of acquiring opportunistic infections or of transmitting HIV infection to others. Immunologic response to antiretroviral therapy is less robust in this population. Although adherence to antiretroviral therapy is generally good, older individuals may be at increased risk for drug toxicity owing to age-related changes in pharmacokinetics.

Among 12,196 HIV-infected, treatment-naive individuals in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) who initiated antiretroviral therapy, CD4+ cell counts after 24 months of therapy were diminished as age increased, starting at age 40 years, but viral suppression was not affected.[3] In another prospective study that evaluated treatment outcomes in 3015 HIV-infected individuals, of whom 401 were older than 50 years, clinical progression to an AIDS-defining illness was more common in older individuals despite better virologic control (hazard ratio [HR], 1.52; 95% confidence interval [CI], 1.2-2.0).[3,4]

With regard to adherence to antiretroviral therapy, the literature suggests an up to 95% adherence rate among older HIV-infected individuals. In a meta-analysis, older age reduced the risk of nonadherence by 27% (relative risk [RR], 0.72; 95% CI, 0.64-0.82).[5] In other studies, older age was associated with a significantly reduced risk of nonadherence in both the short term

(RR, 0.75; 95% CI, 0.64-0.87) and the long term (RR, 0.65; 95% CI, 0.50-0.85).[5]

Among HIV-infected individuals taking protease inhibitors, a higher rate of adverse events was reported in those older than 60 years than in those younger than 40 years (64% and 35%, respectively).[6] In a study of 508 treatment-naive patients, antiretroviral regimen changes owing to toxicity were associated with older age.[7] This increased risk of adverse events may reflect age-related decreases in renal and hepatic function and in serum albumin level, and changes in the cytochrome P450 enzyme system.

Additional clinical characteristics of HIV infection in older persons include acquiring age-related diseases at younger ages than uninfected persons. Neurocognitive dysfunction, some non–AIDS-defining cancers, and a wide range of pulmonary diseases are also more prevalent in older HIV-infected individuals. It is hypothesized that increased immune activation and long-term chronic inflammation contribute to premature aging in this population.

With regard to premature aging, a case-control study involving 2854 HIV-infected patients and 8562 uninfected controls treated at Modena University in Italy from 2002 to 2009 examined noninfectious comorbidities, including cardiovascular disease (CVD), hypertension, diabetes, bone fractures, and renal failure.[8] Independent predictors of polypathology ($P < .001$) included older age (odds ratio [OR], 1.11), male sex (OR, 1.77), CD4+ cell count nadir below 200/μL (OR, 4.46), and duration of antiretroviral therapy (OR, 1.01). The prevalence of polypathology among HIV-infected patients aged 41 years to 50 years was similar to that among uninfected participants aged 51 years to 60 years, suggesting that comorbidities occur in HIV-infected individuals approximately 10 years earlier than in their uninfected counterparts.

With regard to cognitive dysfunction, epidemiologic findings indicate that older age is a risk factor for HIV-associated dementia, although there have been few studies in this regard. In a longitudinal study comparing 106 HIV-infected individuals older than 50 years with 96 HIV-infected individuals aged 20 years to 39 years, with multivariate analysis there was a 3-fold higher risk of dementia in the older group after adjusting for race, education level, presence of depression, substance use, antiretroviral therapy status, CD4+ cell count, and viral load.[9]

With regard to malignancy risk, data from observational studies have suggested that lung, hepatic, and anal cancers occur at younger ages in HIV-infected adults than in uninfected adults. In an analysis of age at diagnosis of non–AIDS-defining cancer using data from 15 HIV and cancer registry databases in the United States, which included data on 212,055 persons with AIDS, lung and anal cancers were found to occur earlier in persons with AIDS than in persons without AIDS (median age 50 years and 54 years, respectively; $P < .001$) than in the general population.[10]

In an analysis of 33,420 HIV-infected individuals and 66,840 uninfected controls matched for age, sex, race, and ethnicity in the Veterans Aging Cohort Study, chronic obstructive pulmonary disease, lung cancer, pulmonary hypertension, and pulmonary fibrosis were more frequent among the HIV-infected individuals.[11]

CVD and Risk Factors

Traditional risk factors for coronary artery disease (CAD) are male sex, increasing age, higher low-density lipoprotein (LDL) cholesterol level, lower high-density lipoprotein (HDL) cholesterol level, hypertension, diabetes mellitus, obesity, cigarette smoking, and a family history of premature CAD. Modifiable traditional risk factors in HIV-infected persons should be identified and managed effectively.

