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Topics in Antiviral Medicine™

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On completion of this activity, the learner will be able to:

- Describe the research strategies and challenges to achieve HIV eradication and remission
- Describe the research around the role of therapeutic HIV vaccines and bNabs
- Detect and manage cardiovascular disease risk in the aging population of persons with HIV
- Identify clinical presentations of immune reconstitution inflammatory syndrome (IRIS) in HIV infection and the best approach for diagnosis

**Intended Audience**

This enduring material is designed for physicians who are actively involved in the medical care of people with HIV and other viral infections and those who are new to HIV care or who want a refresher on the basics of antiretroviral therapy.

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

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**Perspective**

**Advances Toward a Cure for HIV: Getting Beyond n=2**

Achieving a cure for HIV remains a priority in HIV research. Two cases of ‘sterilizing cure’ have been observed—in Timothy Ray Brown and the “London” patient; both patients received allogeneic hematopoietic stem cell transplantation (HSCT) from donors homozygous for the CCR5-delta 32 deletion, which impairs function of an HIV coreceptor on host cells. Other strategies that have been evaluated for achieving sterilizing cure or functional cure—ie, sustained virologic remission in the absence of antiretroviral therapy (ART)—include: HSCT with wild-type CC chemokine receptor (CCR5); early ART to limit size of the HIV latent reservoir; shock and kill strategies using latency reversing agents and/or anti-HIV broadly neutralizing antibodies; and gene therapy, including attempts to modify CCR5 genes, HIV proviruses in autologous host cells, or enhanced T cells. This article summarizes a presentation by Jonathan Li, MD, MMSc, at the International Antiviral Society-USA (IAS-USA) continuing education program held in Atlanta, Georgia, in March 2019.

**Keywords:** HIV cure, CCR5-delta 32 deletion, London patient, post-treatment controllers, early ART, shock and kill, gene therapy.

HIV cure remains a priority of research in HIV infection management and treatment. Pursuing this goal requires identifying and developing strategies to overcome mechanisms of HIV persistence to induce and maintain HIV remission.

**Update on the Epidemic**

The advent of effective combination antiretroviral therapy (ART) has resulted in marked declines in HIV mortality and incidence. However, there remains much work to be done in battling the epidemic. Joint United Nations Programme on HIV and AIDS (UNAIDS)/World Health Organization (WHO) data indicate that there are more than 37 million people globally living with HIV infection. Of these, 23 million are on ART. There are 1.8 million new infections and nearly 800,000 AIDS-related deaths each year. The WHO introduced the 90-90-90 initiative, aimed at achieving awareness of infection status in 90% of infected individuals, having 90% of those individuals maintained on treatment, and achieving virologic suppression in 90% of those on treatment. However, it is currently estimated that only 75% of infected individuals know of their infection status, 59% are on treatment, and 47% have viral suppression.

There are numerous issues that contribute to suboptimal ART treatment and retention in care. Many infected individuals are asymptomatic, leading to delayed diagnosis, denial, or complacency. Other factors that contribute to gaps in the cascade of care include challenges in accessing affordable and consistent care, ART intolerance, pill fatigue, drug-drug interactions, stigma, life chaos, substance abuse, and challenges in connecting with hard-to-reach populations. Further, there are long-term complications of HIV despite ART, including evidence for accelerated aging and increased risks of cognitive dysfunction, cardiovascular disease, renal disease, and other complications. All of these factors provide a strong rationale for pursuing cure for HIV infection.

**Mechanisms of HIV Persistence**

Data from long-term follow-up of a cohort of patients on ART indicate that the HIV reservoir, indicated by levels of HIV DNA in CD4+ cells and peripheral blood mononuclear cells, initially declines during ART but plateaus at around 4 years and remains stable thereafter (Figure 1). Key factors in HIV persistence include viral integration into the host cell genome and that the integrated provirus can become latent or silent, such that little viral RNA or proteins are being expressed that would permit the immune system to recognize and target the infected cells.

Other factors may contribute to HIV persistence. For example, some researchers believe that there continues to be active viral replication in patients on ART, particularly within certain tissues or compartments where ART levels may be suboptimal. However, this is a relatively controversial hypothesis, with the predominance of evidence demonstrating the lack of active viral

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replication in patients on fully suppressive ART. Another cause of HIV persistence lies in the infection of long-lived cells as memory CD4+ cells and hematopoietic progenitor cells. Further, infected cells, particularly CD4+ cells, can undergo homeostatic or clonal proliferation, expanding the HIV reservoir. Finally, B cell follicles within lymph nodes act as an “immune sanctuary” that prevents access of HIV-specific CD8+ cells, potentially allowing persistence of virus within lymph nodes.

Cure—Success Stories

One example of cure is Timothy Ray Brown (initially known as the “Berlin patient”). To understand this case it needs to be understood that HIV requires a CD4 receptor and a coreceptor to gain entry to the host cell, especially the CC chemokine receptor 5 (CCR5). Individuals have been identified who are naturally resistant to acquiring HIV infection with the most frequently transmitted CCR5-tropic virus due to the presence of a deletion in the CCR5 gene, called the CCR5-delta 32 deletion, that impairs expression of the CCR5 receptor.

Timothy Ray Brown was living with HIV infection when he was diagnosed with acute myeloid leukemia (AML). To treat the leukemia, he was to undergo allogeneic hematopoietic skin cell transplant from a donor with the chemokine receptor 5–delta 32 deletion. Abbreviations: AML, acute myeloid leukemia; ART, antiretroviral therapy; SCT, gene for a human hormone secretion. Adapted from Hutter et al.

More recently, details have been presented about the “London patient.” This patient had Hodgkin lymphoma and also received allogeneic HSCT with cells from a donor homozygous for the CCR5 delta 32 deletion. The patient had viral rebound during ART interruption and achieved resuppression with resumption of ART. After approximately 18 months, ART was stopped, and the patient has been free of viral rebound for more than 2 years off ART (Figure 3).

