Special Contribution

A Conversation Among the IAS–USA Board of Directors: Hot Topics and Emerging Data in HIV Research and Care

The IAS–USA volunteer Board of Directors met in October 2016 for its annual meeting. For the second year, the Board conducted a live, hour-long, interactive, round-table webinar covering current questions and issues in HIV research, prevention, and care. Important highlights from the Board's discussion, which was moderated by Paul A. Volberding, MD, are included below. Members of the IAS–USA volunteer Board of Directors are Constance A. Benson, MD; Judith S. Currier, MD; Carlos del Rio, MD; Joel E. Gallant, MD, MPH; Roy M. Gulick, MD, MPH; Jeanne M. Marrazzo, MD, MPH; Douglas D. Richman, MD; Michael S. Saag, MD; Robert T. Schooley, MD; and Paul A. Volberding, MD.

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The IAS–USA volunteer Board of Directors met in October 2016 for its annual meeting. The Board conducted a live, hour-long webinar and discussed hot topics and emerging data in the fields of HIV research, prevention, and care, and associated infectious diseases. Highlights from the Board's discussion, moderated by Paul A. Volberding, MD, are included below.

Dr Volberding: I am happy to have our board together for its 25th year. Today we will be discussing current questions and issues in HIV research, prevention, and care. I hope we get to a wide range of important issues. Let us begin by discussing the antiretroviral drugs that are currently in development.

Dr Gulick: With the currently available drugs, there is only a very small number of people who have experienced virologic failure due to resistance, but they need drugs that work against drug-resistant viruses. There are a couple of compounds in development that we have our eyes on. One of them is a CD4 attachment inhibitor, fostemsavir, an investigational drug with a new mechanism of action that is in phase III testing. It specifically binds envelope glycoprotein 120 (gp120) and prevents the virus from binding to the CD4 receptor. Phase II trial results demonstrated safety and efficacy. Phase III testing is fully enrolled for treatment-experienced patients, and we are waiting for those results.

Another new drug class in development is maturation inhibitors, which act very late in the HIV life cycle. We know that the polyproteins of HIV are cleaved by the protease enzyme, and there are many protease inhibitors (PIs). However, another mechanism is to bind the polyproteins together, and that is how this new class of maturation inhibitors works, distinct from every other drug we have. There are candidate compounds in development.

Dr Volberding: With regard to monotherapy, is using dolutegravir alone successful?

Dr Gallant: For a long time, we have been using 2 nucleos(t)ide analogue reverse transcriptase inhibitors (nRTIs) plus a third agent as the preferred treatment strategy, and that has not really changed. There have been attempts to research dual therapy. Some have not been very successful, such as the use a PI plus an integrase strand transfer inhibitor (InSTI). We have seen some success with use of boosted PIs plus lamivudine, and there is a small study from Argentina looking at dolutegravir plus lamivudine. This regimen worked quite well for the 20 patients in the study, and 2 larger-scale studies of this regimen are being conducted in the United States.

It will be interesting to see what happens. If dolutegravir does have a resistance barrier as high as that of PIs, then it may be a successful strategy.

Dr Gulick: That 2-drug combination (dolutegravir and lamivudine) looks interesting. It is important to remember that it was used in a small pilot study for 20 treatment-naive patients with plasma HIV RNA levels less than 100,000 copies/mL. The AIDS Clinical Trials Group is following up with a bigger study that is enrolling people with HIV RNA levels of up to 500,000 copies/mL.

Dr Benson: The ASPIRE (Dolutegravir Antiretroviral Strategy to Promote Improvement and Reduce Drug Exposure) trial in the United States is examining people who are fully virally suppressed on their antiretroviral regimen and are then transitioned to dolutegravir plus lamivudine for longer-term maintenance therapy. So, I think there are 2 larger-scale trials underway that will better address the question of

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how effective 2-drug therapy might be with an InSTI-based regimen.

Dr Saag: In practice, I am seeing many people using dolutegravir with boosted darunavir, but am not yet aware of any data.

Dr Gallant: There was a study of boosted darunavir and raltegravir, but among those with high viral loads or low CD4+ cell counts, it did not work so well. Maybe it would work better with dolutegravir, but we do not currently have any data.

Dr Volberding: I have seen early data on dolutegravir plus cobicistat-boosted elvitegravir. That is another 2-drug combination that might be of some interest.

Dr Gallant: Coformulated (/) elvitegravir/cobicistat/tenofovir alafenamide (TAF)/emtricitabine plus darunavir 800 mg for treatment-experienced patients worked quite well, but patients could not have more than 3 thymidine analogue mutations, could not have integrase mutations, and could not have darunavir mutations. So, for that select group of treatment-experienced patients on more complex regimens, the 2-pill combination of elvitegravir/cobicistat/TAF/emctricitabine plus darunavir may be a simpler option.

There have been a surprising number of very small observational studies of dolutegravir monotherapy in people who have previously been virally suppressed. Frankly, the results, if you put them all together, are not as good as those seen with dolutegravir and lamivudine, and there have been some treatment failures with integrase resistance, something we do not see with standard 3-drug–containing dolutegravir regimens. Given the safety and low cost of lamivudine, it makes more sense to carefully study treatment with dolutegravir and lamivudine before considering the further study of dolutegravir monotherapy.

Dr Currier: Before we leave the topic of investigational drugs, the unboosted investigational InSTI bictegravir in a single-tablet regimen is currently in phase III testing, and we can expect more information about in the coming year.

Dr Gulick: We should also mention doravirine, an investigational nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) that is in development. It has activity against NNRTI-resistant virus. We have not seen many results outside the treatment-naive population, but this drug may have some promise.

