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# Topics in Antiviral Medicine™

A publication of the IAS–USA

## Perspectives CME



## Commentary

# Topics in Antiviral Medicine™



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# Topics in Antiviral Medicine™

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- Describe the impact of microbiota on HIV infection
- Answer predominant questions about HIV-related opportunistic infections, including issues such as prophylaxis, polymerase chain reaction-based diagnostics, and likely updates to guidelines
- Implement strategies for prevention and treatment of human papillomavirus–related cancers in individuals with HIV infection
- Describe the effects of and potential treatments for opioid use disorders in individuals with HIV infection

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*Perspective*

# The Human Microbiome: Implications for Health and Disease, Including HIV Infection

*Our increased understanding of the human microbiome has brought insight into the role it plays in health and disease, including HIV infection. Studies have shown that the gut microbiome is less diverse in individuals with HIV infection than in noninfected control subjects. Efforts to modify the microbiome to bolster immune reconstitution in people with HIV infection have so far been unsuccessful. The vaginal microbiome affects risk of HIV acquisition, with* Lactobacillus *dominance being protective compared with vaginosis characterized by larger populations of* Gardnerella*. The vaginal microbiome might also affect efficacy of topical tenofovir disoproxil fumarate preexposure prophylaxis. This article summarizes a presentation by Robert T. Schooley, MD, at the IAS–USA continuing education program held in San Francisco in May 2018.*

**Keywords:** microbiome, HIV, gut, vaginal, *Lactobacillus*, *Gardnerella*

The human microbiome is the collection of organisms that lives in and on us. They live on the skin, in the gastrointestinal (GI) tract, and on virtually every other surface of the body. Each human is composed of approximately 37 trillion cells and we carry some 100 trillion microbiologic organisms. Our increasing knowledge of the microbiome has been made possible through use of metagenomics and the decreasing costs of genetic sequencing, obviating the need to grow microorganisms in culture for identification purposes.

The best handle we have on understanding the microbiome is 16s ribosomal RNA (rRNA). Every microbe has this region of RNA, including portions that are conserved across all of our microbiota, because it is the common feature that allows organisms to translate messenger RNA into protein. Amplification of variable regions permits identification of organisms by families and phyla, for example, by evaluating relationships among sequences.

A number of concepts have evolved to characterize microbial communities. One is the operational taxonomic unit (OTU), a group of organisms that share greater than 97% DNA sequence commonality in the rRNA gene. This grouping may or may not reflect what has been traditionally considered a species of microorganism. Diversity in microbial communities is described by the metrics of richness (number of OTUs), evenness (relative abundance of different OTUs), dominance (emergence of a single OTU), and diversity index (calculated index of complexity based on richness and evenness).[1] Antibiotic treatment narrows the rich microbiome (rich diversity of OTUs) in the human gut. Conditions such as obesity and inflammatory bowel disease are characterized by low diversity, whereas bacterial vaginosis is characterized by an unhealthy high diversity in which lactobacilli that are dominant in the healthy vagina are replaced by a wide variety of other organisms.

**Table.** Terms Describing Diversity in Microbial Communities.[1]

| Term | Definition |
|---|---|
| Richness | Number of OTUs |
| Evenness | Relative abundance of OTUs |
| Dominance | Emergence of single OTU |
| Diversity Index | Calculated index of complexity based on richness and evenness |

Abbreviation: OTU is operational taxonomic units.

The National Institutes of Health Human Microbiome Project has produced a number of insights regarding the microbiome over the past 15 years, beginning with the recognition that each individual is not a single ecosystem but numerous ecosystems with differences among body sites. Further, whereas OTUs in the GI tract are very different from OTUs in the oral cavity in a given individual, OTUs from these sites resemble each other across individuals. In addition, in a given individual, the microbial diversity at particular sites changes over time, although the difference in this regard is not as great as the difference between individuals at a given site.

With regard to the gut microbiome in particular, we have identified a number of key characteristics that affect health and disease. (1) The microbiome is established in early life and differs between infants born by cesarean delivery and by vaginal birth. (2) In murine models, transfer of an "obese" microbiome from obese adult animals to a sterile infant mouse affects the growth characteristics of the mouse for life. (3) The microbiome is drastically altered acutely by antibiotic administration. (4) In farm animals (and mice), antibiotic exposure early in life promotes microbiota associated with high caloric efficiency. (5) There is some evidence that early exposure to antibiotics affects humans the same way. (6) After cessation of antibiotics, the antibiotic "footprint" remains—ie, the microbiome reverts toward but does not reach pre-antibiotic richness and diversity for a prolonged period.

The 4 major phyla in the gut microbiome are: firmicutes—Gram-positive organisms (eg, *Staphylococcus*, *Micrococcus*, *Streptococcus*, and *Lactobacillus*), including sporulating Gram-positive rods; Bacteroidetes—3 large classes of Gram-negative, non-spore forming, anaerobic or aerobic, rod-shaped bacteria (eg, *Bacterioides*); Actinobacteria

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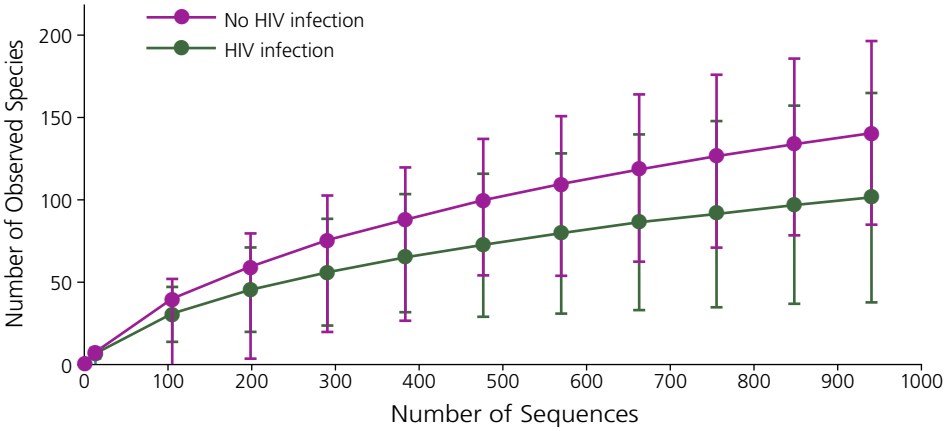


**Figure 1.** Reduced richness of the gut microbiome with HIV infection compared with no HIV infection. Adapted from Mutlu et al.[2]

—primarily Gram-positive bacteria (including those that are acid fast; eg, Mycobacteria and *Gardnerella*); and proteobacteria—primarily Gram-negative rods (eg, *Escherichia coli*, *Salmonella*). The firmicutes, in particular, are highly adept at metabolizing food to help us better absorb calories.

## Gut Microbiome in HIV Infection

An initial study investigating the gut microbiome in HIV infection performed by Mutlu and colleagues demonstrated differences between individuals with and without HIV infection. The study involved 56 samples from individuals with HIV infection (mean CD4+ cell count of 425/µL; plasma HIV-1 RNA level <75 copies/mL in 17 of 21 participants) and 65 samples from 22 age- and sex-matched noninfected control participants undergoing elective colonoscopy (primarily for cancer screening).[2] The microbiome was found to be markedly less diverse in individuals with HIV infection (Figure 1). In addition, the microbiomes of individuals with HIV infection and noninfected control participants contained different bacterial species, with noninfected control participants harboring significantly more *Bacteroides* ($P$ = .0002) and Clostridiales-unclassified ($P$ = .002), and participants with HIV infection harboring more Enterobacteriaceae-unclassified ($P$ = .0002) and *Campylobacter* ($P$ = .0034), as well as more fusobacteria and *Prevotella*.

Some of these differences may be due to changes in the innate and adaptive immune response at the level of the gut, one of the first organs attacked during acute HIV infection. Some differences may reflect use of antibiotics in individuals with HIV infection. Studies that have attempted to evaluate the change in microbiome over time as HIV infection progresses suggest that some of the organisms found more frequently in HIV-infected microbiomes are more associated with inflammation and become enriched as immune response declines.

The microbiome is important from the standpoint of maintenance of the gut barrier. A considerable amount of work has been done over the past decade to ascertain whether translocation of gut bacterial components across the GI tract have an impact on inflammation. The recently reported Promaltia study, performed by Serrano-Villar and colleagues, evaluated whether the gut microbiome could be altered in HIV infection to improve immune reconstitution.[3] In the placebo-controlled study, patients with advanced HIV infection were randomly assigned to receive treatment with a placebo (skim milk) or an immunonutrition mixture of prebiotics, probiotics, oligonutrients, docosahexaenoic acid, eicosapentaenoic acid, gamma linolenic acid, and amino acids for 48 weeks, each in combination with initial antiretroviral therapy. The mixture represented a collation of substances used in prior studies aimed at producing changes in the microbiome. At 48 weeks, there were no significant differences in microbiome diversity between the treatment and placebo groups. Some enrichment of unclassified bacteria from the Lachnospiraceae and Victivallaceae families and depletion of *Blautia* species were observed in the treatment group compared with the placebo group. No differences in inflammatory markers were found between treatment and placebo groups, with no significant differences in changes in CD4+ or CD8+ cell counts being observed between groups over time. Thus, the test of whether or not HIV immune reconstitution can be achieved by changing the microbiome has not really been documented, since the treatment in this study did not change the microbiome. There is more work to be done in this area.

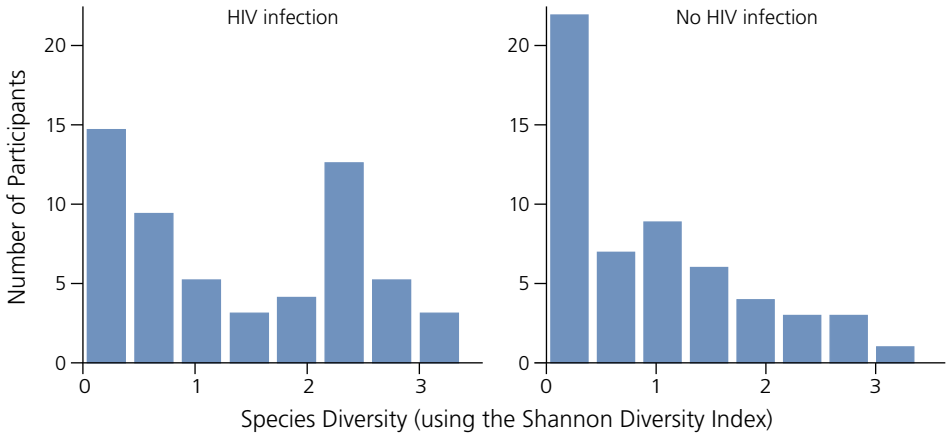


**Figure 2.** Increased risk of HIV infection with greater vaginal bacterial diversity. Adapted from McClelland et al.[5]

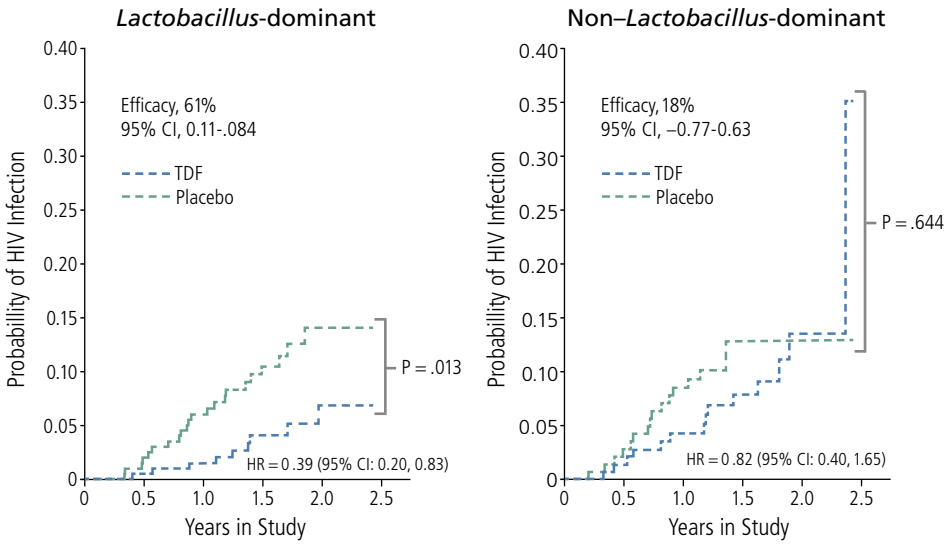


**Figure 3.** Effect of the vaginal microbiome on effectiveness of topical tenofovir disoproxil fumarate (TDF) preexposure prophylaxis in *Lactobaccillus*-dominant and non–*Lactobaccillus*-dominant cell cultures. HR is hazard ratio; CI, confidence interval. Adapted from Klatt et al.[6]

## Vaginal Microbiome in HIV

The vaginal microbiome may be of considerable importance in HIV transmission. The vaginal microbiome tends to be stable over time within individuals. In the healthy state, there is minimal diversity, with dominance of *Lactobacillus*. However, in bacterial vaginosis, there is increased diversity, with dominance of *Gardnerella*. *Lactobacillus* populations are decreased in the context of sexual intercourse (assessed by the presence of prostate specific antigen [PSA] in the sample) and are also decreased in amenorrheic women, but inflammatory mediators (interleukin [IL]-8, IL-12, and MIP-1b) are increased.[4] The presence of inflammatory mediators is also increased in the presence of PSA.