Differences between Mr Brown and the London patient include the fact that Mr Brown was initially heterozygous for the CCR5 delta 32 deletion, whereas the London patient was homozygous for wild-type CCR5 before the transplant. For AML, Mr Brown underwent 2 HSCTs, total body irradiation, and full intensity conditioning chemotherapy. For lymphoma, the London patient underwent a single HSCT, received no irradiation, and underwent reduced-intensity conditioning. The mechanisms for T-cell depletion in the 2 patients also differed. Perhaps the take-home lesson from the comparison is that the highly toxic conditioning regimen and whole-body irradiation Mr Brown received may not be necessary for HIV eradication, that the same result can be achieved with less intense conditioning and without irradiation. Together, the cases point to the importance of the donor being homozygous for the CCR5 delta 32 deletion, but additional studies will be needed to assess the impact of other factors, such as graft-versus-host reactions.
Timothy Brown and the London patient represent achievement of a sterilizing HIV cure, in which there is no functional HIV remaining in the body. However, HSCTs are associated with substantial morbidity and mortality. A more realistic goal may be a functional cure, consisting of sustained virologic remission and HIV suppression in the absence of ART. Such sustained remission has been observed in HIV controllers or long-term non-progressors and in HIV post-treatment controllers (PTCs). A great deal of data from AIDS Clinical Trials Group (ACTG) studies indicate that viral rebound generally occurs between 2 and 4 weeks after interrupting suppressive ART. However, considerable variation has also been observed in time to rebound and there are individuals who are able to maintain viral suppression for a prolonged period after ART discontinuation. Several years ago, the French VISCONTI study identified 14 individuals who started ART early in infection and who maintained virologic suppression after interrupting ART. The identification of these PTCs has led to increased interest in finding strategies for HIV remission.

**Strategies for Inducing HIV Remission**

Among the approaches being investigated for inducing HIV remission and transforming patients into PTCs are: bone marrow transplantation (BMT) with CCR5 wild-type donors; early HIV treatment; shock and kill strategies, and gene therapy, among others.

Individuals who naturally have the CCR5-delta 32 deletion are rare; a gene frequency of approximately 10% is found in those of European descent. Thus, people with HIV are far more likely to receive a HSCT from a donor with wild-type CCR5 cells. The cases of 2 “Boston BMT patients” showed that allogeneic HSCT from donors with wild-type CCR5 resulted in delayed HIV rebound. After transplantation, no evidence of HIV DNA was detected. After analytic treatment interruption, 1 patient maintained virologic suppression for 3 months and the other for 8 months (Figure 4). Although no sterilizing cure was achieved, the findings indicate that depletion of the HIV reservoir can result in suppression longer than the typical 2 to 4 weeks after stopping ART. Both patients were found to have acute retroviral rebound syndrome, likely as their post-transplant immune system was functionally naive to HIV.

Early HIV treatment has been shown to reduce the size of the HIV reservoir to a level below that seen in patients starting ART during chronic infection. It has not been clear whether the reduction with early treatment might preferentially lead to post-treatment control. In the VISCONTI study, all participants had received early ART, and there was no comparison group of participants who had started ART during chronic infection. In the CHAMP (Control of HIV After Antiretroviral Medication Pause) study, 14 North American clinical trials were analyzed and 67 participants were identified who were PTCs. PTCs accounted for 13% of participants who had early ART versus 4% of participants who began ART during chronic infection (P < .01), suggesting that early ART may lower the barrier to achieving HIV remission. Of note, studies of ART initiation during the very earliest stages of HIV infection (i.e., Fiebig I) did not identify any PTCs, which raises the possibility that a slight delay in ART initiation may lead to a more robust immune response.

The shock and kill strategy is an approach to reawaken latently infected cells through use of a latency reversing agent that can stimulate HIV RNA and protein production, while enhancing the immune system’s ability to kill these cells, for example, through the use of a therapeutic vaccine or an HIV broadly neutralizing antibody (bNAB). The approach would be used while patients are maintained on suppressive ART, so that no new infection of cells will occur despite the stimulation of virus production. A recent study...
in SHIV-infected monkeys examined this approach using a toll-like receptor 7 (TLR7) agonist (GS-9620) as a latency reversing agent combined with an anti-HIV bNAb. After treatment interruption, rebound was observed in fewer monkeys receiving both the latency reversing agent and the antibody than in those receiving either alone or neither. There is also some evidence that the use of bNAbs alone may be able to induce long-term HIV remission.

One gene therapy approach that has been investigated is use of zinc-finger nuclease targeting the CCR5 gene. In one study, CD4+ cells were taken from individuals with HIV infection, modified in the laboratory with the zinc-finger nucleases with the aim of modifying the CCR5 gene to contain the deletions, and reinfused into the patient. All participants had viral rebound during treatment interruption, although one participant exhibited suppression before the interruption ended and ART was resumed. This participant was initially heterozygous for the CCR5-delta 32 deletion. It is believed that this particular strategy is not efficient in modifying the cells to contain the CCR5 deletions, but that achieving the modification may be more likely in individuals already heterozygous for the deletion. Some data from ongoing studies support the idea that alteration of viral kinetics with this approach is more likely in heterozygous patients. However, much work remains to be done in this field.

Other approaches that are being evaluated include enhancing T-cell activity with the use of chimeric antigen receptors (CARs), an approach that is currently being utilized in the oncology field and is being evaluated for HIV. There are also attempts to silence the HIV provirus, including through the use of CRISPR proviral gene editing or inhibition of the HIV Tat function.

References

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roviruses and Opportunistic Infections (CROI); February 13-16, 2017; Seattle, Washington.


UPCOMING ACTIVITIES

MARK YOUR CALENDAR FOR SPRING 2020: IAS–USA SCHEDULE OF HIV UPDATE COURSES

The International Antiviral Society–USA (IAS–USA) will present the latest important developments in the HIV prevention and management from the past year in its 2020 series of live regional courses, beginning March 19 in New York City.

These CME course are designed for HIV specialists actively involved in HIV disease management. Our faculty provided advanced-level presentations with balanced, timely, scientifically rigorous, and clinically relevant information about HIV treatment.

Below are 2020 dates and locations. More information will be announced on the IAS–USA website.

New York, New York — Thursday, March 19
Atlanta, Georgia — Friday, April 3
San Francisco, California — Thursday, April 23
Los Angeles, California — Friday, May 1
Washington, DC — Friday, May 8
Chicago, Illinois — Thursday, May 21

Interactive Webinars

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

HCV Post-Cure Monitoring and Management — Tuesday, February 4, 2020 (Archived Webinar Available)
Presenter: Marion G. Peters, MD

The Elements of Taking a Sexual History — Tuesday, March 31, 2020
Presenter: Allison Agwu, MD

CROI 2020 Update: Epidemiology and Prevention — Tuesday, April 21, 2020
Presenter: Susan P. Buchbinder, MD

CROI 2020 Update: The Status of HIV Cure Research — Tuesday, April 28, 2020
Presenter: Katharine J. Bar, MD

Fatty Liver Disease and HIV: What the HIV Clinician Needs to Know — Tuesday, May 26, 2020
Presenter: Jennifer C. Price, MD

Weight Gain: A Growing Issue in Antiretroviral Therapy — Tuesday, July 21, 2020
Presenter: John R. Koethe, MD

