Report—HIV Management 2015: THE NEW YORK COURSE

Introduction

As in each of the past years, the 13th anniversary session of HIV Management: THE NEW YORK COURSE provided attendees state-of-the-art presentations not just on antiretroviral therapy but on a full spectrum of the non-AIDS-defining infectious, cardiovascular, and malignant conditions that now increasingly appear in HIV-positive patients. For the first time this year, the meeting also offered presentations on the principal aspects of research into immunotherapy for HIV disease.

The more than 400 participants in attendance again learned of the most recent developments in virtually every aspect of HIV management—from diagnosis to selection of optimal antiretroviral regimens to recognizing and treating diverse HIV-related diseases. In addition, participants had ample opportunities to interact with a distinguished group of highly experienced HIV clinicians and investigators during the lectures, panel discussions, and case presentations.

Most attendees came from North America, but others journeyed from several countries in Europe and Asia, as well as Australia. This broad representation will mean that many HIV-positive patients will continue to receive state-of-the-art care from clinicians who were able to participate in exchanges with some of the United States' most experienced HIV practitioners.

Attendees' years of experience in managing HIV-infected patients:
- ***> 20 years—37%***
- ***11 to 20 years—30%***
- ***< 10 years—33%***

This report offers recaps of the content of each plenary presentation, followed by a list of faculty-recommended reading materials on the subjects of the presentations.

For a full discussion of the topics covered in this report and to earn CME credit, please review the complete presentations with post-tests available on this website: www.impactid.com.

Panel Discussion

Immunotherapy for Cure

Speaking on "Immunotherapy for Cure," **Steven G. Deeks, MD**, of the University of California, San Francisco, said that in the oncology field, immunotherapy is rapidly evolving and being incorporated into clinical practice, and much of what is being discovered in that arena is gradually being applied in the field of infectious disease, including HIV. When a person begins ART, plasma HIV RNA typically drops from 100,000 to 1,000,000 copies/mL to an undetectable level by commercially available assays within weeks. Then, after about 6 months the amount of virus in a patient's blood reaches a steady state, a set point, at which it persists, generally in the range of 1 to 3 copies/mL. During this time, most virus resides in lymph nodes, where CD4+ T-cells are found. In recent years, research has shifted from controlling HIV in the blood to investigating how to eliminate it from lymphoid tissues. The largest lymphoid viral reservoirs, after the lymph nodes, are the spleen and the large and small bowel (Figure 1).

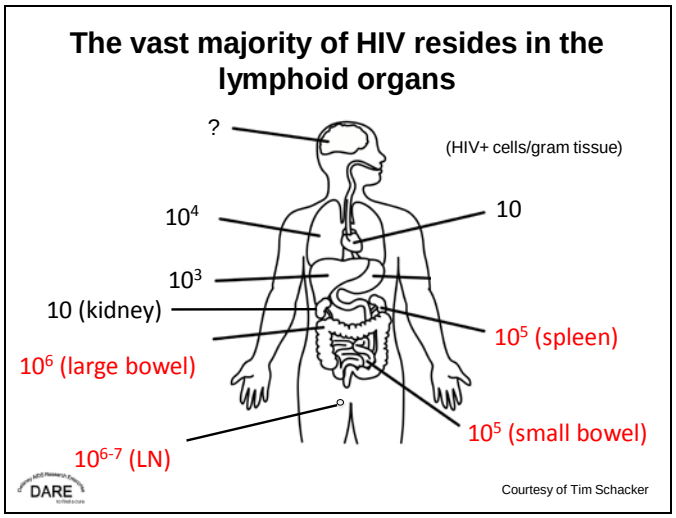

Figure 1. Lymphoid reservoirs of persistent HIV.

If ART is interrupted, HIV rebounds from these lymphoid sites at variable rates among patients, typically 1 to 6 weeks. Dr. Deeks said that viral rebound can be explosive, emerging from multiple organs, sometimes as multiple different viral strains. Within weeks, plasma HIV RNA can return to 100,000 to 1,000,000 copies/mL. Most research indicates that the virus resides primarily in memory CD4+ T-cells, largely within the B-cell follicles of the lymph nodes. There, HIV is sheltered from CD8+ T-cells, the main way in which the host controls the virus. Moreover, antiretrovirals typically cannot penetrate into these sanctuaries. He explained that this is key to HIV cure, because cure will require treatments that can reach the virus within the B-cell follicles.

Whether macrophages also serve as a viral reservoir during ART remains a contentious issue. During advanced, untreated HIV infection, macrophages can be a reservoir; these are thought to be found primarily in the brain. However, Dr. Deeks said that at this time there is no convincing evidence that macrophages continue to harbor virus during long-term ART, although this remains a matter of some controversy.

Immune activation, as measured by CD38+HLA-DR+ CD8+ T-cells, is significantly higher in HIV-infected, untreated individuals compared with both HIV-infected individuals on ART and HIV-negative individuals, although the level of activation in persons receiving ART remains higher than that in uninfected persons. Multiple factors contribute to the persistent inflammation and immune activation during ART:

- Ongoing low-level HIV replication
- ART toxicity
- Cytomegalovirus and other copathogens
- Loss of T regulatory cells
- Microbial translocation
- Comorbidities (cancer, cardiovascular disease, hepatitis)

With more immune and inflammatory activation, Dr. Deeks continued, a person's risk of illness and mortality increases. He then presented a conceptual model of this vicious circle by which ongoing damage can occur (Figure 2). Immune activation leads to immune dysfunction and tissue damage, which contribute to poor T-cell renewal and cell dysfunction, which lead to poor HIV control and excess microbial products, which lead to immune activation, perpetuating the cycle. This cycle, he said, lies at the heart of investigators' efforts to alter the relationship between HIV and the immune system.

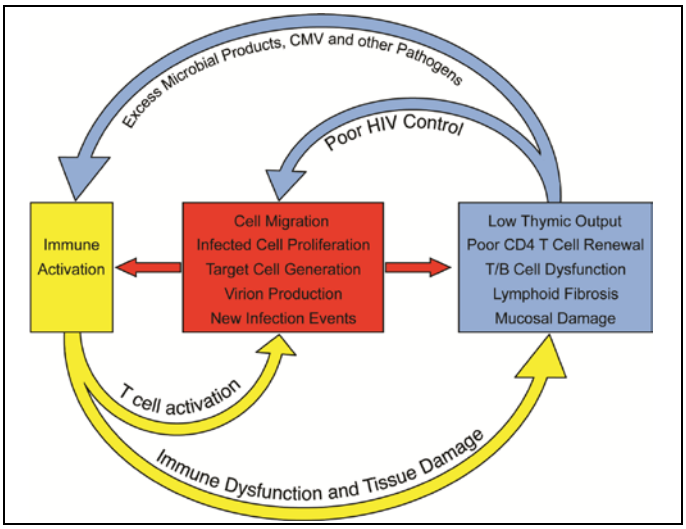

Figure 2. Vicious cycle of immune activation and inflammation.

Dr. Deeks explained that the size of the HIV reservoir appears to be determined by certain immune system cells:

- Proliferating: Ki67, HLA-DR
- Activated: CD38/HLA-DR, CCR5
- Migrating: CCR6
- Inhibited/blocked: primarily PD-1, but also LAG-3 and TIGIT

PD-1, when expressed on the surface of a cell, makes it less able to function. Researchers are investigating the use of antibodies that target PD-1-expressing cells, with the dual goal of inducing them to die and to enable T-cells to attack virus-producing cells.

Translation to the Clinic

A critical next step will be the translation of these findings regarding the relationship between immune activation and persistent infection into clinical trials and practice. A leading approach to HIV cure is sometimes called "shock and kill," meaning the introduction of agents that will shock the HIV DNA that is latent in reservoirs into producing protein that the immune system and ART can then recognize and destroy. A number of drugs are being evaluated for the shock phase of a potential cure: vorinostat, romidepsin, disulfiram, and others. Dr. Deeks said that trials have already shown that some of these agents are able to awaken the virus from latency.

One approach that has generated considerable interest in recent investigations is the use of toll-like receptor 7 (TLR7) agonists. TLR7 plays an important role in pathogen recognition and elicitation of immune response. A recent report of the use of the TLR7 agonist GS9620 found that it increased SIV RNA—ie, increased viral load—both in vitro and in monkeys that were receiving ART. The theory underlying this approach, Dr. Deeks explained, is that serial doses of such an agent would be given to a patient, awakening latent HIV production, so that the virus could be targeted by the immune system and ART. Repetitions of this cycle would eventually lead to eradication of the virus.

He also said that there is considerable interest at this time in vaccines. HIV replicates largely because T-cells are not functioning properly, and, he continued, the best way to get them to work better is to use vaccination. Most such vaccine approaches to date have had no more than modest efficacy. However, one approach that has created substantial interest uses CMV that is engineered to function as an HIV/SIV vaccine. Researchers have reported that, when injected into monkeys, this vaccine produced high levels of killer CD8+ T-cells that targeted the virus and subsequently cleared viral latency during early infection. Human studies of this approach are in development.

Vaccinology has also led to the recognition of a number of neutralizing antibodies that may be capable of detecting HIV-infected cells and turning on effector cells, eg, natural killer cells and macrophages, that would specifically target HIV. In effect, this approach would enhance a host's immune system to clear latent HIV infection.

Natural killer (NK) cells are another area being explored. Much of the interest in this area has arisen from discoveries in recent years concerning NK cell activity in the so-called Berlin and Boston patients, who experienced dramatic improvements after receiving stem cell transplants, and the Visconti cohort in France, who had no viral rebound after discontinuing ART.

Knowledge of HIV cure that has been gained thus far has taken place in small, carefully controlled and moderated experiments. Dr. Deeks cautioned that when immunotherapeutics and other strategies move into clinical trials in HIV patients, complex responses are likely to be generated, making it impossible to predict all of the beneficial and adverse consequences that will follow. He added, however, that no one will ever be cured of HIV infection unless such trials take place.

Summary

- HIV persists indefinitely in memory CD4+ T-cells and perhaps in other cells.
- Latent HIV infection is maintained by cell proliferation, with growing concerns that HIV integration affects this process.
- The HIV reservoir is associated with measures of T-cell activation and may be enriched in cells expressing activation markers, eg, CCR5, PD-1, HLA-DR.

- Rigorous controlled studies involving immune-based therapeutics are needed to determine how the immune environment contributes to the persistence of HIV infection.

Panel Discussion

Immunotherapy for Treatment and Prevention

To complement Dr. Deeks's presentation on current HIV cure research, **Daniel R. Kuritzkes, MD**, of the Harvard Medical School and the Brigham and Women's Hospital, discussed how some of the same approaches may be applied therapeutically. Researchers in the Netherlands have reported that when ART is begun early enough in HIV-infected patients, life expectancy does not differ significantly from that of the general population, assuming that the patient remains adherent to therapy. This, and the dramatic reduction in HIV-related morbidity and mortality in developed regions, Dr. Kuritzkes said, has happened because antiretroviral agents today are generally highly effective, safe, convenient, and tolerable.

To answer the question, "Why obsess if a patient can take 1 pill a day and live a normal life?" he explained that even virologically suppressed persons continue to have certain immunological abnormalities:

- Persistent inappropriate immune activation
- End-organ disease linked to immune activation (eg, cardiovascular events, renal failure, hepatic steatosis, and neurologic dysfunction)
- Close linkage between immune activation and viral persistence (in the vicious cycle mentioned by Dr. Deeks)

Persistent Inflammation

As studies have demonstrated, CD4+ and CD8+ T-cell activation in untreated HIV-infected individuals remains significantly elevated above that in HIV-negative individuals; ART reduces this activation but it remains higher than in uninfected persons. Investigators in the SMART study measured several biomarkers of immune activation and found that several of them, in particular IL-6 and D-dimer, were statistically significantly elevated in both treated and untreated HIV patients and that they were correlated with all-cause mortality and risk of cardiovascular events. A 2014 case-control study evaluated a range of inflammatory markers both at baseline and after 1 year of virologic suppression and reported that higher IL-6 level, soluble tumor necrosis factor receptor (sTNFR)-I level, sTNFR-II level, and D-dimer level at year 1 were associated with the occurrence of a non-AIDS-defining event, eg, myocardial infarction, stroke, non-AIDS-defining cancer or serious bacterial infection, or death; however, they found no association with T-cell activation. Dr. Kuritzkes stressed that this persistent inflammatory condition clearly inhibits HIV patients' well-being.

One driver of persistent inflammation is believed to be damage to the gastrointestinal tract. A 2006 study found that translocation of bacterial products, especially lipopolysaccharide (LPS), was correlated with T-cell activation; the researchers compared LPS levels in HIV-negative and HIV-positive individuals at different stages of infection. LPS levels remain elevated also in HIV-infected patients with ART-

suppressed viremia. Taken together, Dr. Kuritzkes said, processes like ongoing viral replication and microbial translocation contribute to the pathogenesis of non-AIDS complications of HIV infection (Figure 3).