Dr Richman: It is also worth mentioning that for any patient that you are considering for a tenofovir-free regimen, you have to take into account their hepatitis B virus (HBV) serostatus.

Dr Volberding: You raise the issue of HBV infection. Do you want to comment on TAF and HBV, because we are seeing many people switching from tenofovir disoproxil fumarate (TDF) to TAF?

Dr Richman: There are data that have been presented that TAF is at least as good as TDF, and that makes sense for the pharmacology as well, and TAF has now been approved by the US Food and Drug Administration for treatment of HBV infection.

Dr Volberding: What are the latest advances with regard to preexposure prophylaxis (PrEP), including vaginal rings used for HIV prevention, and sexually transmitted infections (STIs)?

Dr Marrazzo: PrEP is being used more frequently, certainly among men who have sex with men (MSM) in the United States. I think the real advances in PrEP are the user-friendly delivery systems that people are moving toward: topical delivery (sustained vaginal ring delivery) and long-acting injectable formulations.

The investigational microbicide dapivirine in a vaginal ring was studied in the ASPIRE (A Study to Prevent Infection with a Ring for Extended Use) study—it shares a name with but is different from the HIV treatment study referenced earlier—and The Ring Study, the results of which were published in the *New England Journal of Medicine* in 2016.[1,2] At first glance, the results are somewhat disappointing in that overall efficacy in this study of young women in sub-Saharan Africa was only approximately 27% to 30% in those who replaced their dapivirine ring each month versus those who received a placebo. However, when the data were broken down, particularly by age group and then by adherence (presented at the 2016 International AIDS Conference), based on some very interesting modeling using residual drug levels, results looked better for women who were adherent.[3] Estimates are that the ring may be substantially more effective if it is used consistently every day. There were no cases of resistance reported in association with the dapivirine ring, and that is important.

The dapivirine vaginal ring is promising and is moving into unblinded, open-label studies in sub-Saharan Africa. TDF- and contraception-containing rings are also in development. Multipurpose, combined prevention is probably going to be the future.

Cabotegravir, which is an investigational dolutegravir analogue, is now being examined in 2 HIV Prevention Trials Network (HPTN) studies as an injectable PrEP option, given every other month for now. The dosing interval was adjusted after data from the ECLAR (Effect of Cell Surface Markers and Lymphoid Cell Distribution on the Arterial Tissue Repair) study because the absorption was faster, trough levels were lower, and peak levels were higher than anticipated. It has been an evolving algorithm, but ultimate dosing frequency is still to be determined.

Dr Gulick: The initial hope was that cabotegravir could be dosed every 3 months, but when investigators looked carefully at the pharmacokinetics, it was changed to every 2 months. HPTN 083 is a large, placebo-controlled study among MSM in the Americas, Asia, and South Africa that will open soon; HPTN 084 is the companion study among women in Africa. One group of participants will be taking 1 pill once a day of TDF/emtricitabine or a placebo. Another group will receive injections of cabotegravir or a placebo.

Dr del Rio: That is an important point. This is the first PrEP study that will compare an active agent with a new agent, and that is a new direction.

Dr Marrazzo: It is a huge paradigm shift. There are no more placebo-controlled studies of antiretroviral PrEP. Also, in the run-in phase of the cabotegravir study, everybody will receive an oral formulation of cabotegravir, so cabotegravir toxicity can be assessed before they receive the injection. Obviously, a huge concern with long-acting injectable agents is sustained safety.

Dr Volberding: What about TAF as PrEP?

Dr Gulick: Do not use it (yet). There is a chance that the pharmacokinetics could be different, and we do not know where the active compound has to be for HIV prevention. A study of TAF for PrEP is currently enrolling participants, but we should wait for the results before recommending it.

Dr Marrazzo: I think we do not know yet. There are not any data.

Dr Benson: Before we leave the topic of pharmacokinetics, I wonder if we could go back to the dapivirine ring studies. I think the concerns are the drug elution pharmacokinetics associated with the ring and the need for tissue levels beyond just where the local elution of drug from the ring stops. One of the concerns about topical therapy is the pharmacokinetics of tissue penetration at the place where you need it.

Dr Marrazzo: This is not only a concern for topical therapy. The biggest concern for women taking oral tenofovir is that you can very quickly get much higher levels in the rectum than you can in the cervicovaginal-vulnerable tissue. This is why women cannot just start taking tenofovir, say, 4 days ago and assume there is protection in the cervicovaginal area.

Dr Gulick: It is the same issue. We do not know where or at what level the active drug has to be to achieve the desired effect.

Dr Volberding: One of the things I think is worth talking about, with regard to prevention, is the issue of transmission among people whose virus is undetectable. The evidence is clear that if one has undetectable virus one is not transmitting HIV. What about STIs and PrEP? I think some may be aware that there is an early meta-analysis suggesting a very high rate of syphilis in the context of PrEP use.

Dr Marrazzo: I will say that the data that are out there are observational. With regard to STIs, the bottom line is that we are seeing what most people would say is an explosive increase in common STIs, certainly in MSM, whether they are HIV infected or not. I do not know that PrEP is making this happen more. I do not think we can say that yet. The research you are referring to indicated that PrEP use among MSM was associated with an increase in all STIs, and in fact, syphilis was 45 times more likely. We need more-sophisticated epidemiologic analyses to confirm this. Nonetheless, practitioners should be aware that there are many STIs occurring in this new generation of MSM.

Dr Volberding: How frequently should MSM taking PrEP be screened for STIs?