Studies have now shown that risk of HIV acquisition is increased with bacterial vaginosis and increased vaginal bacterial diversity. In a case-control study among African women who had undergone microbiomic studies and were at similar risk of HIV infection, McClelland and colleagues found that participants in the control group who did not acquire HIV infection had greater dominance of *Lactobacillus* in their microbiome than in those who acquired infection.[5] Women who acquired HIV infection had greater vaginal bacterial diversity in the context of decrease in *Lactobacillus* dominance (Figure 2). These findings provide some evidence that the microbiomic signature characterized by *Lactobacillus* dominance and less diversity is protective against HIV acquisition. The study also found that presence of particular bacterial species was associated with increased risk of acquiring HIV infection. It is of considerable interest whether further studies confirm that particular species are associated with greater transmission risk and whether this might lead to protective measures.

## Vaginal Microbiome and Topical Preexposure Prophylaxis

The efficacy of topical tenofovir disoproxil fumarate (TDF) preexposure prophylaxis in preventing HIV infection has been lower than anticipated in clinical trials, with poor adherence largely being considered the culprit. However, a recent study by Klatt and colleagues in the population of the CAPRISA (Centre for the AIDS Program of Research in South Africa) trial of topical TDF indicates that the vaginal microbiome affects efficacy.[6] In particular, preventive efficacy was 61% ($P$ = .013) versus placebo among women with *Lactobacillus*-dominant microbiomes, compared with 18% ($P$ = .644) among those without *Lactobacillus* dominance and greater frequency of *Gardnerella* (Figure 3). These investigators found that when TDF was added to cell culture in which *Gardnerella* was grown, the organism degraded tenofovir, metabolizing it to adenine, whereas no such effect was observed when TDF was put into culture containing *Lactobacillus*. These findings indicate that Gardnerella metabolizes tenofovir before it can get into the cells and protect the cells from becoming infected with HIV; as shown in Figure 4, the presence of *Gardnerella* prevents cellular uptake of tenofovir and intracellular conversion to the active diphosphate form. Klatt and colleagues have now also reported that dapivirine is also metabolized and degraded in women with the more diverse, non-*Lactobacillus*-dominant microbiomes.[7] There is no evidence that bacterial vaginosis affects the efficacy of oral preexposure prophylaxis.[8]

## Conclusion

Humans live in concert with an immense array of microbial organisms from birth to death. The microbiome differs from body site to body site

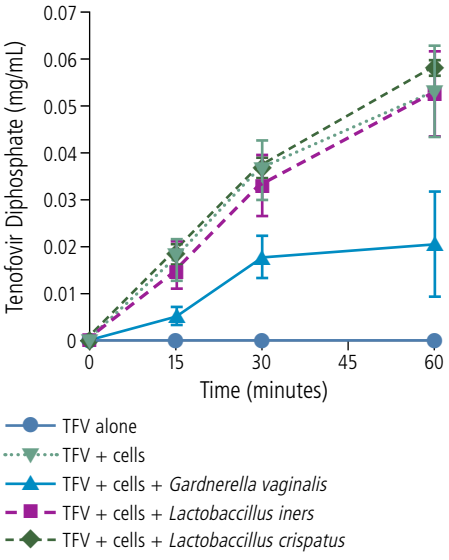


**Figure 4.** Depletion of tenofovir (TFV) by *Gardnerella vaginalis* in culture prevents accumulation of intracellular tenofovir diphosphate. No such effect is observed with *Lactobacillus* species. Adapted from Klatt et al.[6]

and from person to person, but is reasonably stable over time unless it is disturbed by antibiotics. Other environmental factors including food and those with whom we associate also have direct effects on the microbiome. The microbiome influences gut metabolism, systemic immunity, and susceptibility to disease. It changes in health and disease, including in HIV infection. We are only now beginning to distinguish the carts from the horses.

Can we alter the microbiome? Yes, but currently only with the elegance of a meat cleaver, as occurs with antibiotic treatment. Antibiotics are the most dramatic way we affect the human microbiome, usually for the worse, as in the case of *Clostridium difficile* overgrowth and *Salmonella* infection. Other approaches to beneficially change the microbiome, including probiotics, prebiotics, fecal transplantation, and bacteriophage therapy (eg, for *C difficile*), are being investigated.

*Presented by Dr Schooley in May 2018. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Schooley in July 2018.*

*Financial affiliations in the past 12 months: Dr Schooley has served as a consultant to CytoDyn, Pfizer, and Vir Biotechnology. He has received grant support from Gilead Sciences, Inc, and holds stock or stock options in Antiva Biosciences and CytoDyn.*

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*Top Antivir Med*. 2018;26(3):75-78.

*Perspective*

# Recurring and Emerging Questions Related to Management of HIV-Related Opportunistic Infections

*The incidence of HIV-related opportunistic infections (OIs) has dramatically declined with the ability to achieve viral suppression and immune reconstitution with potent antiretroviral therapy. However, a large number of patients remain at risk for OIs because they are diagnosed at late stages of HIV disease, fail to stay in treatment, or fail to maintain viral suppression. Clinicians should remain vigilant for OIs and for changes in recommended management strategies. Issues that often arise in this regard include how to interpret polymerase chain reaction diagnostic results in individuals with HIV infection; whether primary prophylaxis for* Mycobacterium avium *complex is still needed; whether clinicians should screen asymptomatic patients for cryptococcal antigen; and need for amphotericin B in treatment regimens for cryptococcal meningitis. This article summarizes a presentation by Henry Masur, MD, at the IAS–USA continuing education program held in Washington, DC, in April 2018.*

**Keywords:** HIV, opportunistic infections, *Pneumocystis pneumonia*, PCP, *Mycobacterium avium*, MAC, *Toxoplasma*, cryptococcal meningitis, PCR, diagnostics

Despite the success of current antiretroviral therapy (ART) in reducing the burden of HIV-related opportunistic infections (OIs), a large number of individuals living with HIV infection present late in HIV disease or do not maintain viral suppression and thus remain at risk for opportunistic diseases. Management of OIs is thus still relevant for practitioners who care for this patient population.

## HIV Epidemic in Washington, DC

The current state of the HIV epidemic in Washington, DC, provides an example of the ongoing risk of OIs in current patient populations. The good news in Washington, DC, is that, thanks to the efforts of many funding agencies, federal and local health administrations, clinics and hospitals, and health care practitioners, the annual number of newly recognized cases of HIV infection in this district has been reduced from approximately 1100 to approximately 350 over the last 10 years. However, the prevalence and incidence in this district remain unacceptably high. As of 2016, the overall prevalence of HIV infection was 1.9%, including rates of 0.9% among whites, 3.1% among African Americans, and 1.2% among Hispanics/Latinos. Data from 2016 indicate that among individuals with known HIV infection, only 63% are virally suppressed, with only 47% of youth with HIV infection being virally suppressed (Figure 1). Thus, there remains a large patient population with low or declining CD4+ cell counts who are susceptible to OIs. From 2011 to 2015, 21% of newly diagnosed individuals had CD4+ cell counts below 200/µL at diagnosis; at 1 year after diagnosis, 50% of these patients still had counts below 200/µL.

## Surrogate Markers for Incidence of OIs in Recent Years

In the absence of hard data on incidence of OIs in recent years, there are some indices that can provide an idea of the scope of the problem of HIV-related OIs. One such metric is how often the National Institutes of Health (NIH)-Centers for Disease Control and Prevention (CDC)-Infectious Disease Society of America (IDSA) OI guidelines are accessed online. During the period from March 1, 2017, to February 28, 2018, adult OI guidelines were accessed more than 420,000 times; of these, approximately 72,000 page views were for *Pneumocystis jiroveci* pneumonia (PCP), 45,000 for tuberculosis drug dosing, 28,000 for toxoplasmosis, and 25,000 for *Mycobacterium avium* complex (MAC).

## Most-Asked Questions about OIs

Very few controlled trials related to the diagnosis, therapy, or prevention of OIs are currently being performed, in contrast to the numerous studies performed in the 1980s and 1990s. The guidelines currently rely on observational data from patients with HIV infection, and experience in other patient populations that are plausibly applicable to patients with HIV infection. Thus some of the recent changes in the guidelines are based on observational data from patients with HIV infection, and some of the recommendations are extrapolated from other patient populations.

### Polymerase Chain Reaction (PCR)-Based Diagnosis

For the management of HIV-related OIs, clinicians must be aware that microbiology laboratories are changing their testing platforms dramatically. When organisms are grown in conventional media, any growth can often be identified by genus and species within a few hours by techniques such as Matrix Assisted Laser Desorption/Ionization/Time of Flight Mass Spectrometry (MALDI-TOF) Other specimens are tested by qualitative nucleic acid amplification methods that are extremely sensitive for minute quantities of organisms and are highly specific for identifying organisms accurately. Thus, the clinician is getting information faster, and can obtain

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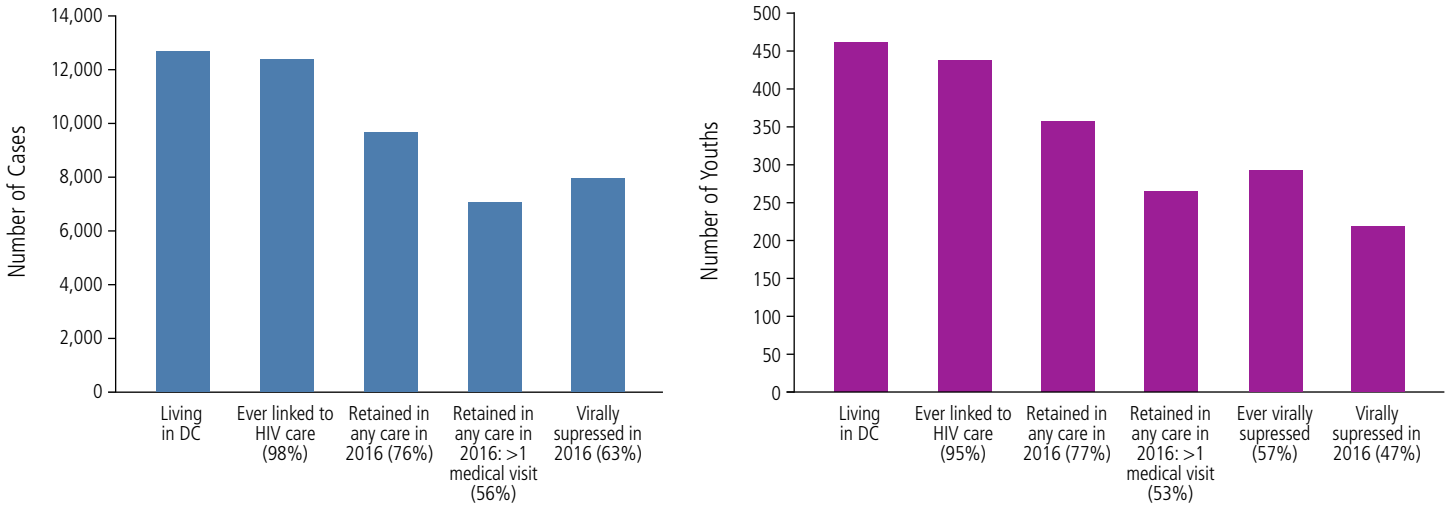