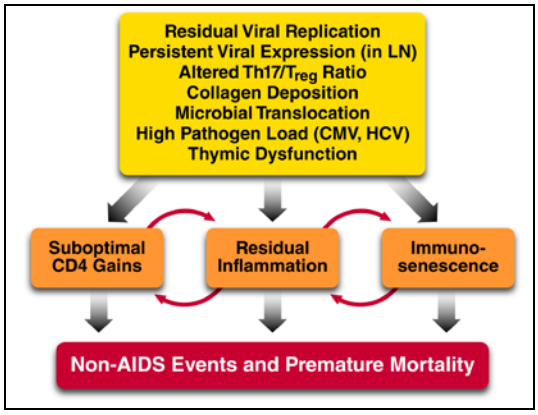

Figure 3. Pathogenesis of non-AIDS complications.

With that background, Dr. Kuritzkes listed the main challenges for immunotherapy of HIV infection:

- Can immune function be reconstituted?
- Can HIV-specific immunity be restored?
- Can lymphoid fibrosis be reversed?
- Can gut integrity be repaired?
- Can immune activation be reduced?

One study found that when patients remain on ART for 7 years, CD4+ cell counts tend to increase throughout that period, but patients who start ART at low CD4+ cell counts generally still had low levels at 7 years. Earlier treatment initiation was also associated with greater likelihood of achieving a normal CD4:CD8 ratio. He continued by saying that a possible explanation of inadequate restoration of CD4+ cell counts is the fibrosis in lymphatic tissues that occurs with HIV infection, as evidenced by the amounts of collagen found in those tissues in HIV-positive vs HIV-negative individuals. He said that investigators are also evaluating ways to reduce fibrosis in certain other diseases, eg, nonalcoholic steatohepatitis (NASH), fibrotic lung disease, and myocardial fibrosis. One study of the use of pirfenidone in SIV-infected monkeys found reduced levels of lymphoid fibrosis in the animals that received the antifibrotic agent.

Saying that trial results have been disappointing, Dr. Kuritzkes listed the approaches to immunotherapy that have been evaluated:

- Cytokine therapy (IL-2, IL-7, IFN-α)
- Immunosuppressive therapy (prednisone, cyclosporine, mycophenylate)
- LPS-directed therapy (rifaximin, sevelamer)
- ART intensification (raltegravir, maraviroc)
- Therapeutic vaccines

Nevertheless, other studies are either ongoing or in development, and he explained the rationales for several of them:

- Low-dose methotrexate

  - Being investigated in HIV-positive persons based on observed reduction in cardiovascular risk in HIV-negative patients taking it for rheumatologic conditions
- Telmisartan
  - Antifibrotic agent being evaluated for potential reduction of lymphoid fibrosis
- Isotretinoin (retin A)
  - Has been observed to improve gastrointestinal integrity
- Sirolimus
- Ruxolitinib
- Aspirin
- Pitavastatin
  - Being evaluated in HIV-infected patient with cholesterol levels not requiring treatment to determine whether it would reduce cardiovascular events

Another approach is examining ways to reduce the arterial inflammation commonly found in HIV-infected persons with the CCR5/CCR2 investigational receptor antagonist cenicriviroc. CCR2 is involved in the activation of monocytes and macrophages, and cenicriviroc inhibits binding of the cytokine MCP-1 to CCR2 to reduce inflammation.

Antiretroviral Effect of Antibodies

Dr. Kuritzkes said that investigators are also exploring the potential antiretroviral effect of antibodies. The HIV viral envelope offers a number of sites that may serve as targets for development of broadly neutralizing antibodies, ie, they are capable of neutralizing a variety of HIV isolates. One such investigational monoclonal antibody is VRC01, which has been reported to neutralize 91% of HIV isolates in vitro. Investigators have also demonstrated dramatic reductions in viremia in monkeys that were infected with SIV in which the viral envelope had been replaced with the HIV envelope (ie, SHIV), when the monkeys were injected with a cocktail of HIV-specific monoclonal antibodies. Other investigators have developed an adeno-associated virus vector bearing a cocktail of neutralizing antibodies in a mouse model of HIV and have reported that the mice were protected from infection when challenged with HIV several weeks after injection. This approach is known as vectored immunoprophylaxis (VIP).

A novel approach involves a completely artificial molecule, eCD-Ig, that acts in effect as an HIV entry inhibitor. eCD4-Ig is a fusion of CD4-Ig with a small CCR5-mimetic peptide that binds to the HIV-1 envelope. The investigators reported high rates of HIV protection in vitro and in humanized mice injected with eCD4-Ig via an adenovirus vector; in addition, monkeys challenged with SIV were also protected from infection. Development of eCD4-Ig as both a therapeutic and preventive vaccine is now under way.

Summary

- Immune activation persists despite ART.
- Immune activation correlates with and is likely a driver of end-organ disease.
- Lymphoid fibrosis may limit immune reconstitution.
- The risks and benefits of dampening immune activation must be balanced carefully.
- Novel agents (broadly neutralizing antibodies, eCD4-Ig) delivered by adeno-associated virus vectors provide novel approaches for prevention and treatment of HIV infection.

Audience Questions

In current clinical practice, do you use any of the markers of inflammation?

Daniel R. Kuritzkes, MD: The answer today is "No," with the possible exception of CRP for some patients. For the other markers, investigators have not yet determined how to intervene on the basis of an elevated marker of inflammation. It is to be hoped that ongoing and planned trials will shed light on how to interpret and manage these markers.

Steven G. Deeks, MD: One marker that I use is the CD4:CD8 ratio. The majority of patients who start ART later do not achieve normal CD4:CD8 ratios, and this failure to normalize is associated with inflammation. In the elderly, such an abnormal ratio is associated with the issues of immunosenescence. I like to advise patients with abnormal ratios to follow some of the measures that appear to be helpful in the persons in the general population who have cardiovascular risk factors: Mediterranean diet, weight loss, lower blood pressure, no smoking, and exercise. In general, the only HIV patients who have normal CD4:CD8 ratios are those who start therapy very early.

Antiretroviral Therapy Progress

To suggest the progress that antiretroviral therapy has made during nearly 30 years, **Roy M. Gulick, MD, MPH, MPH**, of the Weill Cornell Medical College, showed a graph of the history of the approvals of the currently available 28 antiretrovirals, beginning in 1987 with zidovudine through dolutegravir in 2013. For initial therapy, current antiretroviral treatment guidelines generally recommend a combination of 2 nucleoside analogue reverse transcriptase inhibitors (NRTIs) and a third drug, either a non-nucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase inhibitor (II). However, Dr. Gulick explained that the recently revised guidelines from the US Department of Health and Human Services now recommend only integrase inhibitor–based or PI-based regimens for first-line therapy, with NNRTI-based regimens listed as alternatives. This change was motivated by new clinical trial findings, several of which he discussed in the rest of his talk.

ACTG 5257—a head-to-head randomized comparison of 2 NRTIs plus either atazanavir/ritonavir, darunavir/ritonavir, or raltegravir in >1,800 patients—found similar virologic responses but differences in a composite endpoint that incorporated virologic response and toxicity. With regard to the composite endpoint, the raltegravir arm was statistically superior to both PI-based arms (with the darunavir arm being statistically superior to the atazanavir arm). A more recent analysis of data from A5257 reported that there were no significant differences in fat changes—limb fat, trunk fat, subcutaneous adipose tissue fat, or visceral adipose tissue fat—among the 3 regimens. This finding somewhat surprised observers, who had expected greater fat changes in the participants receiving PI-based therapy.

In phase 3 studies, combination regimens including dolutegravir demonstrated superiority over efavirenz- or darunavir/ritonavir-based combination regimens (SPRING-2 and FLAMINGO studies, respectively) and noninferiority to a raltegravir-based regimen (the SINGLE study). Moreover, Dr. Gulick added, among patients who experienced virologic failure with a dolutegravir-based regimen, no one showed evidence of dolutegravir resistance. The VIKING 3 and 4 studies have evaluated the efficacy of dolutegravir, with a dosing schedule of 50 mg twice daily, in >200 integrase inhibitor–experienced patients. Guidelines now recommend that if a patient experiences virologic failure with a raltegravir- or elvitegravir-based regimen, an integrase-specific genotype test should be performed. Dolutegravir retains susceptibility in patients who have experienced virologic failure on a prior integrase inhibitor–containing regimen, except in the presence of a substitution at position Q148, which confers decreased susceptibility.

Dr. Gulick then reviewed several antiretrovirals that are currently in development. The pipeline, he said, contains new agents in existing classes (NRTI, NNRTI, PI, II) as well as 2 new classes of drugs: CD4 attachment inhibitors and maturation inhibitors.

NRTI Class

In the NRTI class, Dr. Gulick said that the main needs are less long-term toxicity and activity against NRTI-resistant viruses.

The investigational agent farthest along in development is tenofovir alafenamide fumarate (TAF), a novel prodrug of tenofovir. The current prodrug, tenofovir disoproxil fumarate (TDF), Dr. Gulick explained, is broken down into tenofovir in plasma and is associated with renal and bone toxicity, whereas TAF is not broken down until it reaches the lymphoid cells, where HIV replication primarily takes place. Investigators hope that since TAF levels in tissues, eg, bone and kidney, are lower, it should

be less toxic to those organs, as well as possibly more potent due to being concentrated in lymphoid cells.

TAF has been evaluated in 2 studies involving >1,700 treatment-naive patients who received coformulations of either elvitegravir/cobicistat/emtricitabine/TDF or elvitegravir/cobicistat/emtricitabine/TAF. With very similar rates of HIV RNA <50 copies/mL, the investigators concluded that the TAF formulation was noninferior to TDF. Perhaps more importantly, Dr. Gulick said, the eGFR with TAF was -6.6 mL/min vs -11.2 mL/min for TDF, and bone loss at the hip and spine were both significantly less with TAF vs TDF. These favorable findings have been presented to the Food and Drug Administration, and approval of TAF is anticipated in 2015. When coadministered with boosted PIs, TAF levels increased significantly, requiring dose reduction. Coformulations of 2 doses of TAF plus emtricitabine are in development for that purpose.

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NNRTI Class

The main needs in the NNRTI class, Dr. Gulick said, are:

- Less toxicity and better tolerability
- Activity against resistant viral strains
- Fewer drug interactions

The leading investigational compound in the NNRTI class is doravirine, for which in vitro data found:

- Potent at low-milligram dose
- Cytotoxicity and animal toxicity studies negative
- Not a CYP450 inhibitor or inducer; metabolized by CYP3A4
- Active against viral strains with K103N, Y181C, G190A, E101K, E138K, or K103N/Y181C resistance variants

Based on a dose-finding study (with average HIV RNA <40 mg/mL rates of 75%), a 100 mg dose is now in phase 2 evaluation. Non-CNS adverse events compared favorably with efavirenz. At 48 weeks, however, doravirine CNS toxicity was significantly better vs efavirenz:

- Dizziness (9% vs 28%)
- Insomnia (6% vs 3%)
- Abnormal dreams (6% vs 17%)
- Nightmares (6% vs 8%)

PI Class

The main need in the PI class, Dr. Gulick said, is reduced pill burden via coformulations. Some of that goal was achieved in early 2015 with the approval of coformulations of atazanavir/cobicistat and darunavir/cobicistat. In development is an investigational formulation, TAF/emtricitabine/darunavir/cobicistat, which would be the first one-pill, once-daily PI-based regimen.

Integrase Inhibitor Class

Dr. Gulick suggested only a single need for the integrase inhibitor class: less frequent dosing than once daily.

Cabotegravir is an investigational integrase inhibitor that is similar to dolutegravir, with similar resistance characteristics. However, it is being formulated through nanotechnology for either subcutaneous or intramuscular injection. Phase 1 data found that cabotegravir demonstrated an extremely long half-life that should allow dosing only once every 3 months. The main adverse event was injection site reactions. The LATTE 1 study evaluated a combination regimen of cabotegravir plus rilpivirine, which is also available in a nanoformulation, in 243 treatment-naive patients. Participants underwent an induction phase of 24 weeks with oral cabotegravir plus 2 NRTIs. Those who achieved virologic suppression at 24 weeks were then switched to maintenance therapy of oral cabotegravir plus oral rilpivirine. There was a comparator arm comprising efavirenz plus 2 NRTIs. At 96 weeks 86% of patients in the cabotegravir arms had undetectable HIV RNA vs 83% in the efavirenz arm. Going forward, the LATTE 2 study will evaluate the nanoformulations of combined cabotegravir plus rilpivirine.