Dr Marrazzo: I think it has to be tailored. I would not object to monthly screening for some men. I know the Centers for Disease Control and Prevention (CDC) recommends every 3 to 6 months, but I think 6 months is a long time. I look at provision of PrEP as an opportunity to get people in to talk about their sexual health and their primary health care.

Dr Currier: I do think that having PrEP available is bringing people into care who were previously not engaged in care, and we have really capitalized on that. We should think about the opportunities for other prevention interventions when people come in for PrEP. With the recent cases of meningococcal meningitis, we are encouraging MSM to get vaccinated.

Dr Gulick: There was a similar outbreak in New York City recently, and the Department of Health recommended that all MSM, HIV infected or not, receive the meningococcal vaccine. Now, we have not seen a case in New York for a while. In 2003, there were outbreaks in Chicago, Illinois, and Toronto, Ontario, with the same strain of meningococcal disease, again in MSM. Vaccinations were widely provided, and the outbreak stopped. However, we really do not know why these outbreaks start and stop.

Dr Marrazzo: Meningococcal meningitis may be a sexually acquired infection because it classically colonizes the oral pharynx and can also cause urethritis and cervicitis, rarely, just like gonorrhea. That may be how it is being transmitted, selectively, among MSM.

Dr Gulick: We do not know that. It could be transmitted simply through oral sex or even kissing.

Dr Marrazzo: Then why would it not be happening equally as much in heterosexual populations?

Dr Gulick: You do need prolonged contact for it to spread.

Dr Marrazzo: I agree—it may simply be close contact in nonsexual settings. In any case, meningococcal meningitis should be addressed in the MSM population.

Dr Volberding: Where is hepatitis C virus (HCV) treatment going, and are there important new drugs in development?

Dr Saag: I think the recent release of velpatasvir creates a plateau of sorts after that initial burst of new drugs.

Every HIV/HCV-coinfected patient should be evaluated for cure of their HCV infection. We should be aware of the HCV serostatus of every patient in our clinics, to know whether they have HCV infection or not. Once that has been determined, if HCV RNA is detectable, most payers will now cover hepatitis C therapy. For practitioners, using the online HCV guidance[4] to decide which drugs to use is important.

The most important thing is to be aware of potential drug-drug interactions. One of the things we can and should be thinking about for new patients establishing care as we evaluate

them for therapy, we should know their HCV serostatus so that we can choose HIV regimens that are less likely to have drug-drug interactions with anti-HCV therapy. Unboosted InSTIs are probably best as anchor drugs for people who are HIV/HCV coinfected.

Dr Schooley: You emphasize the HIV/HCV-coinfected population, but I think practitioners should think about using the same infrastructure for HCV-monoinfected patients. There is no question that the number of people with HCV infection requiring therapy is massive, and it is not going to be covered by the hepatology community.

Dr Volberding: How rapidly is HCV therapy taking off?

Dr Schooley: HCV therapy is continuing to pick up. The drugs are getting simpler and simpler to use. The costs are being covered for most patients.

I think one thing that is different about this therapeutic area is that you often find third party payers forcing you toward one drug or another. Having said that, the drugs all work very well. Some of them are more complicated than others for certain patients, but we are about to be in a situation where we have several once-a-day, single-pill regimens that work for virtually every HCV genotype.

I would encourage those working in hospitals located in 340B-eligible census tracts to review how your institutions are allocating the 340B funds awarded on the basis of your HCV program. 340B is a federal program that provides supplemental funds to institutions providing care to labor (but not procedure)–intensive patient populations, such as those with HIV infection, HCV infection, hemophilia, or cystic fibrosis. The funds are provided to eligible institutions on the basis of the number and distribution of patients under care and are intended to support the programs generating the funds. Unfortunately, a number of institutions collect the funds from the federal government and apply them to general institutional uses rather than to the programs responsible for generating them. Those taking care of these patient populations in eligible institutions should ask the hospital to review the magnitude and allocation of 340B funds. Institutions may be receiving millions of dollars for their HIV and HCV programs and allocating them to the general hospital books while maintaining that they are "losing money" in their provision of HIV and HCV care. Explicit discussions about how these funds are used should be the expectation.

Dr Saag: As far as new HCV drugs that are coming along, as was mentioned, everything is moving toward pangenotypic agents. In the next 2 to 3 years, HCV genotype may not matter as much as it has to date. Still, I think the revolution of HCV therapy is just breathtaking.

Dr del Rio: I think we also need to remember that those who are HCV seronegative, particularly MSM, need to be tested regularly. We are seeing an epidemic of sexually transmitted HCV infection and an increase in acute HCV infection, and we are missing it.

Dr Marrazzo: We are also seeing huge rates of reinfection, which ties back to the idea of using PrEP as an opportunity to think about appropriate rescreening for infections.

Dr Benson: One of the issues that is often raised clinically is how the need for a liver biopsy has been used as a barrier to initiation of HCV therapy. How has the implementation of transient elastography in clinical settings eliminated the need for liver biopsies?

Dr Schooley: I think transient elastography is one of the most important advances in terms of liver disease staging in the last decade. With transient elastography, you can very easily separate people who have early stages of fibrosis from those who have more advanced fibrosis.

Dr Volberding: What is transient elastography?

Dr Schooley: Basically, transient elastography is a variation of an ultrasound, in which you are measuring the stiffness of the liver. What this lets you do, as an infectious diseases physician or as a nonhepatologist, is perform a simple test. You can do it yourself in your office and within about 8 minutes know whether a patient has advanced liver disease. If patients do not have advanced liver disease, there is no reason to send them to a hepatologist for evaluation. If they do have advanced liver disease, many times you can treat it yourself if you are prepared to follow the patients after cure to make certain they do not have hepatocellular carcinoma (HCC). For patients who have evidence of HCC, it would be better to consider liver transplantation before you treat them for HCV infection. The reduction in risk for HCC is one of the major benefits of successful treatment of HCV infection. The risk does not go away in people with more advanced disease, and that is where transient elastography is very helpful, to segregate those people who require more ongoing follow up.