Liver Transplant Among People with HIV — Tuesday, August 25, 2020
Presenter: Christine M. Durand, MD

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

Cases on the Web

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

HIV-2: Clinical Features, Diagnosis, and Management
Authors: Jacqueline T. Chu, MD; Rajesh T. Gandhi, MD
Date of Last Review: February 11, 2019
Expires: February 11, 2020

Considerations in the Treatment of Opioid Use Disorder in Patients with HIV Infection and HIV/HCV Coinfection
Authors: Jennifer Edelman, MD, MHS, Jeanette M. Tetruault MD
Date of Last Review: May 21, 2019
Expires: May 21, 2020

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

**Therapeutic HIV Vaccines and Broadly Neutralizing Antibodies**

Therapeutic vaccines and broadly neutralizing antibodies (bNAbs) represent potential approaches to antiretroviral-free treatment of HIV. Although therapeutic vaccines have been able to produce transient reductions in viral load during analytic treatment interruptions (ATIs), thus far none has been able to induce long-term remission. Pairing with latency reversal agents and immune modulators may improve vaccine efficacy. The bNAbs are investigated as a promising approach to achieving durable virologic control in the absence of antiretroviral therapy. Combinations of antibodies are necessary for increasing overall breadth and potency of coverage and preventing emergence of resistance. The next generation of antibodies includes engineered bispecific and trispecific antibodies that target 2 or 3 independent viral sites. This article is based on a presentation by Magdalena E. Sobieszczyk, MD, MPH, at the International Antiviral Society-USA (IAS-USA) continuing education program held in New York in March 2019.

**Keywords:** HIV, therapeutic vaccines, broadly neutralizing antibodies, viral rebound, antibody targets, bNAbs, bispecific, trispecific.

**Therapeutic Vaccines and Antibodies**

The rationale for investigating antiretroviral-free approaches to HIV treatment is severalfold:
- It is impossible to eradicate HIV from latent viral reservoirs with antiretroviral therapy (ART) alone
- It is important to have treatment options including agents with potential for less frequent dosing
- There are gaps in ART delivery
- ART is associated with long-term adverse effects
- Adherence and retention in care remain a challenge

The rationale for therapeutic HIV vaccines and therapeutic use of anti-HIV broadly neutralizing antibodies (bNAbs) includes evidence from individuals whose immune system naturally controls HIV without ART (ie, long-term nonprogressors, elite controllers) that effective host-mediated anti-HIV immunity is possible. This raises the issue of whether it is possible to augment host immune response to kill infected CD4+ T cells and neutralize circulating virus in the absence of ART.

**Therapeutic HIV Vaccines**

At a minimum, the goals of a therapeutic vaccine would be to simplify ART regimens and allow for periodic analytic treatment interruption (ATI). Optimal objectives would include the ability to eliminate the need for ART either by eradicating the virus or by inducing host immune responses capable of controlling virus replication.

However, in the many placebo-controlled studies thus far that have included interruption of ART to measure therapeutic vaccine efficacy, no therapeutic vaccines have been successful in achieving durable suppression of HIV viremia. For example, a recently reported study showed that a DNA/rVSV therapeutic vaccine was unsuccessful in achieving sustained suppression of virus after ART interruption in individuals who initiated ART early in infection (Figure 1). Similarly, a trial of the MVA-B vaccine showed no substantial effect on viral load rebound after ATI or on the viral reservoir with or without use of a latency reversal agent. Recent studies suggest that eliciting a broad immune response may be associated with greater impact on viral rebound following ATI. For example, a trial examining a DC-HIV vaccine (dendritic cells loaded with heat-inactivated autologous HIV) showed that the vaccine induced broad immune responses and a substantial reduction in viral load during ATI. However that the effect was transient, in a separate study using a dendritic cell platform, broader immune responses correlated with better plasma viral load after ATI. And 2 trials investigating the ALVAC-HIV vaccine and Lipo-6T showed that vaccine-induced CD4+ and CD8+ T cell responses were associated with virologic control and delayed time to resumption of ART following ATI, compared with placebo.

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**Figure 1.** Absence of effect of DNA/rVSV therapeutic vaccination compared with placebo on control of HIV rebound following interruption of antiretroviral therapy (ART). Adapted from Sneller et al.

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Despite such disappointments, the field is looking now at combining therapeu tic vaccines with other agents, such as toll-like receptor 7 (TLR7) agonists and latency reversal agents. For exam ple, a provocative study in SIV-infected rhesus monkeys showed that use of the therapeutic Ad26/MVA vaccine alone induced broad cellular immune responses, but resulted in no clinically significant decrease in viral load set point after ATI. However, with the addition of a TLR7 agonist to the vaccine, there was a 1.75-log copies/mL reduction in viral load, a 2.5-fold delay in viral rebound, and 33% of animals maintained undetectable viral load after ATI.

Thus, although there have been no randomized controlled trials of therapeutic vaccination that have induced any remission after ATI, it is now presumed that vaccines are needed that induce broad host immune responses to recognize diverse escape viral variants after viral rebound. Furthermore, therapeutic vaccines are being paired with potent latency reversal agents (eg, vorinostat) or immune modulators (TLR7 agonist) with the aim of potentially inducing evidence of remission.

Broadly Neutralizing Antibodies

The long-established function of passively administered bNAbs has been to inhibit viral entry into host cells by blocking key binding sites on the viral envelope (neutralizing activity). More recent studies of these antibodies demonstrate their capacity to engage the host immune system through Fc effector functions to mediate killing of infected cells via antibody-dependent cell-mediated cytotoxicity (ADCC), enhancing immune responses against HIV and potentially clear latently infected cells, thereby potentially presenting a strategy for targeting the reservoir.

A minority of HIV-infected individuals (5%-10%) develop the ability to neutralize various heterologous viruses from different subtypes within 2 to 3 years after infection. Very broad and potent neutralizing antibodies have been isolated from these individuals. These antibodies bind to relatively conserved regions of the HIV envelope. Passive transfer of bNAbs is being investigated for treatment, eradication/cure, prevention, and to guide prevenz vaccine design.

Much work has focused on isolating bNAbs and identifying what targets on the HIV envelope they attach to in order to block viral entry into CD4 cells. A number of targets on the virus have been identified as bNAb attachment points that are capable of neutralizing a wide range of HIV isolates, including the CD4 binding site, membrane proximal external region (MPER), the gp41 and gp120 interface, the V3 loop, and the V1/V2 loop (Figure 2). The figure shows some of the bNAbs in clinical development that target these sites.