**Figure 1.** Contact with HIV care and viral suppression among known individuals (left) and youth (right) with HIV infection in Washington, DC (DC) in 2016. Adapted from the DC Health Annual Epidemiology and Surveillance Report, 2017.[10]

far more sensitive testing, often with concurrent information about whether specific resistance-associated genes are present. Thus, the data coming to clinicians must be interpreted with analytic approaches that are considerably different from interpretations that clinicians made when diagnoses were established based on smears of biologic fluids and tissues, conventional cultures, antigen detection assays, and serum antibody tests. For example, increasingly, laboratories are not performing immunofluorescence assays for PCP, with diagnoses being primarily based on PCR assays.

The question is whether the detection of an organism in respiratory sample, stool, cerebrospinal fluid (CSF), or blood is an indication that the identified organism is causing the syndrome of concern rather than being detected as a bystander/colonizer or contaminant. For instance, when bronchoalveolar lavage fluid is tested by the Biofire Platform (Salt Lake City, Utah), does the detection of an organism provide the clinician with assurance that *Pneumocystis* is the causative organism?

Consider a scenario in which a 35-year-old patient recently diagnosed with HIV infection has a nadir CD4+ cell count of 90/μL and is on dolutegravir-based ART, and presents with low-grade fever and cough. For the Biofire 2 panel, the appropriate specimen to detect upper respiratory pathogens is a nasopharyngeal swab (not nasal swab) so that cells in the posterior retropharynx are collected. The Biofire upper respiratory panel tests for a number of bacteria such as *Bordetella*, *Chlamydophila pneumonia*, and *Mycoplasma pneumonia*, and several viruses such as influenza, parainfluenza, coronavirus and adenovirus. If the specimen is positive for coronavirus, for example, how much confidence is there that the identified agent is the cause of the patient's syndrome?

Coronavirus may be present in very small quantities and represent colonization following an acute infection days or weeks before, depending on the patient's immune status (ie, some immunosuppressed persons can shed a respiratory virus for many months after an acute infection). If coronavirus is the only pathogen detected, the clinician might assume that coronavirus has caused the clinical illness, assuming the clinical illness is compatible with what is known about a coronavirus infection. However, the patient may in fact be infected with an organism not tested for by this platform, or missed by this specimen or by a process that is not due to an infection.

For lower respiratory panels, there are similar difficulties with interpreta tion of these sensitive detection systems. Patients may have colonization in their lower respiratory tracts (or in upper respiratory secretions contaminate lower respiratory specimens) with respiratory viruses, or with MAC, *Cryptococcus*, or *Pneumocystis*. Thus, because PCR is ultrasensitive compared with conventional smears and cultures, a negative PCR test is convincing evidence that the pathogen is not present. A positive result, however, must be evaluated in the context of the clinical situation, and what other pathogens or processes are concurrently present. Some pathogens that can colonize the airways of an individual with HIV infection, including herpes simplex virus, cytomegalovirus (CMV), MAC, and *Candida*, are so rarely the cause of pulmonary dysfunction in persons with HIV infection, even those with very low CD4+ cell counts, that they should be considered as extremely unlikely etiologic agents for pulmonary dysfunction.

Conventional cultures can detect colonizers as well, but conventional cultures are not as sensitive as PCR. Thus, when the cultures are positive, the quantity of organisms present is more likely to indicate causality; the same is true for a smear. In addition, in contrast to PCR, conventional cultures can be quantitative or semiquantitative, and can be interpreted in association with smears.

As an example of the diagnostic uncertainty associated with multiplex results, consider a patient who looks toxic, has diffuse bilateral infiltrates, and has an oxygen saturation level of

91% on room air. A pulmonologist performs bronchoalveolar lavage and a lower respiratory tract PCR panel is ordered. If the result comes back as positive for *Pneumocystis*, CMV, *Cryptococcus*, *Toxoplasma*, or coronavirus, which would be convincing as the cause of the patient's pulmonary pathology? Although any of these organisms could be the cause of the pulmonary dysfunction, the most suggestive finding would be *Toxoplasma*, because it is the only organism among these that is not ordinarily found in the respiratory tract as a latent organism. CMV and coronavirus are rarely the cause of serious lower respiratory tract infection in individuals with HIV infection. *Cryptococcus* is not common, but would be a consideration. *Pneumocystis*, as mentioned above, could be the cause of the pulmonary dysfunction or could be colonizing the respiratory tract.

Thus, as we evolve into the era of PCR diagnostics, guidelines are struggling with how to make a diagnosis for *Pneumocystis* if the laboratory does not perform immunofluorescence. Similar considerations apply to the detection of other bacteria, viruses, fungi, and protozoa in these multiplex panels. Clinicians need to be cognizant of what tests the laboratory is performing when they interpret report the presence of organisms in a biologic specimen.

Multiplex PCR platforms are currently being used by many diagnostic laboratories for stool, CSF, and blood. Some platforms also detect the presence of resistance-associated genes for certain pathogens, such as *mecA* and *mecC* for methicillin-resistant *Staphylococcus aureus*. As with respiratory specimens, the issue for clinicians will be how to determine if the presence of a pathogen qualitatively (with no quantitation) is convincing evidence of the need to treat the organisms identified.

## MAC Prophylaxis

The use of chemoprophylaxis for the prevention of OIs is still an important component of HIV care. However, patients will rarely take OI prophylaxis without also taking ART. For patients who respond to ART, once the viral load falls below the level of laboratory detection, the degree of immunoincompetence is diminished substantially, even if the CD4+ cell count has not risen substantially. However, determining when OI prophylaxis can be stopped has been difficult if one is using viral load and CD4+ cell count as interacting factors.

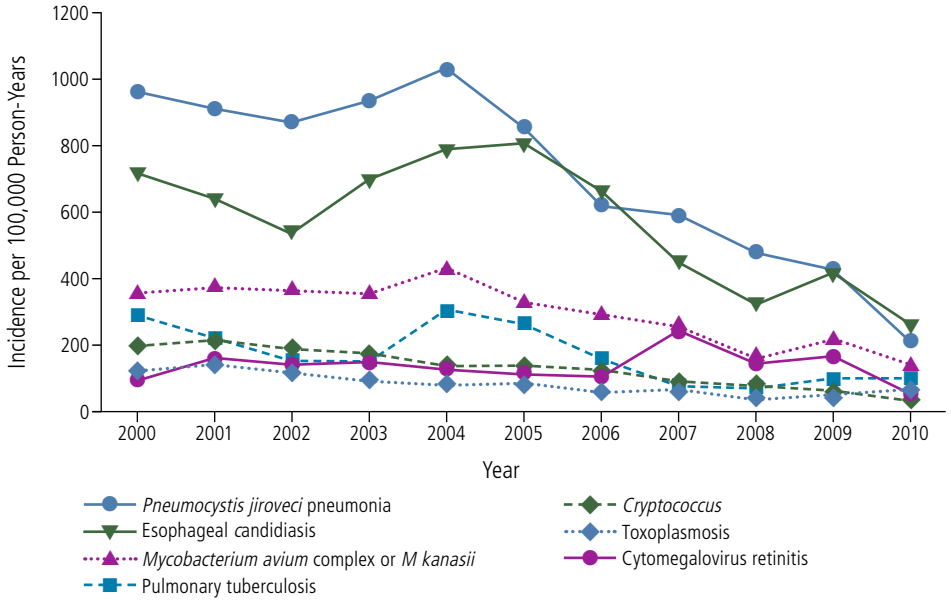


**Figure 2.** NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) data on incidence of HIV-related opportunistic infections in 2000 to 2010 in the United States and Canada (n=63,541). Adapted from Buchacz et al.[4]

Guidelines and most experts still advocate using CD4+ cell count criteria for stopping and starting OI prophylaxis. OI prophylaxis is especially important for patients with low CD4+ cell counts who take their medications regularly, but who have drug-resistant virus and thus low CD4+ cell counts and high viral loads.

There have been few changes in recommendations for prophylaxis except for the recommendations for MAC. The current IAS-USA guidelines[1,2] do not recommend primary MAC prophylaxis for individuals on effective ART, and the NIH-CDC-IDSA guidelines[3] do currently, as of August 2018, recommend such prophylaxis. The latter guidelines are likely to change in the very near future on the basis of accumulating observational evidence about the rare occurrence of MAC in the current era. As shown in Figure 2, data through 2010 show the decline in OIs during the potent combination ART era. Although not exhibiting as great a decline as PCP, the incidence of MAC was reduced by approximately 45% between 2000 and 2010.[4]

Data from HOPS (HIV Outpatient Study) suggests that the risk of MAC is low among patients on ART who have nadir CD4+ cell counts below 50/μL, even in the absence of primary prophylaxis.[5] Of special interest, among patients in the study with CD4+ cell counts below this threshold who were started on ART, there were no cases of MAC among 41 who did not receive prophylaxis nor among 30 who did. This is a small sample size, but it illustrates the dearth of cases in most observational studies.