This is another reason why I think that although the agents themselves are getting simpler to use (the algorithms are getting simpler as the genotype matters less), most HCV therapy will still be prescribed by a relatively small number of practitioners because of the infrastructure required by insurance companies, the need for access to transient elastography, and the need for understanding of how to manage people after cure. So I think it is something that will remain a specialized area of care but one that more practitioners should consider.

Dr Volberding: I want to start a discussion about HIV cure. I think there was a press release about the supposed cure of another person with HIV infection. I think we all recognize and are challenged by that kind of a report.

Dr Richman: That report on the cure of someone with HIV infection who is still taking antiretroviral therapy is premature.

Dr Volberding: The person had undetectable virus but is on antiretroviral therapy.

Dr Richman: Like millions of other people. The issue of HIV cure and the issue of HIV vaccines are, I think, 2 of the most important and exciting research areas in the field.

Dr Volberding: How is vaccine related to cure? We think of a vaccine as prevention.

Dr Richman: HIV cure is probably one of the most exciting and important areas with regard to people who are already HIV infected, and an HIV vaccine would clearly be the most effective preventative measure for those who are not yet infected. What links them is that they are important and exciting research areas, but the prospect of actually achieving an effective HIV cure or a vaccine is quite far off. The practical issue for our patients is that those who are expecting either a cure or an easy method of HIV prevention are going to have to proceed with the understanding that they will need to use what is now available for at least the next 5 to 10 years.

Dr Saag: You are saying what Margaret Heckler said in 1985, that we would have both the cure and a vaccine within a couple of years. It has been a long "2 years" since then.

Dr Richman: It has been a long "2 years," and my prediction is that it will take even longer.

Dr Volberding: Vaccines are now being thought of as something that might help kill HIV-infected cells or at least, maybe, control the expression of the virus. But your bottom line is, "stay tuned"?

Dr Richman: Stay tuned. It is an important research area, but it is not something that will be implemented in the near future.

Dr del Rio: There is much HIV cure research happening, and these are the early stages. People that are volunteering for cure studies are people who are doing well on their antiretroviral therapy, and they are not really getting anything out of these studies other than helping us develop a cure. The altruism that we need in volunteers for cure studies is something to keep in mind. That is also what makes research difficult, because from an ethical perspective, if somebody is doing well on their antiretroviral medications, why should they expose themselves to something potentially toxic that puts them at risk?

I really think that cure research is becoming complicated just as HIV vaccine research is becoming complicated because PrEP prevents HIV infection reasonably well. I think that research is not going to be as simple as it was in the past, but I am confident that working with volunteers, a committed community, and committed scientists will help us achieve our goals.

Dr Volberding: At some point, cure trials will require people to stop their antiretroviral therapy to determine whether a cure has been achieved, and the ethics of that are a real challenge.

Dr Gulick: Vaccine trials are getting, as was said, even more complicated, given that the standards of care now are treatment as prevention and use of PrEP. Vaccine studies will have to be enormous to show a benefit over what we offer now.

Dr Marrazzo: Well, the studies of antibody-mediated prevention that are happening right now are based on the assumption, at least in Africa, that the HIV incidence is at least 5%. If you are using PrEP regularly, you are not going to have this level of incidence. I think this is going to be a rapidly evolving and challenging field logistically and operationally and also in terms of study analysis and design.

Dr Volberding: You raise the issue of broadly neutralizing antibodies. There has been some interest in that with regard to prevention and cure.

Dr Schooley: I think these are interesting studies from a scientific perspective, but I have reservations about some of the approaches being taken, because the more efficacious antibodies are still on the shelf. VRC 007 is a better antibody than VRC 001, and I think we will learn about breakthrough. I think, in the long term, antibodies are not going to be an approach we use with PrEP, and we need studies and to be honest about how these approaches are being studied in our clinics.

Dr Saag: To put it into context, to me the antibody studies are really proof of concept that, potentially, an antibody can protect. Once that has been proven, then you can try to design a vaccine that naturally can produce those same antibodies in vivo. I do not think we will ever be able to afford an antibody infusion as PrEP.

Dr Schooley: Although these studies are interesting science, it is highly unlikely that passive immunotherapy with broadly neutralizing antibodies will ever be of use clinically in the prevention or treatment of HIV infection. Although we have a number of these antibodies in hand after 30 years of effort, we do not know how to design antigens for use in vaccines that can induce humans to make these antibodies. Rather than spending tens of millions of dollars administering these antibodies in clinical trials, we should shift our attention to more basic research focused on antigen and adjuvant design. We have few insights about what these antigens should look like to the human immune system.

Dr Volberding: We talked about treatment as prevention. What about the need, for example, for the uninfected partner in an HIV-serodiscordant couple to continue PrEP even when the infected partner is fully virally suppressed? What is your recommendation for HIV-serodiscordant couples in which 1 partner is infected and the other is not?

Dr Marrazzo: First of all, there is the individualized approach, with a very personal discussion about what the couple's goals and feelings are. In that context, many times TDF/emtricitabine as PrEP is seen as much as an anxiolytic as it is a biologic, and it is an expensive anxiolytic.