Optimizing bNAbs include identification or engineering of more broad and potent antibodies, modifying Fc portion, to using combinations of antibodies, and developing single antibodies with multiple targets

Several seminal studies have shown antiviral activity with bNAb candidates. For example, passive infusion of the anti-CD4 binding site 3BNC117 antibody showed significant reduction of viremia and, in another study, suppressed viral rebound among I3 ART-treated participants with 3BNC117-sensitive viruses. Patients underwent ATI and received 2 or 4 infusions of the antibody. The infusions were associated with a viral rebound delay of an average of 8.4 weeks in all participants versus 2.6 weeks in matched historical controls. The rebound virus was found to have resistance to 3BNC117 with low diversity in most patients.

In another study, the anti-CD4 binding site antibody VRC01 was used in HIV-infected patients who were not screened for VRC01 sensitivity. Patients underwent ATI and 3 to 8 infusions. The median time to plasma viral rebound was 4 to 5.6 weeks, depending on the number of infusions only slightly delaying rebound compared with historical controls. Viral rebound was polyclonal, despite high antibody levels in most patients and attributed to preexisting resistance. A recently reported study of this antibody in Thai adults who initiated ART during acute HIV infection did not significantly delay viral rebound after ART discontinuation.

In general, it has been shown that the antibodies have on average been able to reduce HIV viral load by approximately 1.5 log copies/mL after a single infusion of one antibody in patients with viremia. However, with ATI, viral rebound ultimately occurs and, at least in the monotherapy setting, viruses resistant to the bNAbs emerge after several weeks, strengthening rationale for combination bNAbs. Findings reported at the 2019 Conference on Retroviruses and Opportunistic Infections (CROI) with use of the PGT121 antibody that targets the V3 loop bear noting, however. In viremic patients not on ART, response in terms of virologic control depended on baseline viral load. Those with a high baseline viral load before infusion of the bNAb had an approximately 1.7-log copy/mL drop, with rebound resistant virus in most responders. Patients with low baseline viral load ex-
are ongoing both for prevention and treatment.\textsuperscript{17-19}

Other modifications to the Fc region may increase the effector functions of the antibody, potentially increasing ADCC or phagocytosis and potentially targeting the HIV reservoir. A report at the 2019 CROI described an engineered variant of the antibody PGT121 that enhanced killing of HIV-infected CD4+ T-cells by natural killer cells.\textsuperscript{20}

Combining antibodies may have particular promise for improving therapeutic potential. In studies to date, rebound viruses after bNAb treatment did not demonstrate increased resistance to other antibodies that target different envelope epitopes. Combinations of 2 or more bNAbs have been shown to result in more robust and sustained antiviral effects by increasing overall breadth and potency of coverage and preventing the emergence of resistance.

A recently reported study examined the effects of 3 infusions of the combination of 2 antibodies 3BNC117 and 10-1074 during ART in patients who were virologically suppressed on ART for more than 24 months who had been prescreened for sensitivity to the antibodies. The median duration of viral suppression was 21 weeks for antibody-sensitive virus, a longer duration of suppression than has been seen with single antibodies.\textsuperscript{21} A noteworthy finding is that 2 patients maintained virologic suppression long after antibody levels had waned. This observation may suggest that the effector function of the antibodies is acting to augment host immune response, supporting the investigation of whether bNAbs can be a component of cure strategies. Additionally, this combination was also evaluated in viremic, treatment naive individuals, and resulted in an average HIV viral load decrease of 2.05 log\textsubscript{10} copies/mL in individuals with virus sensitive to both antibodies.\textsuperscript{22}

In short, antibody combinations are likely to be necessary to increase overall breadth and potency of effect and to prevent the emergence of resistance. The number of bNAbs required for effective treatment may differ based on the indication; for example, in active viremia the combination of 3 or 4 bNAbs may be required to cover the swarm of viruses present. This also raises the issue of the need to screen for bNAb sensitivity prior to therapy to potentially reduce the number of bNAbs required for treatment and to amplify efficacy.

Finally, the next generation of bNAbs will likely include engineered bispecific and trispecific antibodies, single molecules that target multiple different epitopes on the virus or a cellular receptor like CD4. Such an approach could potentially lower the likelihood of escape mutations and provide enhanced neutralization potency and breadth in a single molecule. An example of a bispecific antibody in development is 10E8.4/iMab, shown in Figure 4.\textsuperscript{23,24} One arm of the antibody binds an epitope in the membrane proximal external region (MPER) of gp41; the other arm binds the HIV CD4 receptor molecule on T-helper cells. The antibody entered first in human clinical testing in spring of 2019.\textsuperscript{25}

Trispecific antibodies are engineered to bind to 3 sites on the HIV envelope. An example of one that recently entered clinical testing in individuals with HIV infection combines specificities of 3 antibodies binding to the CD4 binding site, V1/V2 loop, and gp41 MPER.\textsuperscript{26} Animal data presented at the 2019 CROI showed that the antibody exerted...
potent Fc effector functions, promising for mediating ADCC and phagocytosis, and potent suppression of viral replication in viremic simian/HIV-infected animals.27,28

Because current bNAbS are engineered as human proteins, antitumor antibody (ADA) responses can be infrequently observed, potentially interfering with activity and resulting in emergence of resistance to this immune therapy. In clinical studies to date, ADA responses have not been detected.29,30

Recent advances in bNAB development are exciting and might offer alternative approaches to HIV therapy or possibly cure. The role of bNAbS in this area will be established by further preclinical and clinical studies. As these products move forward in development, however, and before they are widely adopted for the treatment and possible eradication, it is important to consider their cost, frequency and practicality of dosing intravenously or subcutaneously, their acceptability to diverse populations.

**Summary**

The bNAbS are a potentially promising approach toward durable control of HIV rebound in the absence of ART. They have been shown to be generally safe and well tolerated in clinical studies to date, and are also being actively pursued for prevention as passive prevention and as a platform for design of vaccines. To date, no randomized controlled trials of therapeutic vaccination have shown the ability to induce long-term remission after ARTs. Combination strategies of bNAbS, therapeutic vaccines, and immunomodulators (eg, TLR7 agonist) may be needed to diminish the HIV reservoir.

**References**


**Perspective**

**Aging and HIV Infection: Focus on Cardiovascular Disease Risk**

Effective antiretroviral therapy has extended life expectancy for individuals with HIV. Estimates from 2015 indicate that 47% of persons with HIV in the US were older than 50 years of age and 16% were older than 65 years. These older patients are at increased risk of age-related diseases and conditions. Further, there is substantial evidence that patients with HIV infection accumulate age-related conditions earlier than do those in the general population. There is risk for increased comorbidities and polypharmacy in the aging HIV-infected population. Specific measures for assessing and reducing the risk of cardiovascular disease and other age-related conditions in the aging HIV population are needed. This article summarizes a presentation by Judith A. Aberg, MD, at the International Antiviral Society-USA (IAS-USA) annual continuing education program held in Chicago, Illinois, in May 2019.