The uncommon individuals with HIV infection who do develop disseminated MAC today have much better survival than they would have 1 or 2 decades ago, which is not unexpected given the efficacy of current ART. Data from San Francisco show declining mortality from AIDS-defining OIs, including MAC, with the advent of potent combination ART, with many patients having long-term survival after MAC diagnosis (Figure 3).[6] Based on the facts that there is a lower incidence of MAC in this country, that those who start ART

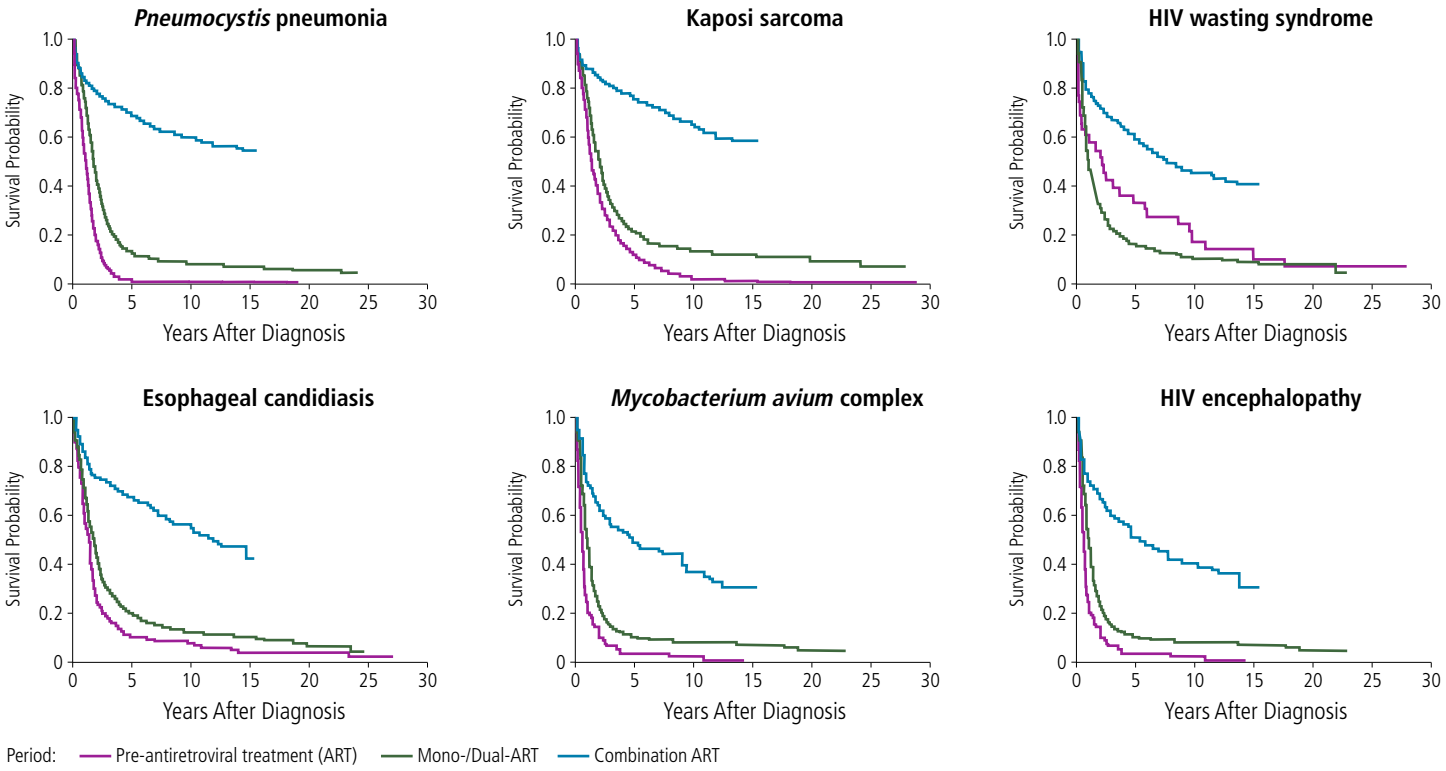


**Figure 3.** Survival after diagnosis of selected AIDS-defining opportunistic infections in San Francisco, California, 1981 to 2012 (n=20,858). Adapted from Djawe et al.[6]

appear to have low risk of MAC disease whether on prophylaxis or not, and that we are managing the disease better, the NIH, CDC, and IDSA will likely also soon recommend that no primary MAC prophylaxis is needed if effective ART is initiated and viral suppression is achieved.

It is also important to note that the incidence of disseminated MAC in this era can be confounded by cases of immune reconstitution syndrome (IRIS) that are associated with lymph node or other culture-positive tissue, ie, some definitions of disseminated MAC may include positive blood cultures for MAC. Incidence and mortality data need to be carefully assessed to determine what patient population is being described, ie, only those with positive blood cultures, or those with positive cultures only from sites other than blood who may have IRIS.

## Screening for Cryptococcal Antigen at CD4+ Cell Counts Below 100/µL

The World Health Organization recommends screening for cryptococcal antigen in patients with CD4+ cell counts below 100/µL, whereas NIH-CDC-IDSA guidelines leave screening to the discretion of practitioners. Most practitioners in the United States do not perform such screening. The practice of US practitioners likely reflects the finding that in the United States, the frequency of asymptomatic cryptococcal antigenemia is low: approximately 2.9% of asymptomatic patients with a CD4+ cell count below 100/µL and 4.6% with CD4+ cell counts below 50/µL have a positive cryptococcal antigen test. The range of antigen titers observed in these cases spans from very low to impressively high. Some patients do develop a syndrome following initiation of ART that may be related to *Cryptococcus*, but it is also hard to determine whether this disease is related to active organism replication, or if it is IRIS.

If screening for asymptomatic cryptococcal antigen is done, and a positive result is obtained, a lumbar puncture should be performed to determine if the patient has asymptomatic meningeal infection. If the patient has a negative CSF cryptococcal antigen test, some clinicians would choose to treat with ART alone. Others would treat with ART plus fluconazole. If the CSF antigen is positive, liposomal amphotericin B plus flucytosine is the regimen of choice.

Thus there remains uncertainty regarding screening in the United States. Potential advantages of screening include the fact that earlier cryptococcal meningitis treatment leads to better outcomes and that risk of IRIS is reduced by treating cryptococcal disease for 2 to 8 weeks before starting ART. To date, there is very little evidence in the United States that survival among asymptomatic patients is better with prospective monitoring than with a strategy that initiates treatment when patients have manifestations due to active cryptococcal disease. These manifestations might include fever, headache, or more obvious presentations of meningitis, sepsis, or other organ involvement.

## Does Amphotericin B Need to be Used in Cryptococcal Meningitis?

Another frequently asked question regarding cryptococcal disease is

whether there are recommended regimens for cryptococcal meningitis that do not include liposomal amphotericin B. Azole drugs are fungistatic, whereas amphotericin B is fungicidal. It has been demonstrated that there is a good correlation between outcome of disease and reduction in CSF cryptococcal titers. A number of studies have examined whether higher doses of azoles can be as effective as amphotericin B. A study reported at the 2018 Conference on Retroviruses and Opportunistic Infections showed that increasing fluconazole doses as high as 2000 mg/day did not provide the same CSF clearance rate as amphotericin B. The proportions of patients with negative CSF cultures at week 10 were 45%, 56%, and 60% with fluconazole doses of 1200, 1600, and 2000 mg/day, respectively, compared with 81% with amphotericin B treatment.[7]

Thus, in the United States, it continues to be recommended that an amphotericin-based regimen be used in all cases of cryptococcal meningitis (fluconazole alone can be used for nonmeningeal disease). Liposomal amphotericin plus flucytosine is the most rapidly fungicidal regimen. Amphotericin B plus fluconazole is also recommended as an alternative regimen, exhibiting similar mortality rate but slower CSF sterilization.

There is also debate about whether corticosteroid therapy should be used empirically when starting therapy for cryptococcal meningitis. One study has shown a higher rate of poor outcomes and adverse events when dexamethasone was added to amphotericin B plus fluconazole. Thus, empiric corticosteroids in the absence of evidence of increased intracranial pressure are not recommended.

### Which Varicella Zoster Virus Vaccine Is Recommended

Another frequently asked question is whether a recently developed varicella zoster virus vaccine should be used in individuals with HIV infection. The previous live attenuated vaccine is contraindicated in patients with CD4+ cell counts below 200/µL. It is recommended for patients with CD4+ cell counts over 200/uL, although their immunologic response is not as robust as individuals without HIV infection.

A newer recombinant adjuvant vaccine has become available—a 2-dose subunit vaccine containing recombinant glycoprotein E in combination with a novel adjuvant. It is 68% effective for reducing the occurrence of clinical varicella zoster virus infection in post-hematopoietic stem cell transplant recipients. However, there are very limited data in HIV infection, with 2 small studies having assessed safety and immunologic response, but not clinical efficacy. Whether this vaccine will become the recommended immunization for individuals with HIV infection with CD4+ cell counts below or above 200/uL is unknown. The use of this vaccine seems plausible because it is not a live virus vaccine. However, the effect of the adjuvant has not been studied in this population, nor has the clinical efficacy been established.

Similarly, there are no robust efficacy data for the new adjuvanted hepatitis B vaccine, nor are there extensive safety data in the population with HIV infection for this adjuvanted product. Thus, at this time this new vaccine is not recommended for populations with HIV infection, although there is no evidence at this time that the vaccine is harmful or less effective than the current product.

### Treatment for *Toxoplasma* Encephalitis

A common question regarding treatment for *Toxoplasma* encephalitis is: If pyrimethamine is either unavailable from suppliers or too costly for insurance plans, is trimethoprim-sulfamethoxazole (TMP-SMX) an appropriate initial therapy. And: Is TMP-SMX superior to atovaquone?

Data from an observational trial reported in 2009 showed good results with TMP-SMX that appeared based on small numbers of cases to be comparable with those reported for pyrimethamine.[8] Clinical response was observed overall in 77 (93%) of 83 patients, including response in 26 of 28 patients who were retreated for second episodes. Treatment-limiting toxicity of TMP-SMX was observed in 6 patients (7%). A small comparative trial reported in 1998 showed no difference in progression rates between 35 patients receiving pyrimethamine-sulfadiazine (14%) and 37 receiving TMP-SMX (16%).[9]

The regimens of choice for toxoplasmosis based on extent and quality of evidence remain pyrimethamine plus sulfadiazine (plus leucovorin) or pyrimethamine plus clindamycin (plus leucovorin). If pyrimethamine is not available, TMP-SMX is the highest-rated alternative. TMP-SMX has the additional advantage that it can be given intravenously, an advantage for seriously ill patients. Pyrimethamine cannot be administered parenterally.

Atovaquone is not quite as reliable as sulfadiazine-pyrimethamine, because the time to steady state levels is 3 to 4 days and absorption can be erratic if the patient is not taking a high-fat diet. Atovaquone with or without another drug is adequate but not considered to be as effective as TMP-SMX.

### Is Hepatitis A an OI?

An outbreak of hepatitis A infection began in San Diego County in California in November 2016 and spread to Santa Cruz, Los Angeles, and Monterey Counties, and now to several other states. On this basis, there have been many questions regarding whether hepatitis A is an HIV-related OI. There was a report of 704 cases of hepatitis A virus infection in this outbreak, with 461 hospitalizations and 21 deaths. Although some cases occurred in patients with HIV infection, the epidemiologic association with acquisition was poor sanitation in the context of homelessness and among individuals who use injection drugs. Presence of hepatitis B virus and hepatitis C virus, but not HIV infection, were correlated with morbidity and mortality. Thus, hepatitis A is not considered an HIV-associated OI and is unlikely to be featured in OI guidelines. However, hepatitis A immunization should be offered to all individuals with HIV infection who are seronegative for antibody to hepatitis A virus.

## Conclusion

OIs remain a major challenge for individuals with HIV infection. A substantial number of people in the United States continue to present with 1 or more OIs as the initial manifestation of their HIV infection. A substantial number of individuals with HIV infection are not in continuous care and do not have durable viral suppression.

Although new antifungal and antiherpes virus drugs and new immunizations are becoming available, few of them have been assessed in populations with HIV infection in robust controlled trials. Thus, updates of guidelines for management of OIs in individuals with HIV infection in terms of prevention or therapy will have to rely on observational studies of individuals with HIV infection and plausible inferences from other populations.

*Presented by Dr Masur in April 2018. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Masur in September 2018.*

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

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*Perspective*

# Human Papillomavirus–Related Malignancies in HIV Infection: Anal and Oropharyngeal Cancers

*Human papillomavirus (HPV)-related cancers, including anal cancer and oropharyngeal cancer, occur more frequently in individuals living with HIV infection than in the general population. Strategies for prevention among individuals with HIV infection include HPV vaccination, anal cancer screening programs, and early initiation of antiretroviral therapy (ART). HPV vaccination is not yet optimally used; a stronger and more persistent effort is needed to increase vaccination rates. Although anal cancer screening is not recommended by all authorities, there is a least some evidence that screening and treatment of anal high-grade squamous intraepithelial lesions may prevent progression to cancer. However, more definitive evidence is needed. Early initiation of ART reduces the risk of infection-related cancers, with some evidence of benefit in preventing HPV-associated cancer in individuals with HIV infection. This article summarizes a presentation by Timothy J. Wilkin, MD, MPH, at the IAS–USA continuing education program held in Los Angeles, California in April 2018.*

**Keywords:** HIV, HPV, infection, anal cancer, oropharyngeal cancer, screening, vaccination

Rates of anal cancer in women and men who have sex with men (MSM) with HIV infection are far higher than in the general population, and higher than current rates of cervical cancer, a human papillomavirus (HPV)-associated disease, in the general population of women in the United States (Figure 1) and globally.[1] Rates of cervical cancer in the general population have been dramatically reduced through prevention services including active screening, and more recently by HPV vaccination. HPV vaccination and screening efforts offer the best chance to reduce risk of HPV-related cancers in the population with HIV infection.