Often, an HIV-seronegative partner will stop taking TDF/emtricitabine as they realize that it is probably not necessary. The data support it not being necessary: in addition to the treatment-as-prevention data there was a study of condomless sex that was just published in the *Journal of the American Medical Association* (*JAMA*) this past year.[5] I believe the results were 12,000 person-years of sexual activity with absolutely no HIV transmission. However, a relatively small number of MSM were included in the study. I would say the data are

supportive but not definitive. Also, there was no real-time monitoring for STIs, and there is a lingering question about transient general shedding in the face of inflammatory STIs, particularly anorectal chlamydia and gonorrhea. I do not think so. If you look at the Kaiser data and the PrEP study that I mentioned before, there was, I think, a 25% incidence of rectal chlamydial and gonococcal infections in that study and no HIV transmissions.[6] These data are very supportive of the protectiveness of treatment as prevention.

Dr Gulick: There is another caveat about that study in *JAMA,* which was impressive (it took place in a number of European countries): the investigators identified people in HIV-serodiscordant relationships who said that they never used condoms. That was a requirement to enroll in the study. Participants were followed prospectively to see if there was HIV transmission, and heterosexual and gay couples were included.

The caveat is that to enroll in the study, you had to say, "We haven't been using condoms." Does that apply to everybody, particularly people who are not in a committed couple? It is probably difficult to extrapolate information to single MSM finding new sexual partners from these data.

Dr Marrazzo: It comes back to my initial point. There should be a very individualized discussion with the couple or with the person. You can extrapolate from these data to the extent that it is helpful, but it really comes back to the individual situation.

Dr Volberding: Another way to think about treatment as prevention is to think about it at a community level. Many cities and even more resource-limited settings are using a city-level approach to treatment as prevention. Can you comment on what the 90-90-90 goals are and on the interface between public health and HIV treatment?

Dr del Rio: The 90-90-90 goals are to have 90% of HIV-infected people diagnosed, in any community; 90% of those who are diagnosed started on antiretroviral therapy; and 90% of those on antiretroviral therapy virally suppressed. Using this model, you could potentially stop transmission of HIV, and that is the ultimate goal. I think the focus on cities is because, although the HIV epidemic is everywhere, it continues to concentrate primarily in urban areas.

Dr Volberding: Except for in the Southeastern United States.

Dr del Rio: Even in the Southeast, there are big cities like Atlanta, Georgia, and Birmingham, Alabama, where the epidemic starts. I think we need to focus our efforts on cities. Many cities have made commitments to meet these goals. I think the interface between clinical care and public health is being strengthened.

In many places, our biggest challenge continues to be people dropping out of HIV care. We know from the data that most HIV transmission in the United States is among people not retained in care.

Dr Volberding: They know they are HIV infected, but they are not in care?

Dr del Rio: People are lost to care for a number of reasons. How do we create the infrastructure that can get those people back into care to achieve the 90-90-90 goals? We need to increase the number of people who are virally suppressed. As a nation, the United States is nowhere close to achieving the 90-90-90 goals. Sweden recently published that they had, as a country, achieved the 90-90-90 goals.[7]

Having said that, I think the proof is pending, except for the observational data from Vancouver, Canada.[8] It has not been proved that achieving those goals is ending HIV transmission. I think the data from the French National Agency for AIDS Research (ANRS), for example, presented at the 2016 International AIDS Conference was very sobering.[9] It clearly showed that in spite of great effort, at a community level, HIV transmission has still continued.

Dr Volberding: HIV transmissions in San Francisco, California, are down after this effort.

Dr Gulick: The same is true in New York. New HIV infections are half as many as they were before this effort.

Dr Benson: We have been discussing sexual transmission of HIV among MSM, but one of the explosive events of this past year was an outbreak of HIV infection among people who inject drugs (PWID) in suburban or smaller rural areas and not among more traditional urban PWID populations. The Indiana HIV outbreak in 2015 was a huge wake-up call to public health officials about what is happening in rural communities of PWID.[10] The corollary to that has been an epidemic of HCV transmission in the same setting. I think insufficient attention has been paid to these kinds of outbreaks and to the emergence of new populations of PWID. These rural and suburban PWID do not fit the vision of disadvantaged PWID in urban areas.

Dr del Rio: The epidemic of opioid use in our country, prescription and illegal opioids, is real. There is some recent reporting in the *New England Journal of Medicine* that there are 2.3 to 2.4 million opioid users in this country,[11] versus 1.2 million people living with HIV infection, and the CDC published results of a study that examined counties and states with high risk for the epidemic Dr Benson mentioned.[12] The next outbreak could be happening in a nearby county, and practitioners need to be aware.

Dr Marrazzo: A very interesting parallel is increases in cases of bacterial endocarditis among younger populations.

Dr Schooley: Also, this epidemic has taught us yet again that needle-exchange programs work. In Indiana, there was a delay in the implementation of needle-exchange programs, but when they were implemented, the HIV epidemic stopped.

Dr Volberding: Coming back to HCV infection, in some places, for example Louisiana, insurance companies still require that individuals have evidence of advanced fibrosis before they are treated for their HCV infection. So, it is important to be aware of local requirements regarding HCV therapy. Can you comment on this?

Dr Schooley: There are other reasons to treat people with HCV infection besides fibrosis, non–liver-associated reasons. For example, HCV-infected women who want to become pregnant should be treated. So, do not just tell people that they are not eligible for treatment and leave it at that. Keep them in mind as more favorable treatment guidelines emerge, which they will.

Dr Gulick: Or speak to your local health officials and make the case, and show them data from other states with fewer treatment restrictions.

Dr Saag: The problem in some Southern states is that Medicaid is bankrupt.