**Keywords:** HIV, aging, comorbidities, cardiovascular disease, diabetes, dyslipidemia, antiretroviral therapy

HIV infection, even when controlled with effective therapy, is associated with chronic immune activation that is superimposed on immunologic senescence in the older adult. Older persons with newly diagnosed HIV infection tend to have more advanced HIV disease at presentation, and there is a less robust immunologic response to antiretroviral therapy (ART) in this population. People with HIV (PWH) accumulate age-related diseases at a younger chronologic age and these conditions account for the majority of deaths in this population. Practitioners need guidance on how best to manage PWH who may develop or already have these comorbidities given the younger age at time of presentation, quicker progression, specific recommendations for PWH, and potential drug interactions.

Since the 1980s, the proportion of PWH older than 50 years has gradually increased. According to data from the Centers for Disease Control and Prevention, in 2015, approximately 47% of PWH in the US were older than 50 years and 16% were older than 65 years. In 2016, 17% of newly diagnosed cases of HIV were in adults aged 50 years or older, with 35% of these persons diagnosed with AIDS (down from 40% in 2015). African Americans accounted for 42% of cases, whites for 37% of cases, and Hispanics/Latinos for 18%. Men having sex with men is the most common mode of transmission in older men, and heterosexual contact is the most common mode in older women.

PWH on suppressive ART have an increased life expectancy compared with those not on ART, although life expectancy is still shorter than that in the general population, particularly among patients with low CD4+ cell counts and those who are on salvage ART regimens, most likely representing a more prolonged period of time with unsuppressed HIV. Issues in aging that need to be addressed include the impact of this increased life expectancy on prevalence and types of comorbidities. Considerations include the fact that older patients are more likely to be treatment experienced and to have had consequences of toxic effects of previous ART regimens (eg, metabolic derangements). A major issue for practitioners, given the likelihood of increased comorbidities with aging is the appropriateness of applying primary care practice guidelines for the general population to the population with HIV. To date, there is no systematic way to predict whether or what guidelines developed for the general population should apply to individuals with HIV, although the consensus appears to be that guidelines for PWH need to be more detailed and comprehensive. The 2013 Infectious Diseases Society of America HIV primary care guidelines are expected to be updated in 2020. The 2018 European AIDS Clinical Society guidelines are comprehensive and easy to use. A revised version was released in November 2019 with expanded drug interaction tables including medications used to treat common comorbidities as well as specific recommendations for elderly PWH.

**Age-Associated Comorbidities**

Health conditions prominent in aging patients include: cardiovascular disease (CVD); endocrine disorders; kidney disease; gastrointestinal and genitourinary malignancies; liver diseases; lung diseases, nervous system disorders; and psychosocial issues including depression and substance use.

It bears continual repeating that the prevalence of cigarette smoking among PWH is much higher than in the general population irrespective of age, sex, race, ethnicity, education level, or income.

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could be made in reducing and preventing comorbidities in PWH with interventions and programs focusing on smoking cessation.

Figure 1 shows the increase in proportion of patients with age-associated comorbidities during the early 2000s as reported by the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design); an update is expected in the near future. As can be seen, this includes an increase in the numbers of patients with numerous comorbidities. These data showed that, as in the general population, hypertension and hyperlipidemia are the most common conditions. Data from an Italian cohort indicate that additional chronic comorbidities accrue in PWH a decade earlier than in the general population aged 51 to 60 years (Figure 2). Data from the New York City HIV Surveillance Registry for 2001 to 2012 showed that the proportion of CVD deaths among all deaths increased in the HIV population from 6% to 15%, and decreased in the general population. The risk of CVD death was significantly higher among those with HIV than those in the general population for every 10-year age group from 25 years to 64 years, whereas no significant difference was observed in the 65 to 74 year age group. It was also found that risk of CVD death was significantly lower among PWH who had viral suppression than among those without full suppression.

In the Italian cohort mentioned above, analysis of patients aged 65 years or older showed increasing prevalence of a number of health conditions by duration of HIV infection. However, there was no significant difference in overall prevalence in the PWH population compared with the general population for CVD or hypertension, whereas significantly higher rates were found among the HIV population for dyslipidemia, chronic kidney disease, and type 2 diabetes. Data from this cohort also showed that number of comorbidities and number of medications in addition to ART increased with increasing duration of HIV infection emphasizing the issue of polypharmacy in this older population. The association of CVD with duration of HIV infection may reflect a longer period of time of viremia especially during the era when ART was not recommended until the CD4+ count was below 200 cells/µL or below 350 cells/µL and more toxic ART with metabolic adverse effects were prescribed.

**As a risk enhancer, the presence of HIV infection can lower the risk-based threshold for initiating statin therapy**

Assessment and Management of CVD Risk in HIV Infection

Despite evidence of the earlier onset of CVD in the PWH population, it still has proven difficult to determine to what degree HIV infection increases risk of CVD or to determine to what degree risk assessment instruments for the general population apply to the PWH. As noted above, smoking remains one of the largest contributors to development of CVD and the incremental increase in risk associated with HIV infection other traditional risk factors has been difficult to calculate. A step toward quantifying additional risk posed by HIV infection has been taken in the 2018 American Heart Association multispecialty guideline on management of blood cholesterol for primary prevention of atherosclerotic CVD.

The new guideline includes measurement of CVD risk in younger age groups than previous guidelines (including 0-19- and 20-39-year age groups) and includes HIV infection as a risk enhancer. As a risk enhancer, the presence...
of HIV infection can lower the risk-based threshold for initiating statin therapy. Thus, for example, in adults aged 40 to 75 years without diabetes and an intermediate 10-year risk of a CVD event (7.5%-19.9%), the presence of HIV infection (or other risk enhancers) favors the initiation of statin therapy. Further, the guidelines encourage discussion of starting statin therapy in patients at borderline risk (10-year risk of 5.0%-7.5%) if HIV infection or another risk enhancer is present. In individuals at intermediate risk who are uncertain about starting statin therapy, coronary artery calcium imaging may be recommended, with a score of 1 to 99 favoring statin therapy and higher scores warranting statin therapy. At this time, imaging for non-calcified plaque remains investigational.

Among statins, rosuvastatin, atorvastatin, and pitavastatin are the best choices for persons with HIV. Simvastatin and lovastatin should not be used in patients receiving an HIV protease inhibitor or cobicistat due to drug-drug interactions, and pravastatin has a drug interaction with boosted darunavir. From a drug interaction perspective, pitavastatin may be the safest although it is more expensive than rosuvastatin or atorvastatin and may not be available on payor formularies. Lipid levels should be measured at the time of HIV diagnosis, at the start of ART, with any change in ART, to assess response to statin therapy, and every 12 months during statin treatment.