The incidence of CAD is higher in HIV-infected individuals than in uninfected individuals matched for age and sex, with studies showing increases in both subclinical atherosclerosis (eg, carotid intima media thickness) and clinical endpoints (eg, acute myocardial infarction [MI]). HIV infection is associated with increased soluble and cellular markers of inflammation, endothelial dysfunction, and altered coagulation, all of which contribute to risk of CVD. The degree to which HIV infection itself, antiretroviral therapy, and other risk factors contribute to increased risk of CVD in HIV-infected patients remains unknown; however, there is a high prevalence of traditional risk factors in this population. With regard to antiretroviral therapy, protease inhibitors appear to be associated with higher risk of CAD, and some data suggest that the nucleoside analogue reverse transcriptase inhibitor (nRTI) abacavir and the nonnucleoside analogue reverse transcriptase inhibitor efavirenz also increase risk. However, discontinuation of antiretroviral therapy is also associated with higher risk of CAD.

Available data suggest a 50% increased risk of acute MI among middle-aged or older HIV-infected individuals compared with uninfected individuals of the same age. For example, an analysis of patients followed from 2003 to 2009 in the Veterans Aging Cohort Study assessed risk of acute MI among those with no CVD at baseline after adjusting for sex, race, ethnicity, hypertension, diabetes, hyperlipidemia, smoking status, hepatitis C virus infection, body mass index, renal disease, anemia, substance use, CD4+ cell count, viral load, and antiretroviral therapy status. The incidence rate ratio (IRR) of MI was significantly higher in HIV-infected individuals than in uninfected individuals, among those aged 40 years to 49 years (IRR, 1.34; 95% CI, 1.04-1.72), those aged 50 years to 59 years (IRR, 1.80; 95% CI, 1.47-2.11), and those aged 60 years to 69 years (IRR, 1.53; 95% CI, 1.03-2.26).[12]

Management of hypertension in HIV-infected individuals is similar to that in uninfected individuals. Hypertension is defined as having a blood pressure reading greater than or equal to 140/90 mm Hg at 3 separate visits over a period of 1 week or more. In the absence of a history of or a physical exam indicating secondary hypertension, baseline evaluation should include testing of renal function and

potassium level, a urinalysis, and an electrocardiogram. Approaches to nonpharmacologic management of hypertension include modest salt restriction, increased physical activity, and weight reduction. Initial drug therapy should consist of a thiazide diuretic, an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker, or a calcium channel blocker in most patients. For individuals with blood pressure readings of more than 20/10 mm Hg above goal, an ACE inhibitor or angiotensin receptor blocker plus a calcium channel blocker is recommended. There are no important drug interactions between antiretroviral drugs and those commonly used to treat hypertension.

Management of diabetes is also similar in HIV-infected and uninfected persons. Diagnosis of diabetes is often based on a glycated hemoglobin (HgbA1c) value of at least 6.5%. Treatment goals include prevention of symptomatic hyperglycemia and vascular complications, with a target HgbA1c value of less than or equal to 7.0%. Nonpharmacologic management consists of weight reduction through dietary modification and increased physical activity. Initial drug therapy generally consists of metformin with a sulfonylurea (eg, glipizide). Metformin may cause lactic acidemia (as do some older nRTIs). There are no other important drug interactions between antiretroviral drugs and those commonly used to treat diabetes. Of note, diabetes and HIV infection have a particularly detrimental effect on renal function.[13]

Cigarette smoking is more common among HIV-infected individuals than the general population, and HIV-infected smokers are less likely to quit.[14] However, there is no evidence that specific smoking cessation interventions are more or less effective. A combination of behavioral interventions and pharmacologic therapy to encourage smoking cessation generally works better than either method alone. Drug options include nicotine replacement therapies (eg, patches, gum, or lozenges), bupropion, and varenicline, and may be used alone or in combination. There are no important drug interactions between antiretroviral drugs and those commonly used for smoking cessation.