Dr del Rio: Also, Medicaid has not been expanded in most Southern states.

Dr Volberding: What should we be continuing to think about with regard to opportunistic infections (OIs) and tuberculosis (TB) in our patients with HIV infection?

Dr Benson: Traditional OIs have become a less important consideration for HIV-infected individuals unless they are not engaged in care. Engaging HIV-infected individuals in medical care and paying attention to the risks for coinfections needs to be part of primary care.

Having said that, there have been some changes in the recommendations for OI prophylaxis. Probably the most important change is that because the rate of *Mycobacterium avium* complex (MAC) disease is now so low and the risk of acquiring it is abrogated so dramatically with antiretroviral therapy, MAC prophylaxis is likely not needed unless someone is not on antiretroviral therapy. Even in those individuals with very advanced HIV disease who present to care, it is more important to initiate antiretroviral therapy than MAC prophylaxis. The 2016 IAS–USA recommendations for prevention and antiretroviral treatment highlight that perhaps prophylaxis is no longer needed for individuals who are taking antiretroviral therapy.[13]

Dr Volberding: If you cannot keep patients on antiretroviral therapy, you probably cannot keep them on prophylaxis.

Dr Benson: There is starting to be some discussion, even with regard to prophylaxis for *Pneumocystis jiroveci* pneumonia, about the preferential need for rapid initiation of effective antiretroviral therapy in those with advanced disease rather than emphasizing initiation of prophylaxis for *Pneumocystis jiroveci* pneumonia first.

TB continues to be an important OI, particularly among HIV-infected populations in resource-constrained settings and among foreign-born HIV-infected individuals in the United States. There has been a renewed emphasis by the World Health Organization (WHO) and the CDC on treating latent TB infection and new guidance from the CDC on targeted screening for latent TB infection among populations at increased risk for TB, including HIV-infected individuals.[14,15]

The other area of screening that is lacking and needs to be reemphasized is screening of people who are foreign-born or who have lived in countries where there is a high background prevalence for TB, as well as people who have lived in or been exposed to TB in congregate settings, such as prisons, jails, homeless shelters, and areas where there is a high risk for transmission of TB. Those individuals should now be emphasized in terms of screening. So, screening for latent TB infection with a tuberculin skin test or an interferon-gamma release assay is an important part of primary care for HIV-infected people and those at high risk for TB.

Dr Volberding: One thing not addressed by the 90-90-90 goals is retention in care. What are some strategies to retain patients in care?

Dr Saag: If somebody does not show up for a clinic visit without calling to cancel, then that is a red flag. There are data showing that not attending clinic visits is associated with mortality compared with routinely attending clinic visits.

I think there are 2 things practitioners can do to address this. First, if somebody does not show up for an appointment, call them to follow up. Ask them what happened and try to reschedule. Second, provide positive reinforcement when patients do keep their clinic appointments. These things show patients that practitioners are paying attention and are a useful first step.

Dr Volberding: I think there was a study in which people were given financial incentives to stay in care, which did not improve retention.

Dr del Rio: That was the HPTN 065 study, the results of which have not yet been published but were presented at the 2015 Conference on Retroviruses and Opportunistic Infections.[16] The study used financial incentives to encourage people to get tested for HIV infection. The goal was to progress the entire treatment cascade and not just to test people and link them to care. In Washington, DC, the intervention only worked in clinics and places that were not doing well with regard to retention. So, I think these interventions can be targeted.

Again, these are not interventions that would work for everybody. Retention in care, I think, should be individualized. A needs assessment should be completed for each patient.

Another issue around retention in and linkage to care that I think is very important is the time it takes to get someone into care. The first National HIV/AIDS Strategy recommended linkage to care within 3 months of HIV diagnosis. A newer strategy recommended 1 month. Many places are now cutting that time down further. For example, in data from South Africa, Haiti, and San Francisco, immediate initiation of antiretroviral therapy was associated with better rates of retention in care.[17-19] In Atlanta, our goal is to link people to care within 72 hours of HIV diagnosis.

Dr Volberding: In San Francisco, we have a very aggressive program in which the effort is to detect cases of acute HIV infection and to find people who are newly diagnosed with HIV infection and start them on treatment the same day.

Dr del Rio: Immediate care and same-day initiation of antiretroviral therapy are improving retention in care in many settings, as can be seen in the data from South Africa, Haiti, and San Francisco.

Dr Volberding: That is the opposite of what we used to think.

Dr Marrazzo: We should also emphasize the link between public health settings and clinics where people are newly diagnosed. It would be optimal to, if needed, walk patients from an STI clinic to an HIV clinic to be enrolled in care.

Dr del Rio: It is more than just a referral.

Dr Marrazzo: There is a very narrow window of opportunity to engage with people and make them realize the importance of HIV care.

Dr Volberding: Can you comment on the increasingly convergent relationship between HIV care and public health? The relationship that treatment programs have with their health departments is crucial, especially as we explore issues related to the treatment cascade.

Dr Gulick: Young men in general, HIV infected or not, are not as engaged in health care as we would like them to be.

Dr Currier: That has been really clear in studies that look at the health of young men initiating PrEP.

I also want to follow up on something that Dr del Rio mentioned that is being discussed in the United States President's Emergency Plan for AIDS Relief (PEPFAR) and in many limited-resource settings: the concept of a differentiated model of care. We think about that as an issue outside of the United States, but we do not think about it enough inside the United States or about how we can be more flexible in making treatment available.

Dr Volberding: We think about implementation science as being almost exclusively an issue for resource-limited settings.