It has been proposed that statins may not work as well in persons with vs without HIV, but this does not appear to be the case. Figure 3 shows results of the INTREPID (Pitavastatin versus Pravastatin in Adults with HIV-1 Infection and Dyslipidemia) trial comparing pitavastatin with pravastatin in PWH with dyslipidemia. Results showed that pitavastatin was superior in reducing low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), and apolipoprotein B at 12 and 52 weeks; these reductions in atherogenic lipids were essentially the same as what is observed in persons without HIV infection. Adapted from Aberg et al.11

![Figure 3. Results of the INTREPID (Pitavastatin versus Pravastatin in Adults with HIV-1 Infection and Dyslipidemia) trial showing the superiority of pitavastatin in reducing low-density lipoprotein cholesterol (LDL-C, top) and non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (bottom) at 12 and 52 weeks. The reductions in atherogenic lipids were equal to what is observed in persons without HIV infection. Adapted from Aberg et al.11](image-url)

Pitavastatin was superior in reducing LDL-C, non-HDL-C, and apolipoprotein B at 12 and 52 weeks; these reductions in atherogenic lipids were essentially the same as what is observed in the general population should be examined the effect of statin therapy on coronary plaque, vascular inflammation, and immune activation.

HIV infection has been recognized as a prothrombotic condition in which a hypercoagulable state places patients at increased risk for deep vein thrombosis or other clotting that increases risk for ischemic CVD events. Activated platelets have been implicated in thrombotic CVD events because of their proinflammatory and thrombogenic effects. PWH have increased circulating platelet-monocyte complexes and their platelets express high levels of P-selectin. Aspirin is a low-risk and low-cost platelet inhibitor that has immunomodulatory properties. It has been shown to decrease risk of mortality and CVD events in individuals with known CVD however aspirin’s role in CVD and cancerprimary prevention in those at risk remains controversial.

Although it may appear that aspirin should be broadly used in PWH, with regard to primary preventive daily aspirin therapy, the PWH who may be most likely to benefit are those aged 40 years or older who have diabetes. The reason for this is that although aspirin has proven benefit in secondary prevention of CVD events, recent data indicate that use of aspirin in primary prevention in individuals at moderate risk of CVD was not associated with preventive benefit and resulted in an increased risk of gastrointestinal bleeds. In the ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events) trial, more than 12,000 patients were randomly assigned to receive 100 mg aspirin daily or placebo over 5 years.12 No significant differences between groups in rates of death, heart attack, or stroke were observed, whereas the aspirin group had a significantly higher rate of gastrointestinal bleeds. However, the primary prevention ASCEND trial in more than 15,000 patients with diabetes randomly assigned to aspirin or placebo for 7.4 years showed a significant reduction in serious vascular events in the aspirin group compared with the placebo group (8.5% vs 9.6% respectively; rate ratio, 0.88; P = .01)13. Risk of major bleeding events was also significantly higher in the aspirin group.
than in the placebo group (4.1% vs 3.2% respectively; rate ratio, 1.29; \( P = .003 \)). Thus, risks and benefits of aspirin therapy must be weighed even among patients with diabetes in the primary prevention setting.

The new American Diabetes Association definition of diabetes is: HbA1c

PWH who may be most likely to benefit from preventative daily aspirin therapy are those aged 40 years or older who have diabetes, but risks and benefits must be weighed

of 6.5% or higher; fasting plasma level of 126 mg/dL or higher confirmed by repeat testing; plasma glucose level 2 hours after 75 g oral glucose tolerance test of 200 mg/dL or higher; or random plasma glucose level of 200 mg/dL or higher with polyuria and polydipsia.

Numerous studies have now shown that HbA1c is not an accurate measure of blood glucose in PWH. Depending on ART being taken, it may underestimate or overestimate blood glucose level. Thus, the new guidelines stipulate that in conditions associated with an altered relationship between HbA1c and glycemia, such as HIV infection and sickle cell disease, only plasma blood glucose criteria should be used to make a diagnosis of diabetes.

**Summary**

There is excess CVD risk in the population with HIV. Risk in persons aging with HIV may be different than that in individuals newly diagnosed with HIV infection. The greatest modifiable risk factor for comorbid conditions is smoking. The etiology of CVD associated with HIV infection is multifactorial, including chronic inflammation, direct viral effects, effects of ART drugs and other medications, and other factors. There remains a need for improved risk assessments for CVD in the PWH population. Fasting blood glucose (or other plasma blood glucose criteria) rather than HbA1c should be used to diagnose diabetes in PWH on ART. The 2018 American Heart Association (AHA) multispecialty guidelines provide more guidance on management of blood cholesterol level among PWH than in prior publications. Following the recommendations of the American Diabetic Association (ADA) and AHA provides additional guidance for the primary prevention of CVD in PWH. For example, those aged 40 years or older with diabetes and LDL-C greater than 70 mg/dL should be on a statin and aspirin if no contraindications are present. Measures to improve incorporating primary care prevention during routine HIV monitoring visits are needed.


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**References**

Perspective

Immune Reconstruction Inflammatory Syndrome in HIV Infection: Beyond What Meets The Eye

A high proportion of individuals with HIV infection currently are diagnosed at an advanced stage of disease (late presenters), increasing their risk for immune reconstitution inflammatory syndrome (IRIS). IRIS typically occurs within 6 months of initiation of antiretroviral therapy (ART) in patients with low CD4+ cell counts and can occur before any marked elevation in CD4+ count is achieved on ART. In addition to low CD4+ count at ART initiation, 2 other major clinical predictors of IRIS are preexisting opportunistic infection (including subclinical infection) and shorter treatment period for opportunistic infection prior to starting ART. Mycobacterial infection-associated IRIS, including tuberculosis (TB)-associated IRIS, and cryptococcal infection-associated IRIS are the most common forms of the syndrome. Corticosteroid prophylaxis and early treatment can be effective in reducing incidence of TB-IRIS and severity of symptoms in select patients. Sterilization of the cerebrospinal fluid should be achieved prior to starting ART in patients with TB meningitis and cryptococcal meningitis. This article summarizes a presentation by Irini Sereti, MD, MHS, at the International Antiviral Society-USA (IAS-USA) continuing education program held in Washington, DC, in April 2019.