## Anal Cancer

Most initial anal HPV infections are cleared by host immune responses. A subset of infection persist, sometimes leading to low-grade squamous intraepithelial lesions (LSILs). In a subset of these cases, infection continues with integration of HPV into cellular DNA and progression to high-grade squamous intraepithelial lesions (HSILs). A subset of HSILs progress to invasive anal cancer. In individuals living with HIV infection, immunosuppression including reduced cell-mediated immunity reduces clearance of HPV and increases risk of progression to HSILs and invasive cancer.

The approaches to prevent invasive anal cancer are HPV vaccination and preventive screening. The goal of screening is to identify precancerous areas (eg, HSILs) of the anus that can be removed to prevent invasive cancer. Screening is performed via cytology (or by HPV testing, although such testing is not approved by the US Food and Drug Administration [FDA] for screening). Diagnosis of HSILs is performed with high resolution anoscopy (HRA). The procedure uses staining with acetic acid and Lugol's iodine to identify areas in which HSILs are suspected; the suspicious areas are biopsied for histologic examination. If HSILs are diagnosed, the areas are treated with ablation or topical therapy. In some cases, early and limited invasive disease may be identified, which can be treated promptly and effectively via excision. However, the majority of anal cancers are already extensive enough at diagnosis to require treatment with chemotherapy and radiation. Such treatment is effective in most cases, but is associated with substantial morbidity. Practitioners performing HRA require formalized training, and substantial experience is needed to reliably identify HSILs for diagnosis and treatment.

MSM living with HIV infection have elevated rates of HSILs (reaching 50% in some studies) and anal cancer, and are thus candidates for screening. Other men and women with HIV infection also have elevated rates of anal cancer, indicating that they, too, are potential candidates for anal cancer screening. A study recently reported by Stier and colleagues[2] found an anal HSIL prevalence of 28% among women

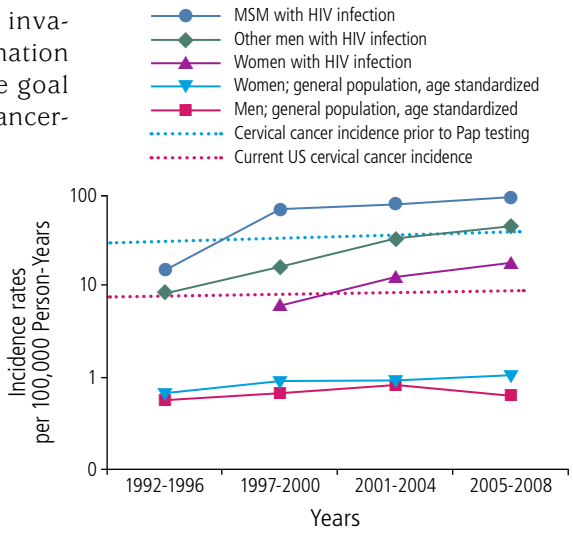


**Figure 1.** Incidence of anal cancer in individuals with HIV infection and the general population in the United States. Dashed horizontal lines indicate incidence of cervical cancer in the general population prior to and after introduction of Papanicolaou (Pap) testing. MSM indicates men who have sex with men. Adapted from Schim van der Loff et al.[1]

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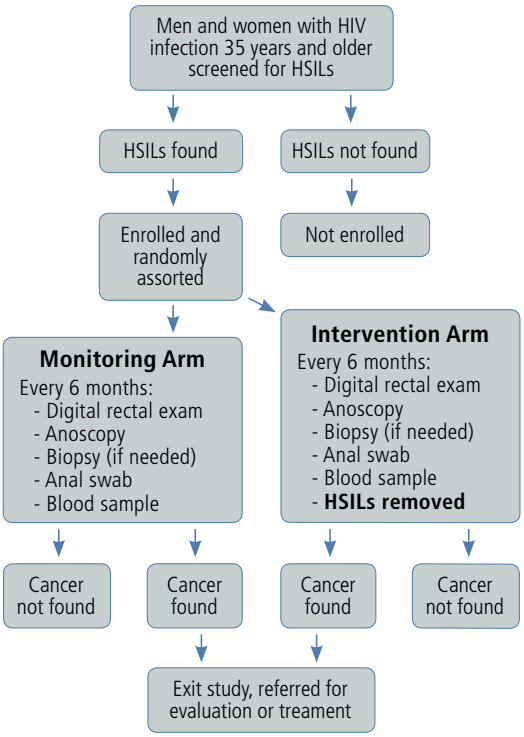


**Figure 2.** Design of the National Cancer Institute–sponsored ANCHOR (Anal Cancer HSIL Outcomes Research) study. HSIL indicates high-grade squamous intraepithelial lesions.[20]

with HIV infection (77 of 253). Most of the HSILs were found in women with an abnormal anal cytology, although 22% of HSILs occurred in women with normal anal cytologic results. Such findings suggest that, similar to cervical cytology, anal cytology must be repeated in serial screenings, with repeated testing being more likely to yield an abnormal result if HSILs are present.

Another issue in cancer prevention is the success in treating HSILs, for which relatively few data are available. The recently reported AIDS Malignancy Consortium 076 trial has shown benefit of ablation of HSILs in clearing disease using infrared coagulation.[3] In the trial, 120 individuals with HIV infection who had relatively limited anal HSILs were randomly assigned to infrared coagulation ablation (n = 60) or careful monitoring for 1 year (control group; n = 60). Complete response was observed in 63% of the ablation group versus 27% of the control group ($P < .001$), with complete or partial response being observed in 75% versus 43% ($P < .001$). Numerous issues in anal cancer screening remain to be confronted. One is that the large majority of people with anal HSILs will never develop anal cancer, meaning large numbers of individuals with anal HSILs must be treated to prevent a relatively few cancers, making the cost-effectiveness unclear. Further, treatments for anal HSILs are not well studied and are clearly less effective than those for cervical HSILs. Recurrent anal HSILs are the norm, with numerous treatments usually needed to clear disease. Accessing HRA and treatment for anal HSILs remains difficult, with a relative dearth of skilled HRA practitioners for patient referral. Currently, screening is not yet recommended by all organizations setting standards for health care maintenance. Anal cancer screening is recommended in HIV Medicine Association[4] and New York State guidelines,[5] but is not recommended in Centers for Disease Control and Prevention (CDC) opportunistic infection guidelines.[6] The age at which to begin screening remains unclear. Although there is a high prevalence of anal HSILs in younger individuals, a screening program should probably target patients age 35 years or older based on cost-effectiveness modeling. Many HSILs resolve without intervention, and younger patients often have more difficulty adhering to HIV medications, without adding additional complicated procedures at an age when the rate of anal cancer is so low. In addition, definitive data that treating anal HSILs reduces the risk of anal cancer are needed.

## Oropharyngeal Cancer

Unlike HPV-related anal, cervical, vulvar, penile, and other cancers, HPV-related oropharyngeal cancer (OPC) does not have an identifiable premalignant lesion and there is no analogous cytologic test to aid in early identification currently recommended. It is possible to do HPV testing, but this is not part of standard clinical practice. Currently, there are no accepted screening programs for prevention of HPV-related OPC.

Approximately 70% of OPC is caused by HPV. Of HPV-related OPC, HPV-16 is the cause in approximately 85% of cases, with the serotypes in the 9-valent HPV vaccine being accountable for 94% of HPV-related OPC.[7] Studies using SEER (Surveillance, Epidemiology, and End Results) data from 2005 to 2008 showed that the incidence of OPC is 2- to 3-times higher in individuals living with HIV infection than in the general population, and 4-fold higher in men with HIV infection than in women with HIV infection.[8] As of 2010, the estimated rates of OPC in men exceed rates of cervical cancer in women in the general population, with the trend projected to continue as cervical cancer rates continue to decline and OPC rates in men increase.[9]

## Reducing HPV-Related Cancer in HIV

The ongoing large-scale National Cancer Institute-sponsored ANCHOR (Anal Cancer HSIL Outcomes Research) study will address whether removal of anal HSILs effectively prevents anal cancer (Figure 2). In the trial, more than 17,000 men and women living with HIV infection, age 35 years or older, are being screened for anal HSILs. Approximately 5000 individuals with anal HSILs are being randomly assigned to a monitoring arm or an intervention arm in which HSILs are treated with the best modalities available including ablative and topical treatments. Participants will be followed up for 5 to 8 years, with those in the intervention arm being treated again upon recurrence of HSILs. Enrollment in the study is open at sites across the United States including Puerto Rico, and information can be found at www.anchorstudy.org/.

With regard to prevention by vaccination, a study reported in 2011 by Palefsky and colleagues[10] showed that the quadrivalent HPV vaccine was approximately 95% effective in preventing persistent anal infection in a

subgroup of approximately 600 young MSM, considered to be a relatively HPV-naive group, with a significant reduction in anal squamous intraepithelial lesions also being observed. The outcome of the trial resulted in FDA approval of the quadrivalent vaccine for preventing anal cancer in both men and women.

Clinical studies have found that HPV vaccination is safe and highly immunogenic in adults and children living with HIV infection. The question then became whether HPV vaccine could be effective in individuals with HIV infection who are already highly exposed to HPV and have high rates of ongoing HPV infection. In the AIDS Clinical Trials Group 5298 study, individuals with HIV infection 27 years of age or older with no history of HPV-related cancers and any CD4+ cell count or plasma HIV-1 RNA level were randomly assigned to receive quadrivalent vaccine or placebo at 0, 8, and 24 weeks.[11] Participants were screened with HRA, anal cytology, and anal and oral HPV testing, followed by anal and oral HPV testing and cytology every 6 months. Men were required to have a history of recent receptive anal intercourse. Treatment of anal HSILs during the study was performed using local standards of care.

The results showed non-statistically significant reductions in the composite of persistent anal HPV of quadrivalent HPV vaccine types or single detection at last visit (n = 26 in the vaccine group and n = 33 in the placebo group; hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.45-1.26) and in persistent anal HPV alone (13 patients vs 17 patients; HR, 0.73; 95% CI, 0.36-1.52), but no impact on anal HSILs (46 vs 45 patients; HR, 1.0; 95% CI, 0.69-1.44). A significant reduction was observed in persistent oral HPV in the vaccination group (1 patient vs 8 patients; HR, 0.12; 95% CI, 0.02-0.98), although the number of cases was low.

Other data support a protective effect of HPV vaccine against oral HPV infection. For example, in a study in Costa Rica, a large number of women received bivalent vaccine (covering HPV 16 and 18) and were followed up for 4 years for cervical infection and disease. The vaccine efficacy in preventing cervical infection was approximately 75%. A one-time assessment at the end of the 4 years showed efficacy of approximately 95% in preventing oral infection and 60% in preventing anal infection.[12,13] The mechanism of protection against oral disease appears to be achieving high levels of anti-HPV IgG in oral fluids. One study showed a high correlation of serum and oral gargle antibodies in vaccine recipients (Spearman's rho, 0.8432; $P<.0001$) after 7 months.[14]

Data from NHANES (National Health and Nutrition Examination Survey) from 2011 to 2014 indicate a vaccine effect in preventing oral HPV infection. Oral HPV infection was found in 22 (1.7%) of 1311 men not receiving vaccine and 1 (0.8%) of 116 who received vaccination ($P = .019$), and in 8 (0.8%) of 1021 women not receiving vaccine versus 1 (0.2%) of 447 who received vaccination ($P = .05$).[15]

## Reducing Risk of HPV-Associated Cancer—Need for Increased Vaccination

A concerning aspect to be noted from the NHANES data mentioned above is that only a minority of individuals eligible for HPV vaccine had received vaccination. There is considerable evidence proving efficacy of HPV vaccination for prevention of HPV infection and associated disease, yet vaccination rates remain less than optimal, representing missed chances at preventing disease.