Dr del Rio: Well, part of our country is resource limited. Looking at the HIV epidemic in the United States, the epidemic is disappearing in parts of the country, while it is increasing in other parts of the country—in the South, for example—as they become less developed. It is not that the HIV epidemic itself is getting worse but that worsening conditions are making the epidemic worse.

Dr Saag: I think that we have had some success, but I do not want to create the image that we have things under control. The most powerful data I saw this year indicated that MSM in the United States, over their lifetime, have a 1:6 chance of becoming HIV infected, and black MSM have a 1:2 chance. That is an overwhelming number.

Dr Volberding: Let me restate that. Half of black MSM have a lifetime risk of becoming HIV infected. That is 50%. That is a crisis.

Dr Saag: That is a crisis. The most striking thing to me is that despite the fact that we have known about HIV for more than 30 years, we are not making that much of a dent except possibly in New York and San Francisco. For the rest of the country, there is much more work to be done.

Dr Marrazzo: We have not discussed the stigma surrounding HIV infection, but this is a huge issue in some areas. Stigma is something that should not be ignored when discussing HIV infection.

Dr del Rio: Also, 40,000 to 45,000 new HIV infections per year is not acceptable. If there were 45,000 new Ebola infections per year, I think Congress would be alarmed.

Dr Benson: There was a recent report about the workforce who are taking care of HIV-infected patients,[20,21] and there may be a looming crisis in terms of physicians taking care of individuals with HIV infection.

Dr del Rio: The patient population is aging but so are practitioners.

Dr Marrazzo: During the Indiana outbreak, no infectious diseases specialists were initially available.

Dr Volberding: What are some of the research questions that drive you the most right now?

Dr Richman: As already mentioned, HIV cure and vaccine are crucially important research areas. However, for objectives that can be more readily addressed right now, I think implementation science and the prospect of long-acting antiretroviral agents as a way to address adherence to antiretroviral therapy are 2 exciting areas.

Dr Saag: Implementation is a word that is frequently used, but let me define it in this context. It means identifying the barriers to accomplishing what we know works and then determining how to remove those barriers. I think we have much to learn from other parts of the world, especially sub-Saharan Africa. Also, I think implementing immediate initiation of antiretroviral therapy is something we really need to focus on.

Dr del Rio: With regard to retention in care, we do not yet know what works, and more research is needed.

In a recently completed clinical trial that focused on trying to improve retention in care and virologic suppression among HIV-infected substance users via a combination of interventions (financial incentives and the assistance of patient navigators), the interventions did not produce a different result than the standard of care.[22]

Dr Benson: I think we should take advantage of some of the newer technologies used for monitoring adherence to therapy and utilize those to encourage adherence and retention in care. There are now smart phone applications that can monitor pill-taking behavior or even which drugs are taken. Making use of the technology available to us, such as devices that can monitor health similar to those that monitor individual fitness parameters, may be helpful. Contacting people if they miss a visit was discussed earlier, and a smart phone application could be used to do this.

We can use more than just face-to-face interaction as people are increasingly using technology. We need more research related to better mechanisms for retaining people in care and to take advantage of some of the newer technologies to help improve retention in care and adherence to therapy.

Dr Currier: I agree with everything that has been said, but another area that we need to make more progress in is keeping people healthy on treatment as they age. Although it seems that with early antiretroviral treatment and sustained viral suppression we can substantially reduce mortality, there are still areas that need improvement. Cancer, for example, is becoming more and more of an issue, and more study is needed on how to prevent cancer in people with long-term HIV infection.

Dr Gulick: I would like to revisit a topic we talked about before, which is 2-drug antiretroviral therapy. We have been using 3-drug therapy since 1996: 2 nRTIs and a third agent. If the 2-drug combination of dolutegravir and lamivudine really works, it would be a game changer. The WHO has calculated that with use of the generic formulations of these 2 drugs, the cost of treatment would be $50 per year. If this drug combination works, it would change how we treat HIV disease.

Dr Volberding: I want to end with some thoughts about the next generation of HIV practitioners. What are we doing to encourage and support them? How do we bring new fellows into the field of HIV medicine?

Dr Schooley: I think it is challenging. I think when many of us entered the field of HIV medicine it was brand new, exciting. The science was moving extremely rapidly in terms of bringing discoveries to patients, which is the sort of thing that physicians love. We are in a phase of the research now where we are focusing on curing the disease but the goals are longer term. The kind of excitement we saw when we were younger is not being translated as well to the new practitioners in the field. I think we need to engage medical residents when they are making decisions about their future careers.

Dr del Rio: Medical students as well.

Dr Schooley: Yes, medical students as well. I think one of the big barriers has been hospitalists. The house staff sees hospitalists 90% of the time. They do not see specialists as much as they did during rotations. They do not get a chance to see what we as HIV specialists do and the impact we have.

I think we should never lose sight of the fact that medical education is indeed education. As hospitals push practitioners more and more into service mode and away from learning the whole breadth of medicine, I think it is negatively affecting our workforce in a way that will have implications for many years to come. I would advocate pushing back against hospital administrations and insisting that new practitioners have access to the whole breadth of medicine during their training.

Dr Gulick: This is not just a crisis for HIV medicine but all infectious diseases. We are seeing the number of infectious diseases practitioners decrease. In a sense, this is because of the success we have had with HIV infection. It has become such a treatable disease. I hear younger physicians say, "HIV primary care is not what I want to do. I do not want to treat hypertension, diabetes, and cholesterol. I went into infectious diseases to treat infectious diseases."

Dr Currier: I think we need to continue to train primary care doctors to handle HIV primary care as well.

Dr Volberding: This discussion has been going on for a number of years. Do we have enough HIV specialists? Do we need more? Is HIV a primary care disease or not?