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Other Classes

A new CD4 attachment inhibitor, BMS-663068, binds to the HIV surface protein gp120 and has demonstrated virologic activity in phase 1 and 2 studies. An agent in this novel class, said Dr. Gulick, would especially benefit treatment-experienced patients who have developed resistance to other drug classes. A phase 1 dose-finding study evaluating BMS-663068 in 50 patients who were either ART-naive or had been off ART for ≥8 weeks found that decreases in plasma HIV-1 RNA from baseline ranged from 1.21 to 1.73 $\log_{10}$ copies/mL. Investigators also reported that some participants had natural resistance to this agent, and participants in future studies will be screened for the relevant polymorphisms. In a phase 2b study, 251 treatment-experienced patients were randomized to tenofovir plus raltegravir and either BMS-663068 or atazanavir/ritonavir. At Week 48, 61% to 82% of patients receiving BMS-663068 had HIV RNA <50 copies/mL, which was similar to the 71% of patients in the atazanavir arm. A phase 3 study will evaluate BMS-663068 600 mg twice daily.

BMS-955176 is a small-molecule second-generation maturation inhibitor, following discontinuation of beviramat due to high levels of baseline resistance; this agent retained activity in participants with resistance to beviramat. A dose-ranging phase 2a study of BMS-955176 in 40 patients reported approximately 1.5 $\log_{10}$ decreases in HIV RNA across the doses, no serious adverse events, and no discontinuations. Phase 2b plans are in development.

Treating HIV: When the Guidelines Don't Fit

Joel E. Gallant, MD, MPH, MPH, of the Southwest CARE Center in New Mexico and the Johns Hopkins School of Medicine, began by saying that the 2 areas he would discuss—patients who cannot take either abacavir or tenofovir and switching therapy in the virologically suppressed patient—are mentioned but not answered in published guidelines. This silence, he said, is because there is not definitive data to support specific recommendations.

Antiretroviral guidelines from the US Department of Health and Human Services (DHHS) and the International Antiviral Society-USA (IAS-USA) provide comprehensive guidance on the treatment of HIV infection, including recommendations for when to start therapy, which regimen to start with, when to change therapy, and the management of treatment-experienced patients. The most recent DHHS guidelines contain 5 recommended first-line regimens; 4 of them are integrase inhibitor–based, 1 is PI-based, and all of them contain either tenofovir/emtricitabine or abacavir/lamivudine.

The Patient Who Cannot Take Abacavir or Tenofovir

Dr. Gallant approached the first topic by presenting the case of RW, a 49-yr-old executive diagnosed with HIV infection 5 years ago.

- Has been reluctant to take ART but now, with CD4+ cell count of 310 cells/mm^3 and HIV RNA of 156,000 copies/mL, agrees to start
- Wild-type virus at diagnosis
- Medical problems:
  - Diabetes (HbA1C 9.0% on metformin; refuses insulin)
  - Hyperlipidemia (LDL 125 on atorvastatin, TG 350 on fibrate)
  - Smokes half a pack of cigarettes per day
  - Non-nephrotic-range proteinuria, creatinine 1.5, eGFR 55 mL/min
- Liver enzymes normal
- HLA B*5701 negative

This patient, he explained, has contraindications to both tenofovir (due to proteinuria) and abacavir (multiple cardiac risk factors). Unfortunately, Dr. Gallant said, the issue of the possible association between abacavir use and risk of myocardial infarction (MI) still does not have a definitive answer, with multiple studies showing an association (typically a 2-fold increase in risk) and others showing no association.

The most recent set of findings concerning this possible association have come from the NA-ACCORD study, a large set of cohort studies designed to explore a range of issues concerning ART among North American patients. A recent complex analysis of findings from NA-ACCORD participants found that recent abacavir use was associated with an increased risk for MI but that the risk was lower after adjusting for traditional and HIV-associated risk factors (older age, smoking hypertension, and others). However, Dr. Gallant stressed that this does not definitively prove an association between abacavir use and MI, and additional analyses from this cohort are continuing. What the findings primarily do, he said, is confirm that current recommendations to avoid abacavir use in patients with cardiac risk factors should continue to be followed.

NRTI-sparing regimens, he said, represent one possible approach for a patient like RW who are not candidates for treatment with either tenofovir or abacavir. Treatment guidelines discuss existing data on NRTI-sparing regimens, but they do not make specific recommendations because of concerns about the NRTI-sparing regimens that have been studied to date. For example, there have been concerns about combinations of a boosted PI plus either an integrase inhibitor or a CCR5 antagonist. Darunavir/ritonavir plus raltegravir did not perform as well as darunavir/ritonavir plus 2 NRTIs in 3 clinical trials, especially in patients with low CD4+ cell counts and/or high viral loads. A study of lopinavir/ritonavir plus raltegravir was small and had few participants with viral loads >100,000 copies/mL. A study of unboosted atazanavir plus raltegravir found more instances of virologic failure and jaundice in the NRTI-sparing arm. A study of darunavir/ritonavir plus the CCR5 antagonist maraviroc was discontinued early because of poorer efficacy compared with standard NRTI-containing therapy.

Other studies, however, have had more appealing outcomes:

- In the GARDEL study of lopinavir/ritonavir plus lamivudine compared with lopinavir/ritonavir plus 2 NRTIs, 88% of patients in the dual-therapy group had HIV RNA <50 copies/mL vs 84% in the triple-therapy group; CD4+ cell count increases were similar.
- In the OLE study, 92% of patients who were switched from triple therapy to lopinavir/ritonavir plus lamivudine had HIV RNA <50 copies/mL vs 91% in the standard therapy arm.

Dr. Gallant said that NRTI-sparing strategies have generally fallen into either of 2 types: a boosted PI plus an integrase inhibitor (or maraviroc in one study) or a boosted PI plus either lamivudine or emtricitabine (NNRTI-light regimens, as he described them). Patients receiving the first type have generally done less well than those receiving standard therapy, whereas patients receiving the second type have generally had outcomes comparable to those receiving standard therapy. In other words, the best NRTI-sparing regimens contain an NRTI, albeit one that nearly everyone can tolerate.

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Dr. Gallant summarized his own preferences in selecting an NRTI-sparing regimen:

- All NRTI-sparing regimens should include a boosted PI, at least for the time being.
  - Lopinavir/ritonavir plus efavirenz was effective but poorly tolerated, but other PI/NNRTI combinations could be considered.
  - Boosted PI plus an integrase inhibitor may not be sufficiently effective, although dolutegravir has not been evaluated in this scenario.
- His own preferences were:
  - Darunavir/ritonavir (or cobicistat) plus dolutegravir, and possibly lamivudine or emtricitabine
  - Darunavir/ritonavir (or cobicistat) plus etravirine, with or without lamivudine or emtricitabine
  - Darunavir/ritonavir (or cobicistat) plus lamivudine or emtricitabine

However, Dr. Gallant said that the appeal of NRTI-sparing regimens may soon come to an end:

- More definitive data on the association between abacavir and MI should be forthcoming.
- A study in which patients with mild to moderate kidney disease were switched to elvitegravir/cobicistat/emtricitabine/TAF reported that participants experienced no worsening of their kidney disease and improvements in proteinuria.

Switching and Simplifying Therapy in a Virologically Suppressed Patient

Dr. Gallant also approached this situation via an illustrative case: JB, a 63-year-old man diagnosed with HIV infection in 1987:

- Has been treated by multiple doctors and has received a variety of regimens since the early 1990s; does not have old records and does not know his treatment history
- Recalls being told he has "some resistance"
- Now on darunavir/ritonavir (600/100 mg twice daily) plus raltegravir plus etravirine plus tenofovir/emtricitabine
- Wants a simpler regimen, once-daily with fewer pills

Dr. Gallant cautioned that the maxim, "If it ain't broke, don't fix it," should not guide treatment decisions

He then cautioned that the maxim, "If it ain't broke, don't fix it," should not guide treatment decisions for patients like JB.

DHHS guidelines offer these recommendations concerning when to consider switching regimens:

- To simplify therapy (reduce pill burden, dosing frequency, improve adherence)
- To enhance tolerability, decrease short- and long-term toxicity
- To change food or fluid requirements
- To avoid parenteral administration (in patients using enfuvirtide)
- To minimize or address drug interactions
- To allow for optimal use of ART during or in the event of pregnancy
- To reduce cost

He presented a list of recent switch studies (Figure 4), most of which reported favorable outcomes with the new regimens, except the HARNESS and SWITCHMRK studies. In the former, patients who were switched to atazanavir/ritonavir plus raltegravir had less favorable outcomes. He added that studies had not yet been done of switches to dolutegravir but that seemed likely to become a popular approach.

Trial	From	To	Outcome
GS-123	TDF/FTC + RAL	TDF/FTC/EVG/Cobi	✔
GS-264	TDF/FTC/EFV	TDF/FTC/RPV	✔
Strategy-NNRTI	TDF/FTC + NNRTI	TDF/FTC/EVG/Cobi	✔
Strategy-PI	TDF/FTC + PI/r	TDF/FTC/EVG/Cobi	✔
SPIRIT	2 NRTI + PI/r	TDF/FTC/RPV	✔
SPIRAL	2 NRTI + PI/r	2 NRTI + RAL	✔
SWITCHMRK	2 NRTI + LPV/r	2 NRTI + RAL	✗
HARNESS	2 NRTI + 3rd agent	TDF/FTC + ATV/r ATV/r + RAL	✔ ✗
SALT	ATV/r + 2 NRTI	ATV/r + 3TC	✔
OLE	LPV/r + 2 NRTIs	LPV/r + 3TC	✔

Figure 4. Recent antiretroviral switch studies (courtesy: David Wohl).

In the SWITCHMRK studies, virologically suppressed patients on lopinavir/ritonavir plus 2 NRTIs were randomized either to continue with that regime or to switch to raltegravir plus 2 NRTIs. Participants who switched to raltegravir had significantly lower rates of HIV RNA <50 copies/mL vs those who continued on lopinavir/ritonavir. Dr. Gallant explained that the reason for the unfavorable outcome seemed to be

that many patients had numerous resistance variants and that by switching from a regimen with a high resistance barrier to one with a low barrier they were not able to maintain virologic suppression.

He then offered 2 caveats regarding switching ART regimens:

- Know the patient's treatment and resistance history.
- Avoid switching from high-barrier to lower-barrier agents when you do not know that history.

Dr. Gallant described the 2 general categories of ART switches:

- Horizontal switches, ie, switching to a drug with equal or higher resistance barrier, eg
  - From ritonavir to cobicistat boosting
  - Switches within the integrase inhibitor class
  - From efavirenz or nevirapine to rilpivirine or etravirine
  - From an older PI (boosted lopinavir or atazanavir) to darunavir/ritonavir
  - From abacavir or zidovudine to tenofovir
  - From anything to a boosted PI
- Vertical switches, ie, switching to a drug with a lower resistance barrier, eg
  - Most drug discontinuations
  - From a boosted PI to an NNRTI
  - From a boosted PI to an integrase inhibitor
  - From darunavir/ritonavir twice daily to darunavir/ritonavir once daily

He added that such switches are feasible but it is important to know the patient's resistance history before making the switch.

Dr. Gallant returned to JB's case by presenting a table of possible switches that may reduce his pill burden while maintaining virologic suppression (Figure 5). Cautions regarding some of the choices in the middle column include: Although JB is likely resistant to tenofovir, knowing his resistance profile would help in deciding whether to discontinue it. The same thing applies to switching to once-daily darunavir. He then said that use of a relatively new test, *GenoSure Archive*^{SM}, which is intended to identify archived viral variants, may help guide those decisions.

Switch	OK?	Comments
RAL → DTG	Yes	• Reduces pill burden • DTG superior in ART-exp'd pts (SAILING)
ETR 200 bid → 400 QD	Yes	• Not approved dose but supported by PK
Discontinue TDF/FTC	Maybe	• NRTIs unnecessary if >2 fully active agents (OPTIONS) • His complex salvage regimen suggests that he probably has TDF and FTC resistance already
DRV/r BID → QD	Risky	• DRV mutations? (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V) • APV and FPV most likely to cause DRV cross-resistance
Change to ABC/3TC/DTG	Risky	• DTG resistance barrier *may* be as high as a boosted PI • NRTI resistance unknown
Change to any other STR	No way!	• Remember SWITCHMRK!

Figure 5. Switch options for JB.

Summary

- Antiretroviral guidelines cannot provide specific recommendations for every patient or clinical scenario.

- Some patients need NRTI-sparing regimens (at least for the time being). Clinicians may need to choose regimens based on extrapolations from existing data rather than using studied but suboptimal combinations.
- Clinicians can make patients' lives easier and better by carefully updating or simplifying their regimens. Viral suppression is not the *only* criterion for success.

Audience Questions

An antiretroviral-naive, newly diagnosed patient presented with an opportunistic infection requiring trimethoprim/sulfamethoxazole and I started a darunavir-based ART regimen. But he developed a serious rash that I assumed was a reaction to darunavir because of its sulfa moiety. So, he was switched to atazanavir. Should I have prescribed an integrase inhibitor instead?

Roy M. Gulick, MD, MPH: The guidelines recommend having a genotype performed for treatment-naive patients, since approximately 16%-17% will have pretreatment resistance variants. For patients like this one who urgently need to start therapy, the guidelines recommend using a PI. Some clinicians prefer an integrase inhibitor, because the incidence of integrase resistance in the community at this time is very low. The patient's rash was more likely due to the trimethoprim/sulfamethoxazole, and the guidelines indicate that darunavir does not need to be avoided in patients with sulfa allergies.