For hyperlipidemia in the general population, a desirable total cholesterol level is less than 200 mg/dL and a desirable LDL cholesterol level is less than 130 mg/dL. Epidemiologic studies show a graded relationship between total cholesterol level and CAD risk. Patients with clinical atherosclerosis or a combination of factors resulting in a greater than 20% 10-year risk of a new cardiovascular event may benefit substantially from statin therapy. Patients without clinical atherosclerosis may have a lesser absolute benefit from statin treatment. The relative risk reduction rate with statin therapy in most studies has been between 20% and 30%.

Two widely used CVD risk calculators are the Framingham risk calculator and the newer American College of Cardiology/American Heart Association risk calculator.[15,16] Each calculates a 10-year risk of MI and provides a threshold for initiating statin therapy. However, it remains unclear how best to incorporate the risk posed by HIV infection and its treatments into these risk calculations.

Dyslipidemia is common among HIV-infected individuals taking antiretroviral therapy, and it may be isolated or seen in combination with other features of lipodystrophy. HIV-infected persons should be evaluated and treated for dyslipidemia in a similar fashion to uninfected persons. CVD risk factors should be assessed when designing an initial antiretroviral regimen. For individuals who are at risk for CVD, protease inhibitors (with the possible exception of atazanavir) and abacavir should be avoided. Protease inhibitors, particularly ritonavir, increase most statin levels. Concurrent use of simvastatin or lovastatin with protease inhibitors and cobicistat is contraindicated. Pravastatin (except with darunavir), atorvastatin, and rosuvastatin may be used as alternatives. It is prudent to start a statin at a low dose and to monitor liver function and creatine phosphokinase level during treatment.

To screen for CVD, HIV-infected individuals should have fasting glucose or HgbA1c measured every 6 months to 12 months, a fasting lipid profile completed every 6 months to 12 months, and regular blood pressure measurements. To assess for body fat maldistribution, a patient self-report should be taken and body weight measured at each visit, with periodic anthropometric measurements of skinfold, waist, and hip. A 1-time ultrasound for abdominal aortic aneurysm is recommended for men aged 65 years to 75 years with a history of smoking. Preventive treatment includes aspirin for prevention of CAD in men aged 45 years to 79 years and for prevention of cerebrovascular disease in women aged 55 years to 79 years when risk of atherosclerosis outweighs risk of gastrointestinal bleeding.

Premature Bone Loss

Osteopenia, osteoporosis, and pathologic fractures have been described in the context of HIV infection. Osteoporosis may present with fractures of vertebrae, forearms, or hips. HIV infection itself, use of tenofovir or protease inhibitors, alterations in metabolism of vitamin D, and lactic acidemia related to use of older nRTIs may be contributing factors to premature bone loss. Immobility, cigarette smoking, excessive alcohol use, chronic renal disease, hypogonadism, hyperparathyroidism, hyperthyroidism, and steroid use accentuate bone loss. The optimal use of bone densitometry as a screening test for HIV-infected individuals is uncertain. Calcium and vitamin D supplements should be given to high-risk patients, and regular exercise and smoking cessation should be advised.