Thus far, 3 HPV vaccines have been FDA-approved: the bivalent vaccine (covering HPV 16 and 18); the quadrivalent vaccine (covering HPV 6, 11, 16, and 18); and the 9-valent vaccine (adding HPV 31, 33, 45, 52, and 59 to the quadrivalent coverage). As noted, the 9-valent vaccine provides coverage against HPV types that are responsible for more than 90% of HPV-related cancers and is the only vaccine that is currently available. The current Advisory Committee on Immunization Practices (ACIP) HPV vaccine recommendations are shown in the Table.[16] For girls, routine vaccination at age 11 to 12 years is recommended, with catch-up vaccination up to age 26 years for those who have not received vaccination. For boys, routine vaccination is recommended at age 11 to 12 years, with catch-up vaccination to age 21 years in the general population. The guidelines state that catch-up vaccination should be extended to age 26 years for men with HIV infection, other immunosuppressed men, and MSM. For the 9-valent vaccine, there is a 2-dose schedule if vaccination is started before the age of 15 years. The standard 3-dose schedule should be used if vaccination is started at an older age or in individuals with immunosuppression.

**Table.** Advisory Committee on Immunization Practices Human Papillomavirus Vaccine Recommendations. Adapted from Meites et al.[16]

| |
|---|
| **Girls and Women** |
| • Routine vaccination of girls ages 11 to 12 years<br>• Catch-up vaccination up to age 26 years |
| **Boys and Men** |
| • Routine vaccination of boys ages 11 to 12 years<br>• Catch up vaccination up to age 21 years<br>• Routine vaccination of boys with HIV infection, other immunosuppressed individuals, and men who have sex with men through age 26 years |
| **Dosing Schedule** |
| • 2 doses (0 and 6 months) when starting prior to age 15 years<br>• 3 doses (0, 1-2, 6 months) after age 15 years and if having any immune suppression |

Another mechanism for reducing risk of HPV-related cancers in HIV infection is to ensure early initiation of antiretroviral therapy (ART). Benefits of early initiation of ART in reducing risk of cancers was demonstrated by the START (Strategic Timing of Antiretroviral Treatment) trial examining early versus delayed ART.[17] The study showed that early initiation of ART reduced risk of HIV-related cancers by 76% ($P = .002$). Additional modeling suggested that early initiation of ART

with yearly cytology or yearly anoscopy could reduce risk of anal cancers by 25%.[18] Statin use was associated with a 72% reduction (95% CI, 0.18-0.90) in anal cancer among people living with HIV in an analysis of the Veteran Affairs population.[19] Broad use of statins may be a potential approach to reducing cancer risk among people with HIV infection.

## Summary

Anal cancer is a common cancer in HIV-infected populations. Screening for anal cancer should be considered for HIV-infected populations, although data to support screening are limited and further study is needed. HPV vaccination is the best hope for prevention of HPV-related cancers. Ideally HPV vaccination should be administered prior to sexual activity for maximal benefit. All HIV practitioners should be advocates for HPV vaccination. Emerging data support the efficacy of vaccination against HPV-related oropharyngeal cancer. It remains a question whether a clinical trial is needed to definitively prove efficacy. A world-wide push for early initiation of ART should lead to reduced incidence of HPV-related cancer.

*Presented by Dr Wilkin in April 2018. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Wilkin in August 2018.*

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*Top Antivir Med.* 2018;26(3):85-88.

*Perspective*

# Opioid Addiction, Opioid Addiction Treatment, and HIV Infection

*Available data indicate that opioid substitution treatment can successfully reduce rates of HIV transmission and that patients receiving such treatment can adhere to therapies for HIV, hepatitis C, and tuberculosis infection. Integration of opioid substitution treatment into the HIV clinic setting can make such treatment easier and improve retention in treatment. This article summarizes a presentation by R. Douglas Bruce, MD, MA, MS, at the IAS–USA continuing education program held in Chicago, Illinois, in May 2018.*

**Keywords:** Opioids, addiction, HIV, methadone, buprenorphine, naloxone

Opioid overdose is a leading cause of accidental death in the United States. Figure 1 shows the increase in deaths involving opioids in this country between 2000 and 2016. Prescribers tend to be the target of blame for the current epidemic of opioid addiction. Although prescribers did have a role to play in the current state of affairs, there are a number of factors that contribute to this problem. Heroin was invented in Europe in the late 1800s, and veterans returning from Germany after World War I brought it to the United States. The situation was so dire that for 1 year, a heroin maintenance program was run in New York City, until it was struck down by the US government for being in violation of the Harrison Narcotic Act. With that Act, the treatment of opioid addiction was removed from the hands of primary care physicians. The problems of opioid use and the connections between opioid use and HIV infection are not limited to the United States; they are truly global issues.

## Opioid Addiction

Addiction can be defined as a state in which an individual engages in compulsive behavior. The behavior is reinforcing (that is, pleasurable or rewarding), and there is a loss of control in limiting the intake of the substance. Drug use is a personal experience, with individuals taking drugs to *feel good*, to have novel feelings, sensations, and experiences, as well as to share them. Or they may take drugs to *feel better*, to lessen anxiety, worries, fears, depression, and hopelessness. Most individuals with addiction are taking drugs to *feel better*; some have been victims of sexual assault, physical violence, or emotional violence. In Africa, female drug users often even feel threatened and intimidated within health care settings.[1] Such individuals are taking drugs, instead of continuing to relive a negative experience, because they want to *feel better*.

As to why some people who use drugs become addicted and some do not, the prevailing model is that addiction represents a continuum between biology and genetics, and the environment. Although someone may have a genetic predisposition to having addiction, this does not necessarily mean that they will become addicted. Often an environmental trigger (eg, domestic violence) or environmental exposure (eg, growing up with people who use drugs) precipitate a movement into drugs. Among people who use drugs, those with a genetic predisposition have a greater probability of becoming addicted. Drug dealers are functionally aware of this continuum when they provide free drugs to new users, knowing the drugs are going to make some proportion of the users feel so much better that they will want more.

Drugs hijack brain circuits designed for survival and strongly influence motivational priorities. Dopamine bursts in the nucleus accumbens are induced by eating a meal, having sex, and using heroin—with heroin use providing the greatest dopamine reward. Many heroin users state that using heroin is "better than sex," giving an idea of the degree to which the substance can make individuals feel better, and an idea of the degree to which the individual's motivational priorities may be directed to continue using the substance. Figure 2A presents a model of a day in the life of the heroin user. The tic marks indicate injection time points, which correspond to the individual's attempt to "feel better." A minority of the day is spent in the "normal" versus "high" state.[2] A problem arises for someone who uses heroin: the body adapts to the presence of these substances (ie, up-regulating receptors) and, over time, the same amount of substance does not produce the same "high." The individual is now tolerant; the same amount of substance that previously led to euphoria now simply helps avoid withdrawal. Avoiding withdrawal becomes a primary motivating factor in the life of the individual who uses drugs. That strong motivation can prompt engagement in many risky behaviors, including risky sexual and drug-using behaviors and the use of large quantities of drugs meant to regain euphoria but often resulting in overdose.

## Opioid Substitution Treatment

In the 21st century in the United States, outbreaks of HIV infection among people who use drugs continue (eg, the Indiana outbreak), even though treatment for opioid use disorders can prevent HIV transmission. A study by Metzger and colleagues reported in 1993 showed that HIV antibody conversion occurred within 18 months in 22% of 103 out-of-treatment people injecting heroin, compared with 3.5% of 152 who received methadone.[3]

Medication-assisted treatment can reduce injection-related HIV risk

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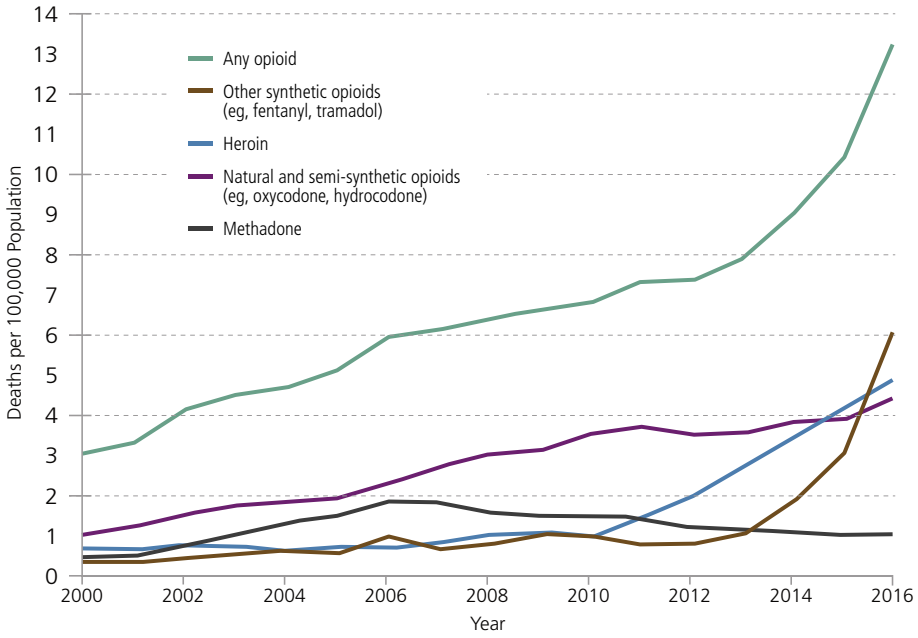


**Figure 1.** Overdose deaths involving opioids, by type of opioid, in the United States from 2000 to 2016. Adapted from the CDC WONDER database.[10]

behavior, decrease psychosocial and medical morbidity, increase access to and retention in antiretroviral therapy (ART), and improve overall health status. It is also associated with decreased criminal activity.

Figure 3 shows cross-sectional magnetic resonance imaging pictures of the brain in the top row and corresponding positron-emission tomography (PET) scans showing μ-opioid receptor availability at increasing doses of buprenorphine. Without any buprenorphine ingested, a high degree of receptor availability is evident on the first row of the PET scan. The nucleus accumbens, a key area of neurobiologic reward in the brain, is visible as a red area in the far-right PET image. Subsequent rows demonstrate a reduction in receptor availability as buprenorphine occupies those receptors and competes with the radiolabeled substance As can be seen, administration of even 2 mg results in high receptor occupancy, with upwards of 95% of μ-opioid receptors being occupied at a dose of 16 mg. In this setting where the "parking lot is full," if an individual takes heroin, it has "no place to park."

Figure 2B presents a model of a day in the life of an individual addicted to heroin who is receiving methadone for treatment. With once-daily dosing of methadone, the individual formerly using heroin now avoids the opioid withdrawal and spends the day in the "straight" zone. Use of heroin after methadone results in a blunted response—the parking lot is mostly full—that does not reach a "high," and thus may result in reduced craving for repeated heroin use.