Many of my patients say that they cannot tolerate PIs and want to switch to an integrase inhibitor, but I'm concerned about the lower resistance barrier.

Joel E. Gallant, MD, MPH: One thing you can do is use the power of suggestion by telling them that the problem is the ritonavir boosting and that switching to cobicistat will alleviate their intolerance. Many people recall the early problems with full-dose ritonavir and are inherently reluctant to use it.

Roy M. Gulick, MD, MPH: I would suggest that you carefully examine the patient's resistance profile for NRTI resistance, and if there is none, then switching to an integrase inhibitor would be appropriate. Also, if a patient really does not wish to take a PI, then there's a real risk that he will not take it.

Clinicians may need to choose regimens based on extrapolations from existing data rather than using studied but suboptimal combinations.

Should clinicians perform baseline integrase inhibitor resistance testing?

Roy M. Gulick, MD, MPH: The guidelines recommend baseline resistance testing only for PI and nucleos(t)ide resistance, largely because of the low level of community integrase resistance. In a specific case, such as the negative partner of a patient taking an integrase inhibitor who then seroconverts, that situation would indicate the need for integrase resistance testing.

Joel E. Gallant, MD, MPH: The other situation in which baseline integrase resistance testing would be wise is for a treatment-naive patient who has extensive resistance to other drug classes.

Behavioral Economics and Improving the ART Treatment Cascade

To begin his presentation, **Kevin G. Volpp, MD, PhD**, of the University of Pennsylvania, stated that a range of studies of how individuals' behaviors affect premature mortality indicate that approximately 40% of premature mortality is due to behavioral choices, with other contributors being genetics, social circumstances, the environment, and inadequate healthcare. Changing those behaviors, he said, can be difficult, which explains why behavior represents such a large portion of premature mortality causes.

Much of economic thinking is based on an assumption that people are perfectly rational and are able to calculate the risks and benefits of their actions now and in the future without making decision errors. According to this model, in estimating the utility, or lack of it, of different choices, people determine through backwards induction the path that has the highest net present value. However, Dr. Volpp said, in regard to health decisions, few people will perform that sort of rigorous algorithm. Behavioral economists, on the other hand, assume that people tend to be predictably irrational and that they make decisions on the basis of what they see in front of them. Other features of this behavior include an aversion to loss, lack of self-control, and a range of emotional considerations. Real-world decisions are also made in a time-inconsistent fashion: For example, when smoking a cigarette, a person may sincerely vow never to smoke again, but when nicotine craving begins, that resolution loses its strength.

Corporations, he explained, realize the value they can gain from the irrationality of human behavior. Over a 15-year period, the number of payday lenders has increased at approximately 3 times the rate of the number of Starbucks outlets. Payday lenders disguise exorbitant interest rates beneath the small fee they charge each month to advance a person an amount of cash against future income. When this happens month after month, the accumulating interest is essentially a path to financial ruin. Lack of understanding is key: A person who signs a payday-loan note indicating an interest rate of 800+% cannot possibly fully grasp the gravity of its implications. Situations like this, Dr. Volpp said, reflect the challenge that healthcare providers face when trying to convince patients to carefully weigh the future implications of current decisions.

People tend to have biases for their present situation, and one way to address this is to offer rewards for beneficial behavior that are frequent and immediate.

Nonadherence Behaviors

Nonadherence to medications for chronic conditions is a common behavior that limits population-wide health effectiveness of medications. For example, Dr. Volpp explained, statins are widely considered highly beneficial, and they are relatively easy to take and have few adverse effects. However, a range of studies has shown that nonadherence rates to statin therapy are approximately 50%. Similarly, the HIV care cascade—which shows that only approximately 28% of HIV-infected patients in the United States have maintained virologic suppression on ART—presents challenges for behavioral economics. Dr. Volpp continued, saying that behavioral economics aims to develop interventions that can improve patients' decision making at each point in the cascade. For example, people tend to have biases for their present situation, and one way to address this is to offer rewards for beneficial behavior that are frequent and immediate.

Regarding the HIV care cascade, he cited 2 points at which interventions could be beneficial:

- Initial diagnosis and linkage to care: use defaults, eg, opt-out HIV screening

- Retention in HIV care, medication adherence, and suppression of viral load: consider use of incentives

Although studies have found that these approaches typically have limited effect, Dr. Volpp said their implementation is often not done appropriately. In countries that have opt-out organ donation programs (ie, a person is considered to be an organ donor unless otherwise specified), participation rates are several times higher than in countries with opt-in programs.

In some contexts, changing defaults may not be feasible. He cited the example of a large pharmacy benefits company and its desire to encourage patients to enroll in its automatic prescription refill program. Opt-out did not seem to be a good choice because of the need to authorize a credit or debit card for each refill. To address this concern, consultants developed "Active Choice," which first explains how automatic refills benefit the long-term interests of the patient, thus allowing them to regard opting in as a "path of least resistance."

Dr. Volpp suggested examples of how defaults and active choice could be used in the HIV setting:

- HIV testing on an opt-out basis in emergency rooms and clinics in high-prevalence areas
- Follow-up appointments made automatically at time of diagnosis
- Enhanced active choice to enroll in automatic refill programs (especially for those on stable doses of multiple medications)

Many incentive/reward plans, he said, are not well-designed, eg, a major insurance company's $150 payment for attending a gym 120 times in a year:

- Once-a-year rewards overlook people's short-range focus
- Such high thresholds target those who already exercise frequently
- To get the reimbursement, a person must pay for gym membership upfront

He said that medication use after a myocardial infarction (MI) is surprisingly low. A clinical trial randomized patients after an MI to regimens with either a standard copayment or no copayment. The investigators reported adherence rates of only 39% in the standard copay arm and 45% in the no copay arm.

Hovering

Disappointing findings like these will require solutions that are more involved in patients' lives.. Americans typically may spend 1-2 hours a year with a doctor, whereas they spend their remaining 5,000+ waking hours elsewhere, ie, going about their daily business. Physicians, he said, do not know much about what patients are doing during these 5,000 hours and do not have good tools to affect patients' behavior (eg, medication adherence, diet and exercise affecting obesity). Proliferation of wireless technologies and advances in understanding of behavioral economics create new opportunities to improve population health. Improved health engagement requires a substantial amount of "hovering."

Traditional approaches have involved the use of staff like case managers, who had little information about the rest of patients' lives; it is also an expensive undertaking, as it relies on a large number of personnel. Automated hovering, Dr. Volpp said, offers a way to watch over those other 5,000 hours by taking advantage of the following important developments:

- Healthcare financing's increased focus on population-based health as opposed to fee-for-service
- Social media and wireless devices
- Behavioral economics and growth in understanding what makes people predictably irrational

One program uses a wireless device to upload information about when a patient takes a medication, uses a scale or pedometer, etc. and the data are uploaded to a central program that calculates individual incentives that are transmitted to the patient, with incentive payments automatically transferred to the participant. The programs are designed to "learn" so that they can focus efforts on patients who need particular attention.

HPTN 065 was one of the first controlled trials to assess the use of incentives to improve HIV testing and treatment:

- 3-year study evaluating the feasibility of community-focused strategy to expand testing, link HIV-positive persons to medical care, initiate treatment, and achieve high adherence
- Conducted in 39 HIV clinics in the Bronx and Washington, DC

HPTN 065 had 2 components: In the linkage-to-care component, half of HIV testing sites gave coupons to persons who tested HIV-positive ($25 for lab tests and $100 gift cards for seeing a provider and developing a care plan), and half provided standard care. In the viral suppression component, half of the clinics provided $70 gift cards every 3 months to patients who maintained undetectable viral load, while half continued usual care. Unfortunately, the study reported no significant impact on the percentage of people successfully linked to medical care after HIV diagnosis, and, at 18 months viral suppression numbers were only 5% higher at the sites with financial incentives.

Dr. Volpp offered some possible explanations for these outcomes. He thought that the financial incentives were probably too small and the feedback to the patient not frequent enough. For example, a wireless pill dispenser that could provide daily feedback would cost about the same amount but with higher efficacy. In short, he said, although well-intended, HPTN 065 was all economics and not enough psychology—ie, it did not adequately consider the 5,000 hour problem.

Implications of Behavioral Economics for HIV Care

- Making medications available for free or low cost will not solve problems with medication nonadherence; it helps a little, but not enough.
- Defaults and enhanced active choice can be used to help increase initial uptake of programs and the convenience of refilling regimens.
- Next-generation incentives will likely leverage wireless medication devices to monitor adherence and behavioral economic strategies to provide frequent feedback.

Psychopharmacology for Every Practitioner

Glenn J. Treisman, MD, PhD, of the Johns Hopkins University School of Medicine, approached his topic by listing the ways that psychotropic medications may be classified:

- Chemical class
- Origin-plant family
- Condition usually treated
- Physiologic actions (sympatholytic, mimetic)
- Receptor activity
- Mechanism of action
  - Agonists, antagonists, partial agonists, reverse agonists
  - Muscarinic, nicotinic
  - Reuptake blocker, precursor

He added that the preferred way to classify them is according to what they do or what conditions they treat:

- Major depression: antidepressants
- Bipolar disorder: mood stabilizers
- Schizophrenia: antipsychotics
- Anxiety disorders: anxiolytics
- Insomnia: hypnotics
- ADHD: stimulants/others
- Dementia: cognitive enhancers

However, his presentation was about more than lists, as keen insights into patient behaviors and health policies flavored his comments.

When most patients present to care, they are most concerned about how they feel, but part of their treatment should be getting them to function better, after which they will begin to feel better.

He stressed that antidepressants are not mood elevators that make a patient feel better after a difficult experience; rather, they are meant to reverse a physiological condition. He then emphasized the importance of understanding what depression is, so that an appropriate therapy can be recommended—ie, accurate diagnosis is key. With many conditions—eg, HIV, HCV—the goal of pharmacotherapy is to select a drug that suits the pathophysiologic target and eradicate the disease. This is not yet available in psychiatry. Most currently practiced psychiatry suppresses a syndrome (eg, depression) or symptom (eg, anxiety), but Dr. Treisman said that this approach ultimately will fail because the patient's brain will compensate for that which is suppressed, eventually making the condition worse.

With therapeutic drugs (antidepressants, neuromodulators), he elaborated, the goal is to improve function, whereas with symptomatic drugs (anxiolytics, opiates), the goal is to make the patient feel better. When most patients present to care, they are most concerned about how they feel, but part of their treatment should be getting them to function better, after which they will begin to feel better.

Dr. Treisman advised that HIV practitioners should familiarize themselves with antidepressants because those are the class of drugs that they are most likely to need to prescribe. He listed the major conditions and types of antidepressants that treat them:

- Major depression—SSRIs, SNRIs

- Panic attacks—most antidepressants
- Chronic pain—tricyclic antidepressants (TCAs) and serotonin and norepinephrine reuptake inhibitor (SSRIs, SNRIs)
- GI disturbance—TCAs inhibit, SSRIs activate
- Migraine—TCAs and some atypical antipsychotics
- Obsessive-compulsive disorder (OCD)—SSRIs, SNRIs, some TCAs
- Attention deficit disorder—TCAs
- Generalized anxiety disorder—SSRIs, SNRIs, TCAs

Treating depression in HIV-positive patients, Dr. Treisman stressed, is key, as untreated depression can contribute to a cycle that leads to risky behaviors, nonadherence to ART, and worsening depression (Figure 6).

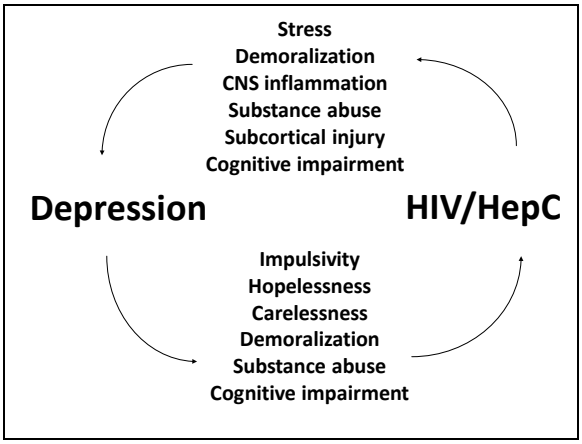

Figure 6. Key role of treating depression in HIV care.

Much of the remainder of Dr. Treisman's presentation was a review of the clinical use, adverse effects, and efficacy of the classes of antidepressants and anxiolytics. One caution he offered was that, whatever drugs a practitioner prescribes, approximately one-third of patients will fail to benefit from their treatment. Therefore, he recommended that clinicians be prepared to prescribe an alternative agent.

Treating depression in HIV-positive patients, Dr. Treisman stressed, is key, as untreated depression can contribute to a cycle that leads to risky behaviors, nonadherence to ART, and worsening depression.