The effect of antiretroviral therapy on cases of osteoporotic fracture that occurred after diagnosis of HIV infection in a case registry from 1988 to 2009 was examined in a multivariate analysis adjusted for race, age, tobacco use, diabetes, body mass index, and presence of hepatitis C virus infection, and in a second multivariate analysis adjusted for all of the foregoing factors plus concomitant exposure to antiretroviral

Table 1. HIV Primary Care Recommendations From the HIV Medicine Association of the Infectious Diseases Society of America

Intervention	Recommendation	Comments
Blood pressure check	Perform annually for all individuals	None
Digital rectal examination	Consider annually for all individuals	Inspect for anal warts and malignancies in all patients, and for prostate abnormalities in men
Ophthalmologic examination	Perform a dilated examination every 6 mo-12 mo for individuals with CD4+ cell counts <50/μL	A tonometry test is advised every 2 y-3 y in all those aged ≥50 y
Depression screening	Perform annually for all individuals	Use a conventional mental health interview or standardized test
Measurement of fasting glucose and HgbA1c	Perform every 6 mo-12 mo for all individuals	Consider testing 1 mo-3 mo after initiation or modification of antiretroviral therapy. Measurement of HgbA1c may be used for screening; consider a threshold cutoff of 5.8%. HgbA1c measurement should be performed every 6 mo for those with diabetes mellitus
Fasting lipid profile	Perform every 6 mo-12 mo for all individuals	Consider testing 1 mo-3 mo after initiation or modification of antiretroviral therapy
Syphilis serology	Perform annually for individuals at risk for STIs	More frequent testing may be indicated for patients at high risk for STIs
Gonorrhea and chlamydia testing	Perform annually for patients at risk for STIs	More frequent testing may be indicated for patients at high risk for STIs. Repeat testing after 3 mo if results are positive
Hepatitis C virus testing	Perform annually for at-risk patients (eg, injection drug users and men who have sex with men)	More frequent testing may be indicated for patients at high risk, especially if serum transaminase levels are increased
Trichomoniasis testing	Perform annually for all women	Repeat testing after 3 mo if result is positive
TB skin test or interferon-gamma release assay	Perform at baseline and annually for patients at risk for TB	No need to repeat for patients with a prior positive TB skin test result; additional TB testing may be indicated depending on potential exposure
Colorectal cancer screening	Perform at age 50 y for asymptomatic individuals at average risk	More frequent testing is indicated for patients with a history of adenomatous polyps; testing at an earlier age may be considered for patients with a strong family history of colon cancer
Mammography	Perform annually for all women aged ≥50 y	Some experts advise starting at age 40 y based on assessment of individual risks/benefits
Cervical Papanicolaou testing	Perform annually for all women after 2 normal Papanicolaou test results documented during the first year after diagnosis of HIV infection	None
Bone densitometry	Perform baseline exam for postmenopausal women and men aged ≥50 y	Detection of premature bone loss requires periodic monitoring thereafter; risk factors include white race, small body habitus, sedentary lifestyle, cigarette smoking, alcohol use, phenytoin use, corticosteroid use, hyperparathyroidism, vitamin D deficiency, thyroid disease, and hypogonadism
Abdominal ultrasonography	Perform once for men aged 65 y-75 y who have ever smoked	Screening test for abdominal aortic aneurysm
Patient education	Address regularly for all patients	May include information on sexual behavior, alcohol and drug counseling, diet, weight reduction, smoking cessation, and seat belt use

Abbreviations: HgbA1c, glycated hemoglobin; STI, sexually transmitted infection; TB, tuberculosis. Adapted from Aberg et al.[18]

therapy.[17] Among 56,660 individuals evaluated, tenofovir use was associated with an osteoporotic fracture HR of 1.06 (95% CI, 0.99-1.12) in the first multivariate analysis and of 1.06 (95% CI, 0.99-1.14) in the second multivariate analysis. Among 32,439 patients taking potent antiretroviral therapy, the association of tenofovir use with osteoporotic fracture became significant, with a yearly HR of 1.13 (95% CI, 1.05-1.21; $P = .001$) in the first multivariate analysis and of 1.12 (95% CI, 1.03-1.21; $P = .011$) in the second multivariate analysis. Exposure to boosted protease inhibitors was associated with a significant HR of 1.08 (95% CI, 1.01-1.15; $P = .026$) in the first multivariate analysis and a nonsignificant HR of 1.05 (95% CI, 0.97-1.13; $P = .237$) in the second multivariate analysis. Among protease inhibitors, the fixed-dose combination of lopinavir and ritonavir was associated with a borderline significant HR of 1.09 (95% CI, 1.00-1.20; $P = .051$) in the second multivariate analysis.