Medications available for the treatment of opioid use disorder include methadone, buprenorphine, and naltrexone. Methadone is available only through opioid treatment programs, and cannot be used in an office-based setting in the United States. Methadone, although suffering under substantial bad press,[4] must be remembered as first and foremost a life-saving medication.[5] It is efficacious in treating opioid addiction and has the best retention rates among medication-assisted treatment for opioid use disorders.[6] Additionally, of the 3 available medications, methadone has the greatest analesgic potential. Buprenorphine has a strong advantage for scale-up because it can be used in an office-based setting. Although it is as efficacious as methadone for those retained in treatment, treatment retention rates are lower than with methadone.[6] This finding appears to reflect the pharmacology of the medication, characterized by fewer withdrawal sym-ptoms when it is discontinued. One possible implication is that buprenorphine may not be as effective as methadone for prevention of HIV infection, because staying on the medication is crucial in this regard.[6] Finally, there is a new depot naltrexone formulation. The oral tablet is not effective because patients simply discontinue its use; however, the new depot formulation offers improved adherence possibilities. In a recently reported

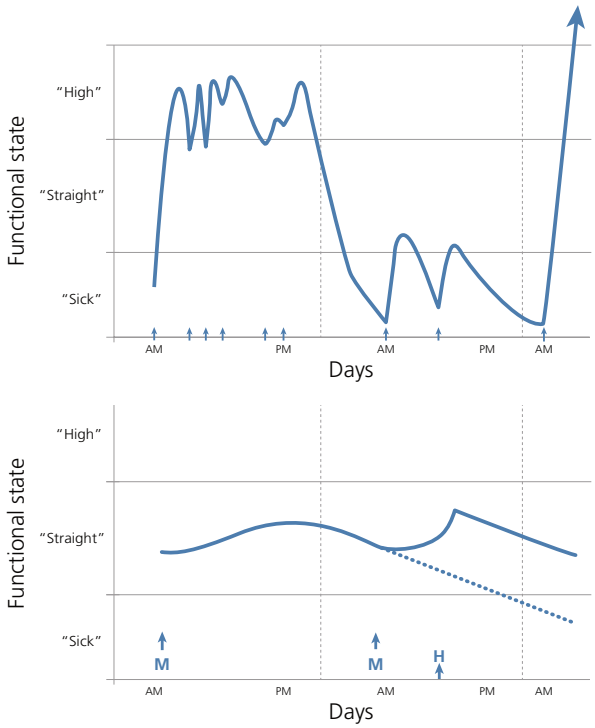


**Figure 2.** Top—Model of functional state of typical "mainline" heroin user. Arrows show times of injection. Bottom—Functional state of heroin user with methadone treatment. M arrows show time of methadone dosing; H arrows, effect of heroin injection under methadone treatment; dotted line, course if methadone is omitted. Adapted from Dole et al.[2]

study in patients with HIV infection who were incarcerated, Springer and colleagues found that the patients randomly assigned to depot naltrexone or a placebo saw a stability or improvement in HIV viral suppression. There was no significant difference at 6 months, however, when compared with placebo.[7] Although it can be used in the office-based setting, depot naltrexone was studied among individuals with HIV infection who started treatment while in prison and were continued post-release. Although some patients clearly benefited, viral suppression between the active arm and the placebo arm were not statistically significant. Although the treatment is effective for some individuals who use the medication, it has a lower retention rate than either buprenorphine or methadone. If available, methadone and buprenorphine are preferred for most patients.

## Integrating Substitution Treatment in the Clinic

Representative data on retention in methadone treatment indicate that if people simply discontinue treatment, up to 82% of people who inject drugs will return to injection within 8 to 10 months. There is thus considerable need to keep patients engaged in treatment. Best practices call for "low threshold"[5] treatment that is easily accessible, and "high volume" treatment that has sufficient ability to address the demand in the community, also known as the "community viral load." The goal is an intervention that is large enough to impact individuals who are not even directly encountering the program. This means that unnecessary barriers must be removed so that a patient who presents in need can be addressed immediately. A failure to address patients pushes them back out into an environment fraught with risk. Treatments must be appropriately dosed to be efficacious. Culturally appropriate counseling for heroin addiction is crucial, and can take a variety of forms, from Narcotics Anonymous to cognitive behavioral therapy. In this regard, the most important element of treatment is engagement with patients; medical therapy

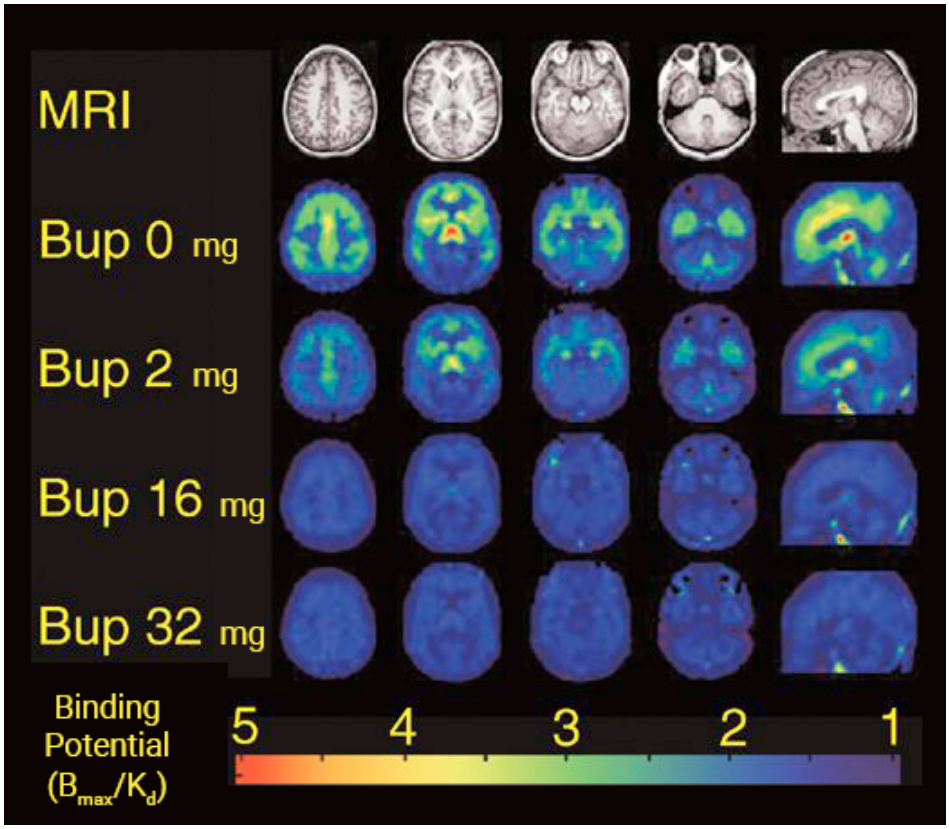


**Figure 3.** Occupancy of μ-opioid receptors by buprenorphine (Bup) dose. Blue indicates receptor occupancy. MRI indicates magnetic resonance imaging; $B_{max}$, the maximum number of binding sites; $K_d$, the ligand concentration that binds to half the receptor sites at equiplibruim. Reprinted with permission from Springer Nature: *Neuropsychopharmacology*. "Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers." Greenwald MK, Johanson CE, Moody DE, et al. © Nature Publishing Group 2003.[11]

is much less likely to be successful in the absence of counseling and therapy. In addition, treatment of the medical consequences of addiction, such as HIV, hepatitis B, hepatitis C, and tuberculosis (TB) infection, remains crucial.

Discrimination persists against individuals who have substance use disorders in terms of providing treatment for HIV, hepatitis C, and TB infection, in the United States and globally. Adherence to treatment regimens for these diseases remains possible, even in the setting of ongoing substance use.

Indeed, in the past, people who inject drugs were denied HIV therapy until they ceased drug use. Although drug use is multifactorial, there was a bias against drug users and a failure to recognize addiction as a medical illness. In contrast, people living with HIV infection with other medical illness were not denied treatment. Indeed, in some settings (eg, HIV/hepatitis C and HIV/TB coinfections), having another medical illness with HIV infection makes ART access a priority. Woods and colleagues in British Columbia showed that in a cohort of 1191 ART-naive patients monitored from the time of ART initiation, antiretroviral drug resistance was found in 25% of the cohort during the first 30 months (protease inhibitor and nonnucleoside reverse transcriptase inhibitor resistance). There was no difference in incidence of resistance between people who inject drugs and those who do not inject. Integration of treatment is now being performed all over the world. In India, there is directly observed therapy with direct-acting antivirals for hepatitis C and buprenorphine. In Tanzania, there are programs for adherence support for HIV and TB medications in the context

| Organization/Guidelines | Website Address |
|---|---|
| American Pain Society | http://americanpainsociety.org/education/overview |
| American Academy of Pain Medicine Research Library | http://www.painmed.org/library/main.aspx |
| Providers Clinical Support System | https://pcssnow.org/resources/clinical-tools/ |
| Substance Abuse and Mental Health Services Administration | https://www.samhsa.gov/medication-assisted-treatment/training-resources/buprenorphine-physician-training |
| 2017 HIV Medicine Association of Infectious Diseases Society of America Clinical Practice Guideline for the Management of Chronic Pain in Patients Living With Human Immunodeficiency Virus | https://academic.oup.com/cid/article/65/10/e1/4157299 |

**Table.** Useful Websites for Pain Management and Opioid Issues

of methadone treatment. In New Haven, Connecticut, HIV and hepatitis C treatments have been integrated into methadone clinics.

In terms of screening for substance use disorders in the HIV clinic setting, 2 standardized questions that have been validated in the primary care environment prove very useful: (1) How many times in the past year have you had 5 or more standard drinks in a day? (2) How many times in the past year have you used an illegal drug or a prescription medication for nonmedical reasons?[8] People who use opioids or other substances can take medications for other illnesses and should be eligible for care for HIV, hepatitis B, hepatitis C, and TB infection. Clinicians should be willing to prescribe naloxone, the drug used to reverse opioid overdose, and should consider obtaining the necessary waiver to prescribe buprenorphine. Clinicians who prescribe opioids must be prepared to prescribe naloxone. Clinicians should also review guidelines on the treatment of chronic pain and reevaluate how they prescribe opioids; useful websites are shown in the Table. The HIV Medicine Association of Infectious Diseases Society of America has recently released a clinical practice guideline on the management of chronic pain in patients with HIV infection.[9]

Buprenorphine treatment for opioid addiction is one of the easier treatments provided by clinicians: easier than HIV care, given factors such as the absence of mutations conferring drug resistance and the relatively high motivation of patients to take the medication. Clinics can maintain patients in HIV care who are also receiving methadone or a buprenorphine-naloxone film, because patients return to the clinic for treatment, permitting more extensive contacts for ensuring other types of care. One clinic employs a waiver-based system that enables patients to pick up buprenorphine-naloxone directly from the on-site pharmacy, with the waiver being available at many points of care within the clinic (eg, outreach workers, at the laboratory, etc). This approach obviates the additional step of forcing the patient to make an additional appointment with a therapist, appointments that frequently are missed, to obtain a voucher before obtaining the medication.