Tricyclic Antidepressants (TCAs)

Conditions for which TCAs may be suitable include: chronic pain, neuropathy, post-herpetic neuralgia, migraine, GI spasm, diarrhea, and insomnia. Dr. Treisman then explained some of the complications in prescribing this class:

- Need to check blood levels
- Alpha blocking, antimuscarinic
- Cause sedation, weight gain, dry mouth, constipation
- Cardiotoxic (dangerous in overdose)
- EKG in overdose predicts lethality

SSRIs

In addition to major depression, Dr. Treisman said that other conditions that may respond to SSRI treatment include gastroparesis, chronic constipation, panic attacks, generalized anxiety, and OCD. SSRIs include:

- Fluoxetine (long half-life, little sedation)
- Sertraline (GI activating)
- Paroxetine (sedating, weight gain, potential for withdrawal syndrome improved with extended release formulation)
- Fluvoxamine (indicated for OCD but also works for depression)
- Citalopram (less activating but not sedating)
- Escitalopram (isomer of citalopram)

With SSRIs, some patients experience akathesia, causing them to be restless or feel that they cannot sit still. Other potential adverse effects include decreased sex drive, apathy, and suicidality, particularly early in use; the last should be watched for but is typically a short-term concern.

Bupropion, which is in a class by itself, has the fewest sexual adverse effects among antidepressants, is the least sedating, and decreases nicotine craving. It is sometimes used for ADHD.

Other Conditions

Psychosis. Dr. Treisman stressed that it is important to distinguish between delirium and psychotic states:

- Delirium—waxing and waning, poor ability to attend, change in level of consciousness, almost always organic and needs urgent workup
- Psychosis—almost always a product of schizophrenia, bipolar disease, or depression; patient in clear consciousness

Schizophrenia. This condition occurs in 1%-2% of the population, including 3.2 million Americans. Schizophrenia, he stressed, is very serious and consumes significant US healthcare resources, eg, 25% of all mental health costs, one-third of psychiatric hospital beds, $62.7 billion in 2002.

He described neuroleptics, the primary treatment for schizophrenia, as “dirty drugs” because of their many serious side effects, although these have lessened with the newer ones:

- Extrapyramidal symptoms (acute dystonic reactions, akathesia, parkinsonism)
- Tardive dyskinesia
- Neuroleptic malignant syndrome
- Others (seizures, dry mouth, blurred vision, urinary retention, constipation, orthostatic hypotension, slowed cardiac conduction, hyperprolactinemia, weight gain, predispose to heat stroke, photosensitivity, lupus-like reactions, cholestatic jaundice, agranulocytosis)

He commented that the atypical neuroleptic that more patients respond to than others is olanzapine and that aripiprazole is likely to see more use, as it will soon be available as a generic. Several neuroleptics are now available as long-acting injections taken every 2 or 4 weeks.

Summary

Dr. Treisman said that there are basically 2 types of psychotropic medications: those with less than 100% compliance and those with more than 100% compliance. The latter are the drugs that everybody wants and include sedative-hypnotics and anxiolytics, stimulants, and opiates. He added that these are drugs that patients often claim have been lost, stolen, or otherwise disappeared so that they can ask for more of them. He then stressed again the importance of correct diagnosis so that clinicians can clearly determine whether any of these agents offer continuing benefit to a patient. For example, stimulants can benefit someone with ADHD, but many persons will want them for other reasons.

He concluded with recommendations about how to manage patients who are already taking narcotics, benzodiazepines, or stimulants:

- Gradually taper them off the drug over the course of a year.
- Use the drug to increase the patient's function.
- It is important to understand that sometimes a clinician must say "no" to a patient's request for more of a drug.
- Get expert advice when you are not certain how to proceed.

Panel Discussion: Infectious Complications

The Curious Intersection of HIV and *Staphylococcus aureus*

Parallel to the evolution of HIV disease, said **Franklin D. Lowy, MD**, of the Columbia University College of Physicians and Surgeons, has been an evolution of the settings in which *Staphylococcus aureus* infection is encountered. In 1882, Sir Alexander Ogston first recognized the *S aureus* organism, and his description of its effects remains applicable today: "Micrococcus [*Staphylococcus*], which, when limited in its extent and activity, causes acute suppurative inflammation (phlegmon), produces, when more extensive and intense in its action on the human system, the most virulent forms of septicæmia and pyæmia." Dr. Lowy said that in modern settings *S aureus* manifestations still can range from minor skin infections to devastating invasive disease.

The nose, Dr. Lowy explained, is one of *Staphylococcus*'s primary reservoirs, with nasal colonization occurring in 20%-40% of "normals," and many of those who are colonized will in fact be infected, usually with the colonizing strain. Colonization is increased in certain groups:

- HIV-infected patients
- Patients with kidney or skin disease
- Diabetics
- Injection drug users
- Persons requiring long-term care

Eradication of colonization is sometimes effective in reducing the incidence of *S. aureus* infections, but his presentation of an S. aureus timeline (Figure 7) suggested how challenging that can be.

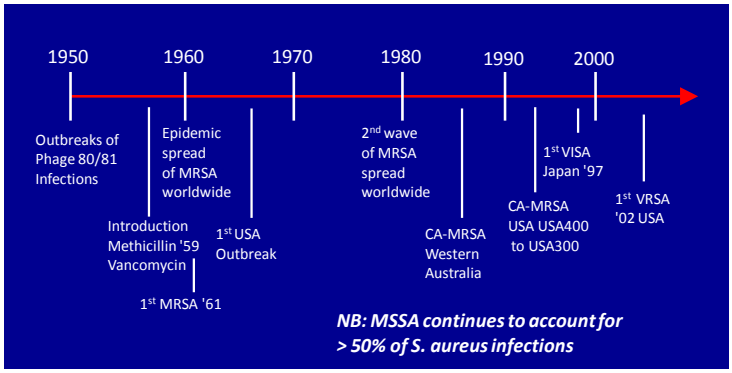

Figure 7. *S. aureus* and MRSA timeline.

In 1999, the first cases of community-acquired MRSA were reported, with the deaths of 4 children in Minnesota and North Dakota; the children had none of the standard risk factors for the infection. This led the Centers for Disease Control and Prevention to announce: "MRSA is an **emerging community pathogen** among patients without established risk factors for MRSA infection (eg, recent hospitalization, recent surgery, residence in a long-term-care facility, or injecting-drug use)." Following this report, Dr. Lowy said, there was a rapid spread of the particular clone that was responsible for the infections, USA300.

A bewildering array of MRSA outbreaks from USA300 appeared in populations across the United States

- Sports participants

- Inmates in correctional facilities
- Military recruits
- Children in daycare
- Native Americans, Alaskan Natives, Pacific Islanders
- Men who have sex with men (MSM)
- Hurricane evacuees in shelters
- Tattoo recipients
- Rural crystal methamphetamine users

This led investigators to evaluate what features these groups had in common. The commonalities identified came to be known as the "5 Cs" of CA-MRSA:

- Contact
- Crowding
- Contaminated items
- Compromised skin integrity
- Cleanliness

More recently, he said, a large number of studies examining the phenomenon of MRSA colonization in HIV-infected persons have found:

- Increased colonization vs HIV-uninfected
- Increased number of body sites colonized
- Increased number of infections (including invasive ones)
- Increased diversity of infections
- Worse outcome, especially for those with AIDS
- Increased number of CA-MRSA infections
- Greater risk of recurrent infections
- No difference in clinical presentation between HIV-positive and HIV-negative individuals

Moreover, he continued, MRSA infections occurred in somewhat different groups in 2 time periods: 1980s and 1990s vs 2000 to the present. In the 1980s and 1990s, *S. aureus* was the most frequently identified bacterial pathogen; more endocarditis occurred among HIV patients, with higher mortality in those with reduced CD4+ cell counts. During this time, many of the MRSA infections were healthcare-associated (invasive procedures, hospitalization, and catheterization). From 2000 to the present, the widespread use of ART was associated with reduced numbers of bacteremias. Linkages to CA-MRSA infections increased, and different risk factors were associated with higher rates in groups such as IDUs and MSM.

Among HIV-infected persons, risks for MRSA colonization generally are classified as environmental factors, host factors, and behavioral factors.

- Environmental factors. Risks vary by geographic location (eg, certain zip codes or residence in public housing). Being homeless or having a history of incarceration also increased one's risk, as does greater contact with healthcare facilities. A study in Chicago found a 6-fold increase in MRSA colonization in an area with large numbers of HIV-infected persons.
- Host factors**.** Among HIV-infected persons, low CD4+ cell count may be predictive of increased risk, and receipt of ART may be protective. Medical comorbidities such as diabetes or renal disease and colonization or prior infection with MRSA also increase risk, as does prior antibiotic exposure.

- Behavioral factors. A leading risk factor is drug use, whether injection or non-injection. Sexual practices, including multiple sexual partners, anonymous sex, and history of STDs increase MRSA risk. Certain activities that can involve physical contact are also factors, eg, sports, social networks, occupation, and children in day care. More recently, household contacts have been recognized as a risk factor.

MRSA Presentation and Management

Localized infections can include folliculitis, furuncles, carbuncles, mastitis, and cellulitis. Invasive infections can often be life-threatening and include a range of both common and uncommon diseases: septicemia, endocarditis, necrotizing fasciitis, pneumonia, osteomyelitis, and pyomyositis.

Among HIV-infected persons, low CD4+ cell count may be predictive of increased risk, and receipt of ART may be protective. Medical comorbidities such as diabetes or renal disease and colonization or prior infection with MRSA also increase risk, as does prior antibiotic exposure.

Persons suspected of having serious MRSA infections should be hospitalized and empiric therapy begun following cultures. For skin and soft-tissue infections (SSTI), Dr. Lowy advised that incision and drainage are critical, and wounds should be covered. A number of drugs are effective in the treatment of MRSA infections, including trimethoprim/sulfamethoxazole, clindamycin, tetracyclines (doxycycline, minocycline), linezolid, and tedizolid. Susceptibility to these drugs, he said, varies by region. In addition, HIV patients who previously have received trimethoprim/sulfamethoxazole are likely to be resistant to that drug. Parenteral agents include vancomycin, daptomycin, linezolid, ceftaroline, tedizolid, telavancin, dalbavancin, and oritavancin; the first 2 are the most commonly recommended.

Recurrent CA-MRSA Infections

Recurrences are relatively common, especially in HIV-infected patients. Repeated exposure to MRSA-infected or -colonized persons increases risk of reinfection, eg, daycare facilities, correctional settings, sexual activity, and sports teams. Body shaving should be viewed as high risk for persistent colonization. Dr. Lowy advised that a number of techniques are available for decolonization; including nasal mupirocin plus chlorhexidine showers, oral rifampin and doxycycline, and bleach baths (1 teaspoon per gallon of water or ½ cup per adult bath) for 15 minutes twice weekly for 3 months. Environmental cleaning, such as in daycare centers, is also important.

Panel Discussion: Infectious Complications

Clostridium difficile Colitis

In reviewing the rise of the *C difficile* epidemic, **John G. Bartlett, MD**, of the Johns Hopkins University School of Medicine, said that although the causative agent of what was later called *Clostridium difficile* colitis had been isolated in 1935, the outbreaks of disease associated with it did not begin until the

introduction of clindamycin in the 1970s, when clinicians began to observe incidents of "pseudomembranous colitis" in patients who had taken clindamycin. In the mid-1970s, the development of a hamster model of *C difficile* infection allowed researchers to discover a great deal of information about the bacterium and its related infection, including antibiotic treatment as the cause, the mechanism of disease causation (2 toxins), and its susceptibility to vancomycin. Eventually, 2 other treatments became available: metronidazole in 1980 and fidaxomicin in 2012. A 2013 study reported that *C difficile* infection was—at an incidence rate of 3.9/1,000 patient days—the most common healthcare-associated infection after central-line bacteremia, ventilator-associated pneumonia, surgical site infections, and catheter-associated urinary tract infections. This incidence rate is important, said Dr. Bartlett, because the Centers for Medicare and Medicaid Services has designated *C difficile* as a priority, with a goal of drastically reducing its incidence.

The principal risks for *C difficile* infection are advanced age, antibiotic treatment, and exposure to the healthcare system; more recent increases have been reported in outpatients, infants, and pregnant women. Symptoms typically are watery diarrhea, cramps, and fever. A review from one HIV clinic covering the period December 2003 to January 2011 reported an incidence rate among HIV-infected individuals of 8.3/1,000 patient years, twice the usual incidence in HIV-infected persons. Another study reported that the majority of hospitalized patients with *C difficile* infection were found to have been already colonized with the bacterium at admission. Dr. Bartlett said that HIV infection itself does not appear to significantly increase the risk of *C difficile* infection; rather, HIV patients' more frequent contact with healthcare environments and use of antibiotics are the probable causes, although CD4+ cell count <50 cells/mm^3 is associated with increased risk.