Current HIV primary care guidelines from the HIV Medicine Association of the Infectious Diseases Society of America (IDSA) recommend bone densitometry screening for men aged 50 years or older and for postmenopausal women.[18] Radiography or magnetic resonance imaging for avascular necrosis of the hips should be performed for symptomatic patients only.

Immunizations

Live attenuated vaccines should be avoided in HIV-infected individuals with low CD4+ cell counts, unless the benefits clearly outweigh risks. Vaccines are generally more immunogenic in

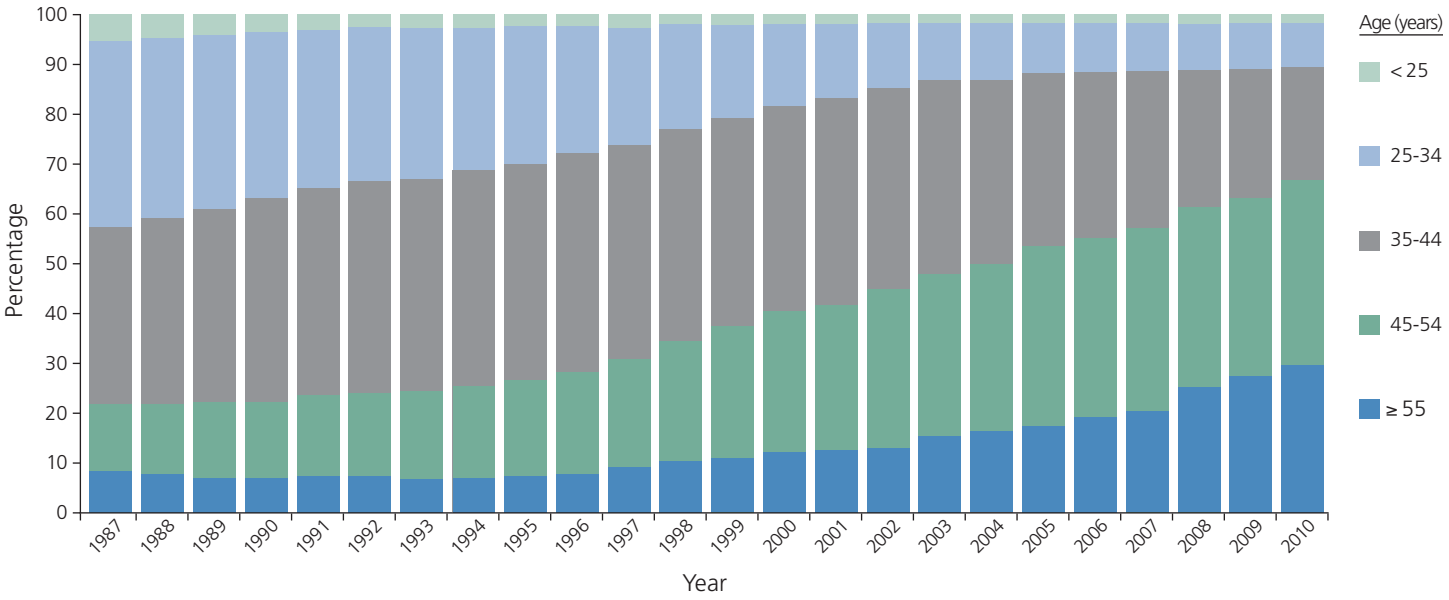

Figure 1. Changes in distribution of deaths attributable to HIV infection in the United States, by age group, from 1987 to 2010. Adapted from Centers for Disease Control and Prevention.[23]

individuals with higher CD4+ cell counts and lower viral loads and should be delayed pending immune reconstitution after initiating antiretroviral therapy when appropriate. Immunologic response to vaccines should be assessed when possible.