Dr del Rio: Results from 2 recent studies show very clearly that more HIV care practitioners are needed,[20,22] given that the population of people with HIV infection is increasing and the number of HIV practitioners is decreasing. There are many things we can do to address this, including talking to our hospital administrators. I also think we need to make it very clear to organizations like the CDC and public health in government that more infectious diseases practitioners are needed.

Dr Volberding: Our board is actively thinking about many of the issues discussed, and we are always thinking about what IAS–USA can do to reach younger practitioners who will be treating HIV and other viral infections in years to come.

A link to the full recorded webinar is available on the IAS–USA website at www.iasusa.org, along with information on upcoming live webinars and courses, online continuing medical education activities, and important scientific meetings, such as the Conference on Retroviruses and Opportunistic Infections and the Ryan White HIV/AIDS Program Clinical Conference.

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Suggested Readings

1. Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women. *N Engl J Med*. 2016;375(22):2121-2132.
2. Nel A, van Niekerk N, Kapiga S, et al. Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women. *N Engl J Med*. 2016; 375(22):2133-2143.
3. Brown E, Palanee-Phillips T, Marzinke M, et al. Residual dapivirine ring levels indicate higher adherence to vaginal ring is associated with HIV-1 protection. 21st International AIDS Conference. July 18-22, 2016; Durban, South Africa
4. AASLD/IDSA. HCV guidance: recommendations for testing, managing, and treating hepatitis C. http://hcvguidelines.org/. Accessed on January 9, 2017.
5. Rodger AJ, Cambiano V, Bruun T, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. *JAMA*. 2016;316(2):171-181.
6. Volk JE, Marcus JL, Phengrasamy T, et al. No new HIV infections with increasing use of HIV preexposure prophylaxis in a clinical practice setting. *Clin Infect Dis*. 2015;61(10):1601-1603.
7. Gisslen M, Svedhem V, Lindborg L, et al. Sweden, the first country to achieve the Joint United Nations Programme on HIV/AIDS (UNAIDS)/World Health Organization (WHO) 90-90-90 continuum of HIV care targets. *HIV Med*. 2016;[Epub ahead of print].
8. Montaner JSG, Lima VD, Harrigan PR, et al. Expansion of HAART coverage is associated with sustained decreases in HIV/AIDS morbidity, mortality and HIV transmission - The "HIV Treatment as Prevention" experience in a Canadian setting. *PLoS One*. 2014; 9(2):e87872.
9. Iwuji C, Orne-Gliemann J, Balestre E et al. The impact of universal test and treat on HIV incidence in a rural South African population: ANRS 12249 TasP trial, 2012-2016. 21st International AIDS Conference. July 18-22, 2016; Durban, South Africa
10. Peters PJ, Pontones P, Hoover KW, et al. HIV infection linked to injection use of oxymorphone in Indiana, 2014–2015. *N Engl J Med*. 2016;375:229-239.
11. Van Handel MM, Rose C, Hallisey EJ, et al. County-level vulnerability assessment for rapid dissemination of HIV and HCV infections among persons who inject drugs, United States. *JAIDS*. 2016; 73(3):323-331.
12. Volkow ND, McLellan AT. Opioid abuse in chronic pain-misconceptions and mitigation strategies. *N Engl J Med*. 2016;374(13):1253-1263
13. Günthard HF, Saag MS, Benson CA, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society–USA panel. *JAMA*. 2016;316(2):191-210.
14. Getahun H, Matteelli A, Abubakar I, et al. Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries. *Eur Respir J*. 2015;46(6):1563-1576.
15. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for latent tuberculosis infection in adults: US Preventive Services Task Force recommendation statement. *JAMA*. 2016;316(9):962-969.
16. El-Sadr W, Branson BM, Beauchamp G, et al. Effect of financial incentives on linkage to care and viral suppression: HPTN 065 [CROI Abstract 29]. In Special Issue: Abstracts From the 2015 Conference on Retroviruses and Opportunistic Infections. *Top Antivir Med*. 2015; 23(e-1):12-13.
17. Rosen S, Maskew M, Fox MP, et al. Initiating Antiretroviral Therapy for HIV at a Patient's First Clinic Visit: The RapIT Randomized Controlled Trial. *PLoS Med*. 2016;13(5):e1002015.
18. Koenig S, Dorvil N, Severe P et al. Same-day HIV testing and antiretroviral therapy initiation results in higher rates of treatment initiation and retention in care. 21st International AIDS Conference. July 18-22, 2016; Durban, South Africa
19. Pilcher CD, Ospina-Norvell C, Dasgupta A, et al. The Effect of Same-Day Observed Initiation of Antiretroviral Therapy on HIV Viral Load and Treatment Outcomes in a US Public Health Setting. *J Acquir Immune Defic Syndr*. 2017;74(1):44-51.
20. Gilman B, Bouchery E, Hogan P, Trent-Adams S, Cheever L. The HIV clinical workforce in the United States. *HIV Specialist*. 2016;8(3):2-9.
21. Weiser J, Beer L, West BT, Duke CC, Gremel GW, Skarbinski J. Qualifications, demographics, satisfaction, and future capacity of the HIV care provider workforce in the United States, 2013-2014. *Clin Infect Dis*. 2016;63(7):966-975.
22. Metsch LR, Feaster DJ, Gooden L, et al. Effect of patient navigation with or without financial incentives on viral Suppression among hospitalized patients with HIV infection and substance use: a randomized clinical trial. *JAMA*. 2016;316(2):156-170.

Top Antivir Med. 2017;24(4):142-151.