Enzyme immunoassay (EIA) and polymerase chain reaction (PCR) assay are the standard diagnostic tools for *C difficile* infection. PCR offers the advantage of sensitivity, but it lacks specificity and is costly. However, EIA, although it lacks sensitivity, is substantially less expensive. Dr. Bartlett added that a more sensitive tool is a beagle dog. Netherlands researchers trained a beagle to detect the unique scent of p-Cresol, which is produced by *C difficile* infection and found that diagnosis by beagle was 100% sensitive for *C difficile* infection.

Treatment

Dr. Bartlett then discussed a case to illustrate the treatment of *C difficile* infection. A 50-year-old man with a dental infection was prescribed clindamycin and subsequently experienced diarrhea, which PCR testing showed to be positive for *C difficile*. He was treated with oral vancomycin 125 mg 4 times daily for 10 days. Oral metronidazole 500 mg 3 times daily for 10 days works nearly as well, he added. Relapse occurs in 20% to 30% of cases and should be treated by either a repeat of the initial treatment or with fidaxomicin. However, advised Dr. Bartlett, a second relapse should be managed with one of 3 treatments:

- Vancomycin 125 mg 4 times daily for 10 days, followed by 125 mg twice daily for days, then 125 mg daily for 7 days, then 125 mg every other day for 4 weeks
- Fidaxomicin 200 mg twice daily for 7 days
- Vancomycin for 10 days, then rifaximin for 10 days

For a third relapse, guidelines suggest the use of stool transplant. Since the first successful use of stool transplant in 1952, Dr. Bartlett said, a number of studies have evaluated its efficacy in hundreds of patients and have found cure rates of 80% to 90%. A 2011 literature review covering 1958 to 2010 found that stool transplant was associated with an approximately 90% cure rate, whether it was administered

by enema, endoscope, or nasogastric tube, and that it could be performed in a hospital or clinic or at home. A 2014 ruling by the Food and Drug Administration now requires that stool transplant requires patient consent, that either the patient or the clinician must know the donor, and that the donor must be screened for a variety of infectious agents. Dr. Bartlett added that the screening costs approximately $600 and that most insurers will not pay for it. A 2014 study reported 90% cure rates with the use of oral stool capsules prepared with donations from healthy individuals.

Dr. Bartlett concluded by briefly discussing a hopeful development in the fight against *C difficile* infection: In the United Kingdom, a rigorous program to reduce the incidence of *C difficile* infections reported a 70% reduction through the use of not only standard infection control protocols but also carefully monitored use of antibiotics to reduce the number of persons put at risk of the disease.

Panel Discussion: Infectious Complications

Sexually Transmitted Diseases

Epidemiology

A resurgence of sexually transmitted diseases (STDs) is occurring among HIV-infected patients, said **Jeanne M. Marrazzo, MD, MPH**of the University of Washington Seattle STD/HIV Prevention Training Center. In a 2012 prospective cohort study, 557 HIV-positive adults in 4 cities were screened and treated for STDs at enrollment and again at 6 months. The researchers reported that 13% had an STD at enrollment and that 7% had an incident STD at 6 months. Of the new infections, 94% were in men who have sex with men (MSM), the most being rectal chlamydia and oropharyngeal gonorrhea. The primary infection risks were polysubstance use and having >4 sexual partners in 6 months.

She continued, saying that an analysis of findings from a pre-exposure prophylaxis (PrEP) trial found that a diagnosis of syphilis was predictive of HIV infection: 2.8 HIV diagnoses per 100 person-years for participants without syphilis vs 8 HIV diagnoses for those with syphilis (hazard ratio, 2.6). Data from the Centers for Disease Control and Prevention (CDC) showed a significant rise in both primary and secondary syphilis among MSM during the 2009-2012 period; 40% to 70% of cases are also HIV-infected. Dr. Marrazzo said that findings such as this suggest that young HIV-negative MSM who are diagnosed with an STD should be counseled that initiation of PrEP would be appropriate.

Data from the Centers for Disease Control and Prevention (CDC) showed a significant rise in both primary and secondary syphilis among MSM during the 2009-2012 period; 40% to 70% of cases are also HIV-infected.

Dr. Marrazzo stated that many clinicians have expressed concerns that the incidence of neurosyphilis may be increasing. She said that CNS invasion can occur at any stage of syphilis and that rates may be as high as 30% to 40%, although most are asymptomatic. Symptomatic forms occur after months to a few years, presenting as meningitis, hearing loss, visual disturbances, meningovascular effects (stuttering

stroke), and altered mental status. Late symptoms (>2 years) can present as *Tabes dorsalis*, ie, syphilitic myelopathy, manifesting as muscle weakness, difficulty walking, loss of reflexes.

Other STDs that clinicians should be alert for are extragenital chlamydia and gonorrhea (ie, rectal and pharyngeal), as CDC data report increasing incidences of both infections in recent years. She further mentioned that hepatitis C virus infection can be transmitted sexually in MSM, particularly those who participate in unprotected receptive anal intercourse or engage in other sexual activities that can lead to abrasions or bleeding.

Screening

HIV treatment guidelines recommend that clinicians should screen all HIV-infected patients for STDs. Dr. Marrazzo expanded on those recommendations:

- Syphilis: at entry to care and periodically thereafter, depending on risk
- Gonorrhea: at entry to care and periodically thereafter, depending on risk
  - Rectal testing if receptive anal sex
  - Oral testing if receptive oral sex
- Chlamydia: at entry to care and periodically thereafter, depending on risk
  - Rectal testing if receptive anal sex
- Trichomoniasis: vaginal test in women

She stressed that it is important for clinicians to become accustomed to and comfortable with asking patients about their sexual histories and then performing STD screening based on that information.

Pharyngeal and rectal gonorrhea in men. The majority of such cases are asymptomatic, and she cautioned that clinicians need to screen specifically at those sites even in the absence of symptoms. There is some evidence that gonorrhea isolates in the rectum and pharynx are less susceptible to erythromycin and that infections there contribute to increased HIV shedding.

Dr. Marrazzo stressed that it is important for clinicians to become accustomed to and comfortable with asking patients about their sexual histories and then performing STD screening based on that information.

HPV testing. Although there are no clear guidelines concerning use of high-risk human papillomavirus (HPV) DNA testing and cervical Pap smear in HIV-infected persons, Dr. Marrazzo said that a 2012 study reported that current evidence suggests that the usual testing algorithm is suitable. Regarding anal Pap screening and HPV DNA testing, she added that it is not recommended, as the positive predictive value is low because such a large number of HIV patients have HPV.

Diagnostic lumbar puncture. Studies have documented clinical and cerebrospinal fluid (CSF) abnormalities consistent with neurosyphilis in patients with CD4+ cell count ≤350 cells/mm^3 or rapid plasma reagin (RPR) ≥ 1:32, although there is no change in clinical outcome in asymptomatic patients. Therefore, Dr. Marrazzo recommended against lumbar puncture in that setting. In addition, the CDC has indicated that, in the absence of neurologic symptoms, there is no evidence that CSF exam is associated with improved outcomes.

Chlamydia and gonorrhea. Nucleic acid amplification tests (NAAT) are recommended in both men and women, ideally using first-catch urine in men and vaginal swabs in women. Repeat testing, she said, is not necessary.

Syphilis treponemal testing. The Food and Drug Administration has approved treponemal tests for clinical use; they are automated and less expensive to perform. However, she cautioned, they cannot distinguish between active and old disease, and because they do not show titers, they cannot be used to monitor therapy.

Treatment

Dr. Marrazzo stated that antibiotic-resistant gonorrhea is currently a topic of great concern. An increasing proportion of isolates have laboratory evidence of decreased susceptibility, and there have been case reports of oral cephalosporin treatment failures in diverse areas worldwide, as well as of extended-spectrum cephalosporin resistance.

A 2013 analysis reported that, across the United States, gonococcal isolates from MSM were significantly more likely to exhibit higher minimum inhibitory concentrations (MICs) of ceftriaxone and azithromycin than isolates from men who have sex with women (MSW) and that MSM had a high prevalence of resistance to ciprofloxacin, penicillin, and tetracycline. The researchers recommended that clinicians monitor for treatment failures among MSM diagnosed with gonorrhea.

Dr. Marrazzo said that the new CDC STD treatment guidelines recommend ceftriaxone 250 mg as a single intramuscular dose (if not an option, cefixime 400 mg orally in a single dose) plus oral azithromycin 1 g as the only treatment for uncomplicated gonococcal infections. She described these developments as a sentinel public health event, emphasizing that patients' partners should be treated, a test of cure performed 1 week after treatment, and cases should be reported to the CDC via state or local public health authorities.

Summary

- Screen appropriately!
- Rescreen for chlamydial and gonococcal infections 3 to 6 months after an initial positive finding.
- Be aware of antibiotic-resistant gonococcal infections.
- Recognize that syphilis continues to be a serious problem, know what the EIA is, and recognize neuroinvasive disease.
- Sexual health:
  - Vaccinate for HPV (but continue Pap test screening).
  - Counsel patients regarding current STD prevention recommendations.

Audience Questions

Can you comment on the potential effect of tenofovir on herpes simplex virus type 2 (HSV2)?

Jeanne M. Marrazzo, MD, MPH: Tenofovir does have anti-HSV2 activity, but the concentration that would be needed to provide effective treatment is too high. However, the CAPRISA PrEP study found that there was a significant reduction in HSV2 acquisition in women using tenofovir gel. Other PrEP studies have also reported a modest reduction in the number of genital ulcers in participants who received tenofovir-containing regimens.

Would you recommend use of the HPV vaccine in MSM who have had abnormal anal Pap smears?

Jeanne M. Marrazzo, MD, MPH: The vaccine does not appear to have a therapeutic effect, although there are no good data on its use with anal neoplasia. For prevention, guidelines recommend vaccinating men up to 21 years of age. However, older patients do ask to be vaccinated, and they may benefit if they have not yet been exposed to all 4 high-risk HPV types.

Is there a concern that patients who have had fecal microbiota transplant to treat* C difficile *and later are prescribed antibiotics could experience a relapse of* C difficile*?

John G. Bartlett, MD: There have been no reports thus far of relapse in patients who were treated successfully with fecal transplant. Regarding those who subsequently received antibiotics, data are limited but there are no indications of risk of relapse.

Is there a role for the use of probiotics for primary or secondary prevention of* C difficile*?

John G. Bartlett, MD: There is limited evidence that probiotics help in the prevention of antibiotic-associated diarrhea, but the data on their use for prevention of *C difficile* are not impressive. It's also important to realize that the microbiome is comprised primarily of organisms that cannot be cultivated and commercialized. Probiotics add to the colon something that is not normally present there, rather than reconstituting normal flora.

Management of HIV and Cardiovascular Disease

Like many of the presentations at this meeting, this one concerned one of the many critical medical issues that arise in managing HIV-infected patients beyond the selection of an effective ART regimen. **Priscilla Y. Hsue, MD**, of the University of California, San Francisco, began her presentation with a concise summary of the range of cardiovascular (CV)-related morbidity and mortality concerns in the HIV-infected population. A growing number of studies have demonstrated that HIV-infected individuals are at higher risk for cardiovascular disease (CVD), including acute myocardial infarction, diastolic dysfunction, and sudden cardiac death. This elevated risk persists even in the setting of treated and suppressed HIV infection, although the reasons remain largely unexplained but are likely multifactorial, including traditional risk factors, HIV infection, antiretroviral medications, chronic inflammation, and immune activation. The optimal risk calculators and biomarkers to predict CV risk in HIV patients remain unknown, and most clinicians apply methods designed for the general population, which may not capture some HIV-associated aspects of CV risk.

She approached her presentation via the case of a 48-year-old HIV-positive male who is referred to the cardiology clinic with shortness of breath:

- CD4+ cell count = 440 cells/mm^3 and undetectable HIV RNA (lopinavir/ritonavir plus abacavir/lamivudine)
- Cardiac risk factors
  - Blood pressure: 135/90
  - Cigarette smoker
  - HDL: 32 mg/dL, TG: 236 mg/dL, LDL: 160 mg/dL, TC: 244 mg/dL
  - Weight: 135 pounds and slowly decreasing over past 10 years

To diagnose this patient and develop a treatment plan, the clinic performed a treadmill test, which showed worrisome signs of CV problems, and he was referred for cardiac catheterization, which identified coronary artery disease requiring bypass surgery. A 2014 study reported these findings on myocardial infarction (MI) risk in HIV patients:

- HIV associated with a 50% increased risk of acute MI after adjustment for risk factors
- Ongoing increased risk among those with virologic suppression
- Impact of HIV on risk comparable to traditional risk factors, including older age, hypertension, diabetes, and hyperlipidemia

CVD Morbidity and Mortality

She added that mortality is higher following MI among HIV-infected patients vs the general population and that HIV patients are less likely to be referred for procedures such as angioplasty and anticoagulant treatment, which has been proven to increase survival. Moreover, cardiovascular disease (CVD) is now the second leading non-HIV-related cause of death (approximately 15%) among HIV-infected persons in the United States, and CVD mortality is significantly higher in all age groups through age 65.