HIV-infected individuals are at increased risk for serious pneumococcal infections, including pneumonia and bacteremia. This increased risk may result from altered antibody production, leading to decreased opsonization. It is now recommended that previously unvaccinated individuals receive the 13-valent pneumococcal conjugate vaccine followed by the 23-valent polysaccharide vaccine at least 8 weeks later, with a second dose of the 23-valent vaccine 5 years later. For those who have previously received the 23-valent vaccine, the 13-valent vaccine should be given at least 1 year after the last 23-valent vaccine dose. For those who require additional doses of the 23-valent vaccine, the first dose should be given no sooner than 8 weeks after the 13-valent vaccine dose and at least 5 years after most recent 23-valent vaccine dose.[19]

HIV-infected individuals may also be at increased risk for complications of influenza, although there are limited data in this regard. It is currently recommended that all HIV-infected individuals receive an inactivated seasonal flu vaccine.[20] Live (intranasal) preparations of influenza vaccines should not be used for HIV-infected individuals.

The zoster vaccine may be considered for some HIV-infected patients aged 60 years or older. In a study of 395 patients on stable antiretroviral therapy who had CD4+ cell counts greater than 200/μL and were randomly assigned to receive 2 doses of zoster vaccine or placebo, antibody titers were increased in vaccine recipients at 24 weeks, with no substantial difference in frequency of zoster cases between the 2 groups; the only substantial difference in safety was a higher incidence of local reactions in those who received vaccine instead of placebo.[21]

Other Aspects of Routine Health Care

A summary of routine health care maintenance assessments from current IDSA HIV primary care guidelines can be seen in Table 1.[18] Annual screening for depression in all individuals is now recommended by the US Preventive Services Task Force (USPSTF) via conventional mental health interview or a variety of standardized tests.[22] However, screening should only be done in settings in which interventions for depression (ie, pharmacotherapy and care from a mental health professional) are available.

USPSTF recommendations for cancer screening include the following. For breast cancer, biannual mammography for women aged 50 years to 74 years is recommended, with individualized screening recommended for younger women. For cervical cancer, annual Papanicolaou testing is recommended for women after documentation of 2 normal Papanicolaou test results; the role of human papillomavirus testing for HIV-infected women is unclear. For colon cancer, a colonoscopy every 10 years starting at age 50 years is recommended, with earlier and more frequent screening performed for patients with a history of polyps or inflammatory bowel disease. For prostate cancer, annual digital exams for men aged 50 years to 74 years should be considered; prostate-specific antigen testing is no longer recommended for most men, but a conversation with the patient about potential benefits and risks is appropriate. Annual screening for chlamydia, gonorrhea, and syphilis is recommended for adults who are at ongoing risk for sexually transmitted diseases. Annual purified protein