Keywords: HIV, antiretroviral therapy, IRIS, immune reconstitution, CD4+, tuberculosis, cryptococcal meningitis, corticosteroids

The risk of immune reconstitution inflammatory syndrome (IRIS) is highest in individuals with HIV infection who initiate antiretroviral therapy (ART) with advanced HIV disease (ie, in those with lower CD4+ cell counts who have history of or an active opportunistic illness). It is unfortunate that a high proportion of HIV-infected individuals are still diagnosed and begin ART during advanced disease. Despite some improvement in earlier diagnosis and initiation of treatment from preceding years, a recent study of trends across 55 countries estimated that in 2015, 37% of patients initiating ART had advanced HIV infection indicated by CD4+ cell counts of less than 200/µL. US data from 2007 and 2008 indicate that 35% of new diagnoses occurred at a CD4+ count of less than 200/µL, including 42% of new diagnoses in black individuals and 46% in Hispanic individuals.

Morbidity and mortality are markedly increased among patients initiating ART at low CD4+ cell counts, particularly during the first 6 months to 1 year after starting ART. Contributors to excess mortality include ongoing opportunistic infections during recovery of CD4+ cell count, infectious and thromboembolic complications, toxicity associated with polypharmacy, and IRIS.

IRIS Risk and Presentation

IRIS can be defined as a worsening of manifestations or abrupt or atypical presentation of infections or tumors related to infections after HIV patients start ART. The syndrome can be ‘paradoxical’, in that a pre-existing condition worsens as ART improves CD4+ cell count and immune function, or can occur as the unmasking of an occult infection. The reported incidence of IRIS has ranged from approximately 3% to almost 50%, depending on patient population, study cohort, or rate of recognition of this complication. IRIS typically occurs within 6 months of ART initiation in the setting of successful virologic suppression and when treatment of an opportunistic infection has resulted in a successful microbiologic outcome (in paradoxical IRIS). Thus, for example, a patient with tuberculosis (TB) can be TB culture-negative when IRIS occurs; it is not the infection, but the immune response to the residual antigen that is ‘out of control’.

The 3 major clinical predictors of IRIS are: severe CD4+ cell depletion at initiation of ART, pre-existing opportunistic infection (even if subclinical); and shorter treatment period for an opportunistic infection before starting ART, which can be associated with presence of higher antigen loads.

Presentations of IRIS are shown in Figure 1. The upper left shows a patient who had TB and developed persistent and relapsing IRIS in the form of necrotic lymphadenitis that caused blockage of the thoracic duct and chylothorax. Adapted from Hsu et al, and from Barber et al.

Figure 1. Upper left: a patient with tuberculosis (TB) who developed persistent and relapsing immune reconstitution inflammatory syndrome (IRIS) in the form of necrotic lymphadenopathy. The patient had undergone several drainages when the photograph was taken. Upper right: a patient who came to the US from Mexico and presented with disseminated histoplasmosis and mycobacterium avium complex (MAC) and exhibited enlarged and inflamed lymph nodes after ART initiation. Bottom left: a patient who had unmasking MAC lymphadenitis that caused necrotic lymphadenopathy that was compressing the trachea and jugular vein. The condition required corticosteroid treatment and lymph node drainage. Bottom right: a patient with miliary TB, TB arthritis, and osteomyelitis who developed severe persistent IRIS that caused blockage of the thoracic duct and chylothorax.

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lymphadenopathy; the patient had already undergone several drainages when the photograph was taken. The upper right shows a woman who came to the US from Mexico and presented with disseminated histoplasmosis and mycobacterium avium complex (MAC), and exhibited enlarged and inflamed lymph nodes. The bottom left shows a patient who also had an unmasking MAC lymphadenitis that caused necrotic lymphadenopathy that was compressing the trachea and jugular vein; the condition required corticosteroid treatment and lymph node drainage. The bottom right shows a patient who had miliary TB, as well as TB arthritis and osteomyelitis, and who developed severe persistent IRIS that caused blockage of the thoracic duct.1

IRIS Pathogenesis

IRIS is characterized by production of inflammatory cytokines by CD4+ cells. Figure 2 shows computed tomography (CT) scans of a patient originally from Cameroon who presented with mostly extrapulmonary TB.2 The scan before the initiation of ART shows lymphadenopathy, but the patient’s condition had markedly improved while on treatment for TB. After starting ART, the patient developed worsening lymphadenopathy, high fever, and elevated C-reactive protein (CRP). The bottom of the figure shows proportions of interferon-gamma (the cytokine that is measure in gamma release assays) expressing CD4+ cells in response to TB antigens. The blue spots indicate the CD4+ cells that produced interferon-gamma and the inflammatory cytokine tumor necrosis factor (TNF). As can be seen, there was minimal production of the inflammatory cytokines prior to ART, whereas extremely high concentrations occurred after the start of ART in the context of a rapid expansion and improved functionality of CD4+ cells. IRIS is also characterized by increased monocyte production of the inflammatory cytokines TNF, interferon-gamma, interleukin (IL)-18, and IL-6, the latter of which results in augmented CRP production in the liver. Measurement of CRP can be used to test for suspected IRIS in the clinical setting. The author and colleagues have also found in a small pilot study that 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) can be used to predict and diagnose IRIS in patients with opportunistic infections. Glucose uptake is high in inflammatory cells. Figure 3 shows results of 18F-FDG-PET before and after the start of ART in a patient who had MAC at baseline and subsequently developed IRIS. It can be seen that FDG uptake is increased post-ART. Overall, patients who developed IRIS were more likely to have more areas of increased FDG uptake prior to ART, with an additionally marked increase in uptake and distribution being observed after ART.3 These increases in concentration and distribution of inflammatory cells were correlated with levels of inflammatory cytokines in patients with IRIS.

Underlying Diseases in IRIS

Among the underlying opportunistic conditions associated with IRIS, the most common are mycobacterial infections, including TB and MAC and other non-TB infections, and cryptococcal infections. Others include cytomegalovirus retinitis, progressive multifocal leukoencephalopathy (PML), herpesvirus infection, Kaposi sarcoma, non-Hodgkin lymphoma, candidiasis, viral hepatitis, human papillomavirus infection, and Pneumocystis infection. TB-Associated IRIS. TB is one of the most common underlying diseases worldwide in IRIS cases (although MAC is more common in the US). The reported incidence of TB-associated IRIS ranges from 7% to 50%. In most reports, it is associated with the initiation of ART, with onset most commonly being observed 2 to 6 weeks after the start of treatment. The incidence is higher at very low CD4+ counts (ie, <50µL). The spectrum of the syndrome includes exacerbation of existing disease, development of new manifestations or new sites of disease, and dissemination or death. ART cannot be delayed in patients with CD4+ counts below 50µL, since such delay is associated with increased AIDS-defining illnesses and...