*Presented by Dr R. Douglas Bruce in May 2018. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Bruce in August 2018.*

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

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# UPCOMING ACTIVITIES

## Fall and Winter 2018

## Interactive Webinars

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

**Flexner's Fabulous Formulations: A Review of Long-Acting Antiretrovirals and Other New Investigational Drugs—October 11, 2018**
Presenter: Charles W. Flexner, MD

**What to Do After the Hepatitis C Virus Cure—October 25, 2018**
Presenter: Marion G. Peters, MD

**New Insights Into Hepatitis C Virus Infection From The Liver Meeting® 2018—December 4, 2018**
Presenter: Andrew I. Aronsohn, MD

*Prior webinars are available for CME credit for up to 1 year after the live broadcast. Visit the IAS-USA website for a full list of archived webinars.*

## Small-Group Hepatitis Workshops

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

**Memphis, Tennessee—Friday, October 12, 2018**

**Southern Alabama/Northwest Florida—Friday, October 19, 2018—WORKSHOP IS FULL**

**Portland, Maine—Thursday, October 25, 2018**

**Charleston, South Carolina—Friday, November 2, 2018**

**Milwaukee, Wisconsin—Tuesday, November 6, 2018**

## Spring 2019

## Annual Full-Day HIV Courses

*These live, full-day CME courses continue to feature cutting-edge, scientifically rigorous topics presented by leading experts in the field of HIV medicine. Visit the IAS–USA website for up-to-date information and podcasts of prior courses. This spring, IAS–USA courses focusing on the management of HIV infection will be held in:*

**New York, New York—Monday, March 18, 2018**
Chairs: Gerald H. Friedland, MD; Paul A. Volberding, MD

**Atlanta, Georgia—Friday, March 29, 2018**
Chairs: Michael S. Saag, MD; Jeffrey L. Lennox, MD

**Washington, DC—Monday, April 29, 2018**
Chairs: Michael S. Saag, MD; Henry Masur, MD

**Los Angeles, California—Monday, May 6, 2018**
Chairs: Constance A. Benson, MD; Ronald T. Mitsuyasu, MD

**Chicago, Illinois—Thursday, May 23, 2018**
Chairs: Paul A. Volberding, MD; John P. Phair, MD

**San Francisco, California—Date TBD**
Chairs: Stephen E. Follansbee, MD; Robert T. Schooley, MD

## Year-Round

## *Cases on the Web*

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

**Primary Care Issues in HIV Infection**
Author: Rebecca Glassman, MD
Expires: December 1, 2018

**Geriatrics and HIV**
Authors: Harjot K. Singh, MD, ScM; Eugenia L. Siegler, MD
Expires: January 22, 2019

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

*Commentary*

# Policy and Advocacy for the HIV Practitioner

*In no field of medicine has advocacy, including physician advocacy, been more crucial in shaping policy for delivery of care than in HIV/AIDS. Although the historic tradition is strong, there is an urgent need to re-energize advocacy efforts nationally and internationally to support programs that fund care, change policies that perpetuate stigma and discrimination, and change the public perception that the HIV/AIDS crisis is over. Established programs that require ongoing advocacy attention include the Ryan White Comprehensive AIDS Resources Emergency Act, a US program that serves as a payer of last resort for care for patients with HIV infection, and international programs like the President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria. Newer issues have emerged, including the need to ensure fair drug pricing and guarantee sustained access to care and medications. Amidst the opioid epidemic, the preservation and establishment of policies to support syringe services programs take on new urgency, and ongoing efforts are necessary to decrease stigma about HIV infection, maintain protection of LGBTQ rights, and reform HIV criminalization laws. All stakeholders in the HIV community, including practitioners, individuals with HIV infection, and professional organizations, need to make their voices heard as they have done in the past in order to effectively continue to address the epidemic. This commentary was submitted by Carlos del Rio, MD, and Wendy S. Armstrong, MD, in March, 2018, and accepted in July, 2018.*

**Keywords:** HIV, policy, advocacy, community

The HIV community has a long history of advocating for improving care and support efforts to improve outcomes for individuals with HIV infection. From the early years of the epidemic, activism has played a major role in advancing science and policy in the United States. For example, in 1988 activists played an important role in pressuring the US Food and Drug Administration (FDA) to offer alternative pathways to drug approval that allowed access to medications faster than ever before.[1] They also successfully fought for enhanced funding for HIV research and care. The relationship between scientists and the advocacy community was not always smooth, but over time increased trust and cooperation led to advances in HIV research and care. Advocates ensured that HIV was a part of the public conversation that could not be ignored. They also developed expertise in the design and conduct of clinical trials. Criticism about the slow pace of progress led to collaborative discussions among physicians, clinical researchers, activists, and others to develop alternate trial designs. These innovations have had a lasting impact on the way clinical trials are conducted and have focused attention on meaningful involvement in treatment and prevention efforts by individuals living with a serious medical condition (in this case HIV infection).

HIV practitioners are an important part of the advocacy community, and have had and can continue to have a substantial impact at the local, regional, and national levels. These efforts largely revolve around issues related to access to care, including HIV care as well as mental health and substance abuse services, and access to medications, as well as policy issues that reduce stigma and impede the ability of practitioners to provide evidence-based care and prevention services. To effectively advocate for HIV prevention and care, practitioners need to have a basic understanding of the various programs funded by the US government that help provide care for individuals living with HIV infection in the United States and globally. In the United States, the Ryan White Comprehensive AIDS Resources Emergency (CARE) Act, enacted by Congress on August 18, 1990, is vital to providing care for un- and under–insured individuals with HIV infection by serving as the payer of last resort.[2] Despite increased costs of care and a consistent rise in the number of individuals with HIV infection in the United States, since 2010 the Ryan White HIV/AIDS Program has been flat funded at approximately US $2.3 billion dollars per year.[3] The Ryan White Program consists of several parts and includes the AIDS Drug Assistance Program (ADAP), which provides HIV-related prescription drugs to individuals with HIV infection who lack medication coverage.[4] In 2015, more than 250,000 individuals had their medications supported by ADAP and more than 500,000 individuals receiving care used Ryan White services.[5]

Internationally, the United States supports the President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund for AIDS, Tuberculosis and Malaria, both of which have had a substantial impact on global HIV infection. PEPFAR was enacted in 2003. At that time, only about 50,000 people were on antiretroviral therapy (ART) in Africa.[6] Now, PEPFAR supports ART for 13.3 million people in partner countries, most of which are in Africa, and US funding in 2017 was US $6.56 billion, representing the largest commitment by any nation to address a single disease globally.[7] Unfortunately, the US contributions to PEPFAR have been flat for many years, and other nations are reducing their contributions. Additional resources are desperately needed if we are to reach the Joint United Nations Programme on HIV and AIDS (UNAIDS) 90-90-90 targets: 90% of all people with HIV infection will know their HIV

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status; 90% of those diagnosed with HIV infection will be on ART; and 90% of all people on ART will be virally suppressed. PEPFAR is the most successful global public health program that has ever existed, not only because of the health benefits it has brought but also due to its role in promoting economic growth and political stability. It has also been a major foreign relations success for the United States.

The Global Fund is a multilateral financing mechanism, and, unlike PEPFAR, is an implementing agency. The US government is an important donor to the Global Fund, having most recently pledged US $4.3 billion for the funding period of 2017 to 2019. In the era of treatment as prevention, programs like these take on renewed urgency because there is an impact on both individuals and the public health. Advocacy to support the Ryan White CARE Act and these global HIV programs is necessary if we are to achieve the UNAIDS 90-90-90 goals in the United States or abroad.

Although advocacy for continued funding for these programs is needed, advocacy for policies that support access to care, medications, and basic rights for those living with or at risk for HIV infection is also vital. With regard to policy advocacy, there is a need to engage in issues such as expanding Medicaid, ending HIV criminalization, and opposing the uncontrolled increase in the cost of pharmaceuticals, among others. Medicaid expansion through the Patient Protection and Affordable Care Act has provided enhanced access to care in participating states and has been associated with favorable virologic outcomes.[8] In addition, we are confronting an unprecedented opioid epidemic that has had a profound effect on many and carries risks of expanding the HIV and hepatitis C epidemics as well. Medicaid covers access to addiction care for 4 in 10 nonelderly adults with opioid addiction,[9] and therefore, Medicaid expansion may be the single most effective step to turn the tide on the opioid epidemic. Advocacy for policies to expand and fund syringe services programs is also crucial. Finally, advocacy is needed to reform HIV criminalization laws and to protect lesbian, gay, bisexual, transgender, and queer (LGBTQ) rights—2 important issues that affect HIV-related stigma. Without protection of human rights the epidemic will never be over.

Another pressing issue is fair drug pricing, which is necessary to maintain access to medications. The story of Daraprim® is an example of how the price of a medication can soar dramatically: the price of this drug rose from $1.00/tablet until 2010 to $750/tablet in 2015. The response of the practitioner community and the HIV Medicine Association was immediate, with a media firestorm erupting after the publication of an article in *The New York Times* on September 20th, 2015, an important example of the impact of advocacy to move these issues into the national consciousness.[10]

Despite dramatic gains in this epidemic, as the 22nd International AIDS Conference concluded, the data clearly showed that we are at a crucial juncture in the global HIV response. The data released by UNAIDS in their most recent annual report on the epidemic suggest that we are doing better than ever: 21.7 million people globally are on ART, new infections have dropped to 1.8 million annually, and fewer than 1 million people died with AIDS in 2017.[11] Yet we also realize that the UNAIDS 90-90-90 targets will not be met in 2020; an additional 2.8 million people must be initiated each year on ART, and there are no new resources to fund this scale up. There is also a prevention crisis, and the benefits of HIV preexposure prophylaxis have yet to be realized. Despite grandiose discussion in earlier years about the "End of AIDS," HIV infection and AIDS are not close to eradication and many are concerned that the epidemic could once again worsen, largely driven by infection in youth.

In conclusion, renewed advocacy is urgently needed to make possible what many think is impossible: ending AIDS in our lifetime. Not only is this the right thing to do, but we owe it to our patients. The public health impact is undeniable.

*Financial affiliations in the past 12 months: Dr del Rio has served as a consultant for ViiV Healthcare. Dr Armstrong has no relevant financial affiliations to report.*

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1. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Updated December 2015. Available at http://www.icmje.org. Accessed September 26, 2018.

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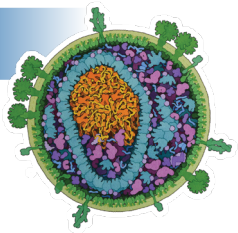

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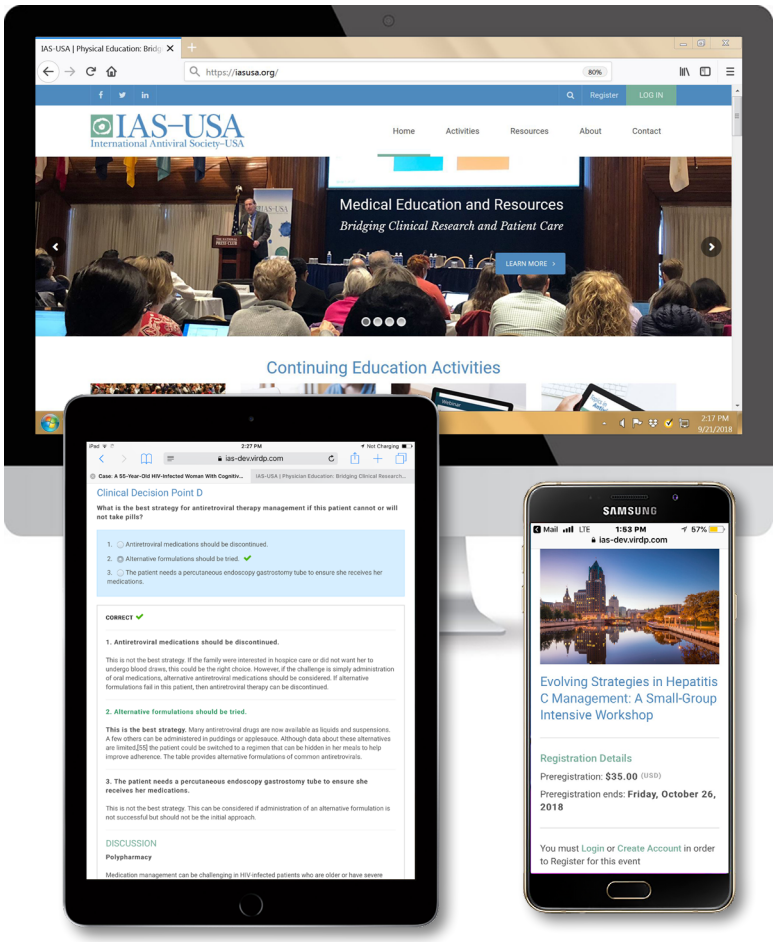


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