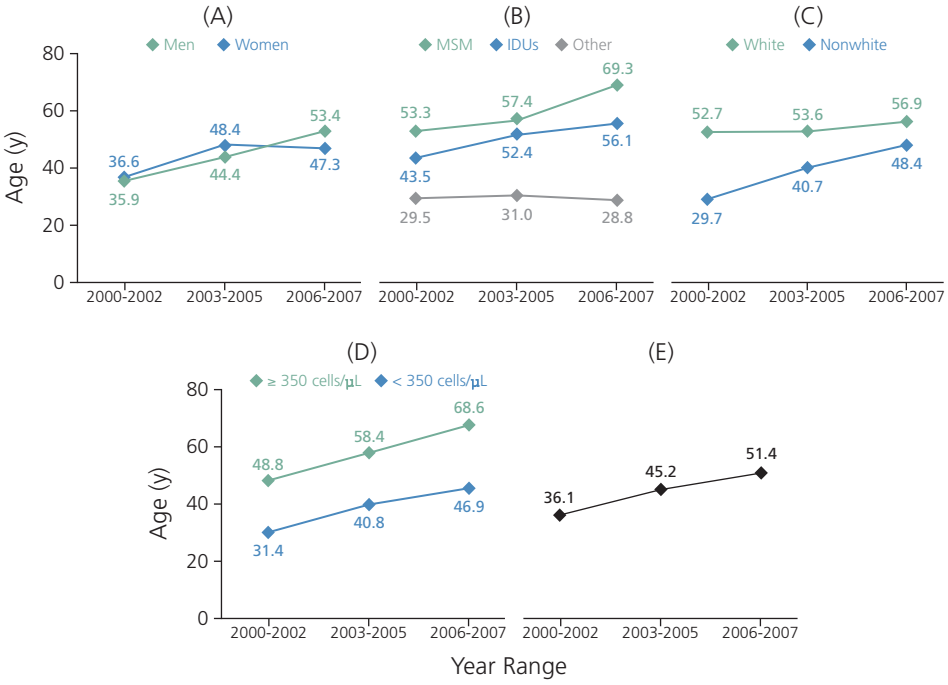

Figure 2. Midpoint life expectancy estimates for individuals diagnosed with HIV infection at age 20 years, by sex (A), transmission group (B), race (C), CD4+ cell count at time of initiation of antiretroviral therapy (D), and overall (E). IDUs indicates injection drug users; MSM, men who have sex with men. Adapted from Samji et al.[25]

derivative or interferon-gamma release testing is recommended for adults at ongoing risk for tuberculosis infection.[18]

Mortality

As individuals with HIV infection are living longer with the use of potent antiretroviral therapy, an increasing proportion of deaths related to HIV infection have occurred in older age groups. However, as of 2010, there was still a higher proportion of deaths related to HIV infection among individuals aged 45 years to 54 years than among those aged 55 years or older (Figure 1).[23]

Available data on mortality trends include those from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study, which has been ongoing since 1999. There have been 3909 deaths observed in the study among 49,731 patients followed up through 2011, and the overall crude mortality rate is 12.7 per 1000 person-years, although it decreased from 16.9 per 1000 person-years to 9.6 per 1000 person-years over the follow-up period. Twenty-nine percent of deaths were attributable to AIDS-related causes, 15% to non–AIDS-related cancers, 13% to liver disease, and 11% to CVD. Over the course of follow-up, the proportion of deaths attributable to AIDS-related events has decreased from 34% to 22% and the proportion attributable to non–AIDS-defining malignancies has increased from 9% to 23%.[24]

Figure 2 shows how projected life expectancy increased among individuals with HIV infection between the periods from 2000 to 2002 and 2006 to 2007.[25] Overall, life expectancy for an individual diagnosed with HIV infection at age 20 years has increased from 36 years to 51 years. There are differences in projected life expectancy based on sex, transmission group, and race, and according to CD4+ cell count at initiation of antiretroviral therapy. However, many HIV-infected individuals are expected to live 70 years or more.

Summary

Aging is characterized by progressive physiologic changes associated with an increased susceptibility to many diseases. HIV infection, even when controlled, is associated with chronic immune activation that is superimposed on immunologic senescence in older adults. Older persons may be diagnosed later and may have more advanced HIV infection at the time of diagnosis, and there is a less robust immunologic response to antiretroviral therapy in this population. HIV-infected individuals generally acquire age-related diseases at younger chronologic ages than the general population, and it is hypothesized that increased immune activation and long-term chronic inflammation contribute to such premature aging.

Lung, hepatic, and anal cancers occur at younger ages in HIV-infected adults than in uninfected adults. The incidence of CAD is higher among HIV-infected individuals than among uninfected individuals matched for age and sex. Results of CAD risk calculation should be interpreted in the context of this increased risk. HIV infection and its treatments have been associated with premature bone loss. Age-related immunizations and screening tests for cancers and other conditions should be addressed. Mortality in HIV-infected persons has decreased substantially over the past 2 decades, with non–AIDS-related conditions now accounting for the majority of deaths.

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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.

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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 June 17, 2015.

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