Since 2013, the American College of Cardiology (ACC) guidelines have 4 categories of individuals who should receive lipid reduction therapy:

- Patients with known CVD, eg, stroke, peripheral arterial disease, coronary heart disease
- LDL ≥190 mg/dL
- CV risk equivalent, eg, diabetes, LDL 70–189 mg/dL

- Calculated risk equivalent >7.5%

The ACC guidelines also categorize statin therapy according to intensity as high, moderate, or low. Without knowing the results of the 48-year-old patient's cardiac catheterization test, the risk calculator would show a 10-year CVD risk of 15.8% and a lifetime risk of 69%, which would merit moderate- to high-intensity statin therapy. Dr. Hsue then explained that most statins have a large number of potential drug-drug interactions, including with antiretrovirals. Most statins are metabolized by cytochrome P450 (CYP3A4) system, which is downregulated by all PIs, meaning that coadministration of a statin and a PI can lead to an increased area under the curve for the statin and subsequently rhabdomyolysis. Therefore, for patients receiving PI therapy, simvastatin and lovastatin are contraindicated, atorvastatin can be used at low doses with monitoring, and pitavastatin and fluvastatin are probably safe to use. A newer agent, rosuvastatin, is not metabolized by CYP3A4, although interaction with lopinavir has been reported; a low dose can be used in patients receiving lopinavir. She recommended the HIV drug interactions website to determine potential risks before prescribing a statin: www.hiv-druginteractions.org.

There is a differential effect on lipid levels among antiretrovirals, with integrase inhibitors apparently having some of the least impacts. Dr. Hsue said that HIV clinicians often wonder whether a patient's ART regimen should be switched in the event of dyslipidemia, and she cautioned that the issue of reducing lipids must be weighed against the potential loss of virologic control. A patient receiving a PI that is associated with dyslipidemia could possibly be switched to an integrase inhibitor or an NNRTI (eg, rilpivirine); switching from lopinavir to atazanavir may also be beneficial to lipids.

Dr. Hsue recommended the HIV drug interactions website to determine potential risks before prescribing a statin: www.hiv-druginteractions.org.

The 2013 ACC panel did not conduct a systematic review of issues related to elevated triglycerides, although Dr. Hsue said that elevated triglycerides increase CV risk but most of the risk decreases after adjusting for low HDL and other features of the metabolic syndrome. Triglycerides >500/ dL should be treated with a fibrate to prevent pancreatitis. Moreover, CVD risk predictors were developed in non-HIV populations and may not adequately predict risk in HIV-positive patients due to differing etiologies.

For patients with known CVD, Dr. Hsue said, aspirin has clearly been shown to be beneficial as secondary prevention, but its use as primary prevention has not yet been clearly established. A recent study of the use of aspirin in HIV patients reported no reduction in MI risk, although she added that the study had a number of limitations.

Association Between ART and CV Risk

Concerning whether the presentation's case patient should discontinue abacavir therapy, Dr. Hsue does not yet have a clear answer, since a number of studies have produced evidence finding either some association between abacavir use and MI or no association. There are some indications that recent abacavir use may be a key issue, rather than cumulative use.

A Veterans Administration study reported that ART was associated with a reduction of CVD risk, whereas findings from the DAD Study pointed to a 26% relative increase in the rate of MI rate associated with ART. She said that considerable evidence indicates that use of PI therapy is associated with a higher rate of MI per year of exposure. However, she added, more recent evidence supports the idea that early

ART initiation, and perhaps ART intensification, may contribute to reducing inflammation and CVD risk in HIV patients. Moreover, findings from the SMART study indicate that patients with untreated HIV infection have a higher CVD risk vs those on ART.

Chronic Inflammation

The role played by chronic inflammation in a spectrum of diseases, including CVD, in HIV patients is a topic of great interest currently, Dr. Hsue indicated. In fact, after adjusting for traditional risk factors, inflammatory biomarkers—such as IL-6 and D-dimer—remain moderately elevated during long-term ART. One subject of continuing debate involves which biomarker is the optimal indicator of CVD risk in HIV patients; further research should shed light on which of these can be targeted most effectively with treatment.

With regard to the presentation's case patient, Dr. Hsue explained that several questions need to be answered concerning how best to reduce his risk for CVD, such as whether to:

- Treat his HIV disease aggressively and early
- Put him on aspirin and a statin
- Treat his traditional CV risk factors
- Target microbial translocation
- Give him low-dose methotrexate
- Consider immune based therapies

Two studies examined the use of rosuvastatin in HIV-positive (the SATURN study) and HIV-negative (the JUPITER study) patients. The investigators reported greater reductions in LDL cholesterol in HIV-negative vs HIV-positive patients (50% vs 28%, respectively) and no impact on inflammatory markers in HIV patients vs a 37% reduction in HIV-negative patients in JUPITER. Dr. Hsue said that findings such as these underline the challenges faced in determining how to target and reduce inflammatory markers in HIV-infected patients. She added that the studies of reducing chronic inflammation in HIV disease that are now underway should provide valuable information that can also be applied in the treatment of CVD generally.

Summary

- CVD and other non-AIDS conditions are increasing health concerns among HIV-infected individuals.
- Traditional risk factors, eg, smoking and hypertension, are common in HIV patients, and recognizing and treating them is essential.
- Treatment of HIV infection likely reduces CV risk.
- Chronic inflammation remains elevated during effectively treated and suppressed HIV infection, and a range of emerging studies are evaluating how to reduce inflammation.
- Emerging, possibly HIV-related, CV conditions include pulmonary hypertension, atrial fibrillation, and diastolic dysfunction.
- Unanswered questions:
    - What is the best test to assess CV risk in HIV?
    - What is the best biomarker to assess CV risk?
    - Will targeting traditional risk factors be enough?

Pulmonary Arterial Hypertension in Patients with HIV Infection

Pulmonary arterial hypertension (PAH), said **Harrison W. Farber, MD**, of the Boston University School of Medicine, likely is not something to which most HIV practitioners have given much thought. He added that PAH is a somewhat orphan disease in the general population and even more so among HIV-positive persons. He cautioned, however, that an individual with PAH has an approximately 50% risk of mortality in the next 6 to 12 months.

The first case of PAH in HIV disease, Dr. Farber said, was reported in 1987. The next group of patients in which it was reported were all HIV-positive hemophiliacs, and at the time researchers thought that something about the comorbidity of hemophilia itself along with HIV infection could be the cause. However, subsequent HIV-related PAH cases were reported in patients without hemophilia, and, to date only approximately 250 cases have been reported in the literature. Currently, the PAH incidence is approximately 0.5% (ie, 1 in 200) in HIV-infected patients (6- to 12-fold greater than the incidence of idiopathic PAH). He added that that incidence has been the same both before and after the introduction of ART, suggesting that ART does not appear to reduce the risk of PAH.

The demographics of HIV-PAH, he explained, are limited because the disease has been so little investigated. He cited some general findings:

- Mean age: 32 years (lower than in the general population)
- Male to female ratio: 1.3-1.6:1 (in the general population, PAH much more common in women)
- HIV risks:
  - Intravenous drug use (IVDU) (42%-50%)
  - Men who have sex with men (MSM) (20-25%)
  - Hemophilia (13%)
  - Heterosexual sex (10%)

Presentation and Diagnosis

Dr. Farber said that the main presenting symptom of PAH is dyspnea, which is by no means unique to this condition. In addition, there is no correlation with a history of opportunistic infections, CD4+ cell count, or HIV RNA level. It is, however, correlated with duration of HIV infection, with most patients having been infected >10 years. Older studies, he said, found that PAH was more aggressive and more lethal in HIV-positive patients, probably because the patients presented late and were near death. More recent studies have found that HIV-PAH mortality, when it is identified, is significantly reduced with the use of pulmonary vasodilators..

Earlier studies reported a very poor prognosis for HIV-PAH, with 34% of patients dying within 5 days of diagnosis and a 1-year survival of 50% to 60%. In nearly three-quarters of patients, PAH was the direct cause of death, but newer analyses have reported a very good response to treatment with vasodilator treatment. Regarding pathologic features of HIV-PAH, Dr. Farber said that it strongly resembles idiopathic PAH and a pathologist likely would not be able to distinguish the cause from any other PAH etiology.

The pathogenesis of HIV-PAH remains far from clear, he explained, as is the pathogenesis of PAH in general. Several theories have been suggested (Figure 8):

- No direct HIV infection of the relevant cell types, ie, endothelial cells or smooth muscle cells
- No evidence of BMPR2 mutations, which are associated with idiopathic PAH
- Association with HLA-DR6 & HLA-DR 52
- Human herpesvirus-8 infection
- HIV viral particles (*tat*, *gp 120, nef*), now a favorite theory

In short, he said, investigators and clinicians do not have a clear idea at this time about how HIV causes PAH. In part, this is attributable to the limited number of HIV-PAH patients who are available to evaluate.

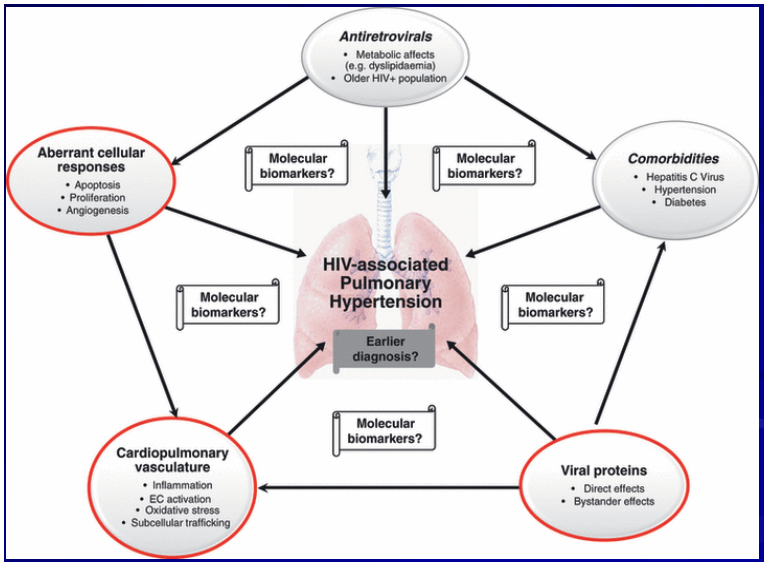

Figure 8. Proposed etiologies of HIV-PAH.

Further complicating investigation of the pathogenesis is the fact that several predictors of PAH in general also occur in a large number of HIV patients, including intravenous drug use, chronic liver disease (HCV, HBV), and coagulation abnormalities. The gold standard for diagnosis of PAH is right-heart catheterization. Dr. Farber said that, although many institutions use echocardiogram to diagnose PAH, the false-positive incidence shown by this method is quite high.

Treatment

There have been no randomized controlled trials in HIV-PAH; the literature consists of case series and case reports. Studies of PAH in the general population have excluded HIV-infected persons, in part because of the large number of interactions between antiretrovirals and the drugs used to treat PAH. These drugs include oral vasodilators (calcium channel blocker, bosentan, ambrisentan, sildenafil); inhaled prostaglandins (iloprost); and intravenous prostaglandins (epoprostenol, treprostinil).

A French case series of 15 HIV-PAH patients reported improvement in participants' 6-minute walk distance and their hemodynamics with 16 weeks of bosentan treatment. Another uncontrolled study of ambrisentan in 17 HIV-PAH patients found clinically relevant improvements in exercise ability, dyspnea,

and WHO functional class. In addition, epoprostenol therapy improved survival in a series of 80 HIV-PAH patients, 20 of whom were treated with IV epoprostenol. Dr. Farber stressed that the key inference from these studies is that the currently available treatments for PAH are also effective in HIV-PAH patients. He added that it is very unlikely that there will ever be a randomized controlled trial of HIV-PAH because of the paucity of patients, as well as pharmaceutical companies' lack of interest. Clinicians will need to rely on case reports such as these and anecdotal data.

Most antiretrovirals are associated with alterations in the concentration of the agents used to treat PAH, with the largest effects being with PIs. Integrase inhibitors, however, do not seem to have such interactions. For this reason, Dr. Farber said that he prefers to manage the ART for the HIV-PAH patients who are in his care. He concluded by advising clinicians that patients who present with dyspnea for which there is no evident cause should be suspected for either coronary artery disease or PAH.

Characteristics of Common Cancers in the Setting of HIV

Although several cancers are considered AIDS-defining and the incidence of other cancers is increasing among HIV-infected individuals, **Alexandra M. Levine, MD, MACP**, of the City of Hope National Medical Center and the USC Keck School of Medicine spoke about how 3 of the most commonly occurring cancers affect HIV-infected patients. Data from the D:A:D study, which has followed some 23,000 HIV-positive patients since 1999, showed that approximately 25% of all deaths among participants have been due to cancer, 37% of them AIDS-defining cancers (lymphoma, Kaposi sarcoma, and cervical cancer) and 63% non-AIDS-defining (NAD) cancers. Dr. Levine said that patients with NAD cancers typically have higher CD4+ cell counts than those with AIDS-defining cancers and are younger than HIV-negative patients with the same cancer diagnoses. She added that HIV-infected individuals with NAD cancers are significantly less likely to receive cancer treatment (approximately 2-fold risk of not getting treatment).

Lung Cancer

Lung cancer is the most common cause of cancer death globally, as well as in the United States, with >170,000 deaths each year—more than breast, colorectal, and prostate cancer deaths combined. Approximately 75% of patients diagnosed in the United States each year will have advanced disease at diagnosis. Prognosis is poor, with approximately 18% of patients alive 5 years after diagnosis.

Risk factors. The greatest single risk factor for lung cancer is tobacco use, and HIV-infected persons are significantly more likely to smoke than members of the general population (approximately 60% of HIV patients in developed regions) and are less likely to quit smoking.

Other factors, she continued, may also be involved, including chronic lung disease (recurrent bacterial pneumonia, AIDS-defining pneumonia, or asthma), or chronic inflammation due to cigarette smoke. HIV viral sequences are absent in lung cancer tissues, and about 90% of HIV patients with lung cancer have virologic suppression and CD4+ cell counts of 300-350 cells/mm^3 at diagnosis. However, HIV-1 tat

protein may modulate proto-oncogene expression in bronchoalveolar carcinoma cell lines, and microsatellite alterations and loss of heterozygosity have been reported in lung cancer tissue from HIV-infected subjects. Still, a study of HIV-positive and -negative women from the Women's Interagency HIV Study (WIHS) found no difference in lung cancer incidence among infected vs noninfected women. Furthermore, a recent multivariate analysis from the WIHS and the Multicenter AIDS Cohort Study (MACS) demonstrated that HIV infection per se was not associated with an increased risk of lung cancer, although both men and women with a history of AIDS-defining pneumonia had significantly increased risk. All lung cancer patients had a history of smoking.

Clinical characteristics. HIV-infected patients tend to develop lung cancer at an earlier age (median age in the 40s) vs HIV-negative individuals (median age in the 60s), and tend to present with more advanced disease. Pathologically, HIV-infected persons are more likely to be diagnosed with adenocarcinoma as opposed to other pathologic types (38% in HIV vs 13% in HIV-uninfected). Nonetheless, the median survival for lung cancer in HIV-infected patients is low, at 9.5 months for women and 6.2 months for men, with longer survival associated with diagnosis in more recent years, and shorter survival in those with a history of injection drug use.

Screening. Recent large randomized trials have shown a survival advantage to use of low-dose CT scan to screen high-risk persons, although the studies did not include HIV-infected persons. The National Lung Study Trial (NLST) enrolled 53,000 persons, 55 to 74 years of age, with history of ≥30 years of smoking in current smokers or those who quit <15 years before study entry. Participants were randomized into 2 groups, one with annual low-dose CT scanning and the other with annual chest X-rays. The study was closed when a predefined cut-off point of 20% improved survival in the CT arm was reached.

A cost-effectiveness study has determined that the cost of $81,000/quality adjusted life year (QALY) gained and $52,000/life year gained were within the threshold of $100,000/QALY considered reasonable in the US. Multiple associations have endorsed the recommendations made by the NLST investigators. A grade B recommendation by the US Preventive Services Task Force (USPSTF) in favor of low-dose CT scanning for high-risk patients has now required CT scanning to be covered as an essential benefit without copay under the Affordable Care Act. In addition, the Centers for Medicare and Medicaid Services (CMS) has released a coverage decision to pay for this service for individuals up to 77 years of age. Dr. Levine said that a small study of the effectiveness of CT scanning in HIV-infected patients reported similar outcomes.

Smoking cessation. Cytisine, a plant-based partial agonist of nicotinic receptors, is available as a generic drug that has been used in Eastern Europe since the 1960s. It is inexpensive, at a cost of $20 to $30 for a 25-day course (vs $112 to $685 for a full 8- to 10-week course of nicotine replacement therapy). In a trial of 1,310 smokers in New Zealand, cytisine was found significantly superior to nicotine replacement therapy for smoking cessation, with 42% of cytisine users quitting at 1 month, 38% at 2 months, and 31% at 6 months (vs 33%, 32%, and 30% for nicotine replacement, respectively). Dr. Levine expressed a hope that cytisine will become more familiar in the US because of both its efficacy and lower cost.

Prostate Cancer

Prostate cancer is the most common cancer in men, but the risk is not increased in HIV-infected men; however, she added, most men are likely to develop it if they live to old age.

Screening with annual prostate-specific antigen (PSA) testing has been the norm for many years, but recent evidence indicates that screening may lead to over-treatment of low-risk ("indolent") cancers (diagnosed in 35% to 70% of men), with resultant complications and costs, but without greater survival compared with men managed by active surveillance. Nonetheless, the natural history of prostate cancer is measured over decades, and early, promising results from withholding therapy may change with longer follow-up. Men with low-risk prostate cancer are those whose tumors are graded as Gleason ≤6, pretreatment PSA <10 ng/mL, and clinical stage I or IIa disease. Those with high risk for aggressive prostate cancer are Black men, those with family history of prostate cancer, and those who have taken alpha reductase inhibitors, eg, finasteride and dutasteride.

Screening. Annual digital rectal exam (DRE) and serum PSA testing may lead to diagnosis at a lower stage and grade of cancer, with presumed early treatment leading to prolonged survival. This annual testing should be performed starting at age 50 for men at high risk for aggressive cancer.

Several studies have failed to show a survival advantage for men who were screened and found to have prostate cancer vs men who were not screened. However, with longer follow-up times beginning at 11 years, a European study of 162,388 men randomized to PSA screening vs no intervention has recently demonstrated a survival benefit to screening followed by treatment. Nonetheless, treatment by radical prostatectomy or radiation therapy can have chronic complications, including urinary incontinence, chronic diarrhea, and erectile dysfunction. Recent studies have demonstrated no survival benefit in men with low-risk prostate cancer who undergo active surveillance vs definitive treatment. These data also may change with longer follow-up. Nonetheless, these studies have resulted in the current recommendation that routine PSA screening no longer be performed.

Vickers and colleagues have proposed a shared decision making tool with which clinicians and patients can decide together whether to screen for prostate cancer; see Figure 9 for the details.

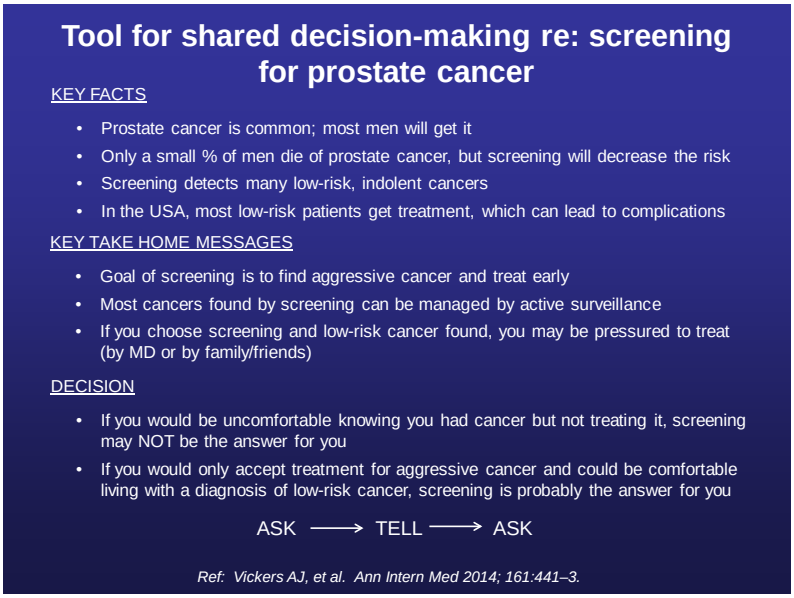

Figure 9. Proposed model for shared decision making.

Screening in HIV-infected men. Prostate cancer is not increased in the setting of HIV, and decisions about prostate screening should be similar to those for HIV-uninfected men, advised Dr. Levine. For men

at high risk, screening with PSA should begin at age 50, with a baseline PSA at age 40. In men at average risk, the shared decision making model is appropriate.

Breast Cancer

Breast cancer incidence is not increased among HIV-infected women; in fact, the risk may actually be lower. Recent studies have demonstrated that breast cancer and hyperplastic breast cells express the CXCR4 receptor. When CXCR4-expressing HIV is cocultured with breast cancer cells, apoptosis of the cancer cells occurs. WIHS investigators evaluated chemokine coreceptor tropism among a group of 19 HIV-infected women with breast cancer vs 55 HIV-infected controls. Women expressing the HIV-X4 tropism had a 90% lower risk of developing breast cancer vs those with exclusive HIV-R5 tropism. The apoptosis of hyperplastic or early breast cancer cells by HIV-X4 viral tropism may be responsible for the reduced risk of breast cancer among HIV-infected women, explained Dr. Levine.

Screening. Screening mammography has been the norm for more than 3 decades and has resulted in a 15% decrease in relative breast cancer deaths among women aged 40 to 49 years and a 35% decrease among women aged 60 to 69 years. For average-risk women, multiple organizations have endorsed annual mammography, beginning at age 40 years, with clinical breast exam beginning at 20 to 25 years of age. However, in 2009, the USPSTF recommended that mammography be initiated at age 50, that it should be performed every 2 years rather than annually, and that at age ≥75, evidence was insufficient to assess either the benefits or harms of screening. These guidelines have been very controversial and have not led to major changes in screening behaviors in the United States. For HIV-infected women, Dr. Levine recommended annual mammograms starting at age 40—ie, the standard guidelines for all women.

Risk factors. A meta-analysis of 66 studies found the following factors to be associated with an increased risk of breast cancer in women 40 to 49 years of age: extremely dense breasts, first- or second-degree relative with breast cancer, previous breast biopsy, heterogeneously dense breasts, current oral contraceptive use, having never given birth, and age ≥30 at birth of first child. Additional biological risk factors include mutations in *BRCA1* or *BRCA2* genes, Peutz-Jeghers syndrome, Cowden syndrome, receipt of chest radiation at a younger age (10 to 30 years), and others. She added that women with these factors should undergo annual mammography beginning at age 40.

Women expressing the HIV-X4 tropism had a 90% lower risk of developing breast cancer vs those with exclusive HIV-R5 tropism. The apoptosis of hyperplastic or early breast cancer cells by HIV-X4 viral tropism may be responsible for the reduced risk of breast cancer among HIV-infected women, explained Dr. Levine.

Summary

- 25% of all deaths in HIV patients are due to cancer.
  - Non-AIDS-defining cancers are the most common (63%).
- Lung cancer is associated with smoking and history of pulmonary infections or inflammation. Screening with low-dose CT is indicated: age 55–74 or 77; ≥30 PY; having quit <15 years ago.
- Prostate cancer incidence is not increased, but clinicians should be aware of recent trends in screening.
- Breast cancer incidence may be decreased; screen in the usual manner.

Audience Questions

Is there a way to predict which patients may be at risk for sudden cardiac death?

Priscilla Y. Hsue, MD: In a study now under way at our clinic, we now perform autopsies on every HIV patient who dies suddenly to try to discover the root causes. Our ultimate goal is to develop a calculator so that we can then put into place appropriate interventions.

Can you address the place of physical or chemical castration in prostate cancer?

Alexandra M. Levine, MD, MACP: Either of those procedures is a treatment for prostate cancer, typically for metastatic or locally advanced disease. It has no role in prevention.

If a patient presents with dyspnea and the echocardiogram suggests arterial hypertension, should the patient be referred to pulmonology?

Harrison W. Farber, MD: In such a patient, especially if there are right-heart abnormalities, catheterization should be performed; even if the echocardiogram finding is a false positive, you do not want to take the chance of missing PAH. Also, if a patient has an abnormal echocardiogram that has been done for any reason but the patient is asymptomatic, that patient should still be referred for catheterization.

What is your advice concerning anal cancer screening in asymptomatic patients?

Alexandra M. Levine, MD, MACP: The recently launched ANCHOR study aims to develop a definitive answer to whether such screening is advisable. In countries where cervical Pap smears are done routinely, cervical cancer has gone from the most common cancer in women to the least common. The same HPV strains are responsible for anal cancer, so it seems sensible to me to perform anal Pap smears to try to bring down the incidence of anal cancer, although the utility of it has not clearly been proven. I prefer to be more aggressive with screening than to have to treat cancers that might have been avoided.

A patient was diagnosed simultaneously with Burkitt lymphoma and HIV infection, and the oncologist did not want to start ART right away because of concerns about drug interactions. What would you advise?

Alexandra M. Levine, MD, MACP: A study by Barta and colleagues evaluated the timing of ART initiation in >1,500 HIV-positive patients being treated for non-Hodgkin lymphoma and found that concurrent use of ART was associated with improved rates of complete response to chemotherapy for the lymphoma.

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