Figure 2. Rapid expansion of activated CD4+ T cells during tuberculosis-associated immune reconstitution inflammatory syndrome. Top shows computed tomography scans prior to (left) and after initiation (right) of antiretroviral therapy with axillary lymphadenopathy. Bottom shows concentrations of CD4+ cells producing inflammatory cytokines. Adapted from Boulougoura and Sereti.2

Figure 3. 18F-fluorodeoxyglucose positron emission tomography before (left) and after (right) the start of ART in a patient who had Mycobacterium avium complex at baseline and subsequently developed immune reconstitution inflammatory syndrome (IRIS). Fluorodeoxyglucose uptake is markedly increased during IRIS. Adapted from Hammoud et al.3
**Figure 4.** A: Overall survival in the COAT (Cryptococcal Optimal ART Timing) trial comparing early and delayed antiretroviral therapy (ART) in patients with cryptococcal meningitis. Adapted from Boulware, *N Eng J Med*, 2014. B and C: Trial in patients with cryptococcal meningitis showing reduced risk of neurologic deterioration in patients with culture-negative results and reduced risk of immune reconstitution inflammatory syndrome (IRIS) in patients with sterile cerebrospinal fluid at the start of ART. Adapted from Chang et al.

mortality. An exception is in patients with TB meningitis; the recommendation in this setting is to sterilize the CSF before starting ART. Multidrug-resistant TB should be included in the differential diagnosis.

The International Network for the Study of HIV-associated IRIS (INSHI) definition of TB-associated IRIS includes the major clinical criteria of: new or enlarging lymph nodes, cold abscesses, or other focal tissue involvement; new or worsening radiologic features of TB; new or worsening central nervous system (CNS) TB; and new or worsening serositis (pleural effusion, ascites, or pericardial effusion). Minor clinical criteria (≥2 required) consist of: new or worsening constitutional symptoms; new or worsening respiratory symptoms; and new or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy.

**Cryptococcal Infection-Associated IRIS.** The INSHI definition of cryptococcal IRIS includes the antecedent criteria of cryptococcal infection that has improved with antifungal treatment and the clinical criteria of clinical deterioration within 12 months of starting ART, with the development of meningitis, intracranial lesions, skin lesions, pulmonary nodules, or lymphadenopathy. Nonadherence to ART and other diagnoses, including other infections or malignancies, must be excluded.

As in the case of TB meningitis, ART should not be started until cerebrospinal fluid (CSF) is sterile and infection controlled in patients with cryptococcal meningitis. As shown in Figure 4A, the COAT (Cryptococcal Optimal ART Timing) trial in patients with cryptococcal meningitis showed 6-month overall survival of 55% and 70% (P = .03) in the earlier ART and delayed ART groups, respectively. The survival curves for the treatment groups diverged sharply within the first month of the trial, such findings support the potential lethality of cryptococcal IRIS and the need to effectively treat the infection before initiating ART. As shown in Figure 4B, another study found that patients with cryptococcal meningitis who were CSF culture-negative at the initiation of ART had a greater than 60% reduction in risk of clinical deterioration than those who were culture-positive and that those

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**Box 1. Illustrative Case 1—Not Your Usual Hiccups**

A 38-year-old patient with a recent diagnosis of HIV infection presented with persistent hiccups and anemia. The patient was found to have thrush, weight loss, chills, fatigue, and cough. The CD4+ cell count was 10/µL and HIV RNA level was 350,000 copies/mL. Acid-fast bacillus (AFB) assay of bronchoalveolar fluid was positive, with *Mycobacterium avium* complex (MAC), although blood culture was negative. The patient improved on azithromycin and ethambutol. The patient was started on elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate. Two weeks later, the patient had worsening hiccups; a CD4+ cell count of 63/µL, an HIV-RNA level of 237 copies/mL, and high-sensitivity C-reactive protein (CRP) up to 51 mg/L from baseline of 14 mg/L. Four weeks later, the patient had high fevers, hiccups, CRP of 120 mg/L, CD4+ count of 163/µL, and indeterminate TB test results. A repeat chest computed tomography (CT) was performed. The figure shows CT scans before and after antiretroviral therapy (ART), with evident cavitation, and the course of the patient’s CRP levels. As noted, corticosteroid treatment should not be started without additional workup. The best course of management at this point would be to repeat bronchoscopy or sputum testing to exclude other diagnoses or progressing or resistant MAC and possibly to add moxifloxacin to the antibacterial regimen.

**Box 1 Figure.** Computed tomography scans before and 1 month after initiating antiretroviral therapy (ART) demonstrating the development of infiltrates and cavity lesions (arrows) and course of changes in high-sensitivity C-reactive protein (CRP).
Hepatitis Flares. IRIS in the form of hepatitis flares is most commonly observed in patients with hepatitis B (HBV) or hepatitis C virus (HCV) infection. The incidence of such IRIS is as high as 20% in people with chronic hepatitis and fatalities have been reported. Risk of IRIS is increased with higher HBV viral burden (adjusted odds ratio per log₁₀ increase, 1.36; \( P = .003 \)) or HCV viral load (adjusted odds ratio per log₁₀ increase, 1.30; \( P = .04 \)). It has also been observed in patients who are HBV core antigen (HBCAg) antibody-positive (HBCAb+) alone. The syndrome has been associated with increased levels of IL-10, IL-18, and CXCL10. Despite the clinical deterioration or liver function test abnormalities, it may lead to clearance of HBV envelope antigen (HBeAg) or seroconversion. Differential diagnosis should include drug toxicities.²⁻⁴

Considerations in the Management of IRIS

Patients at higher risk for IRIS are those with very low CD4+ counts, disseminated disease (associated with higher antigen loads), lack of immune response in cryptococcal meningitis, or severe anemia. IRIS is a diagnosis of exclusion. It is important not to ‘blindly’ start corticosteroid treatment, since patients are still immunocompromised.

Figure 5. Risk of tuberculosis-associated immune reconstitution inflammatory syndrome in patients receiving prophylactic prednisone or placebo. Adapted from Meintjes et al.¹

with sterile CSF had a greater than 60% reduction in risk of IRIS than those without sterile CSF.¹¹

A 30-year-old patient presented with a Kaposi sarcoma skin lesion. The CD4+ cell count was 7/µL and the patient was hepatitis A virus (HAV) antibody-negative, hepatitis C virus (HCV) antibody-negative, HBsAg-positive, HBsAb-negative, HBCAb-positive, and HBeAg-positive. The patient was started on antiretroviral therapy (ART) with efavirenz/emtricitabine/tenofovir disoproxil fumarate. For ART, efavirenz was stopped and raltegravir added to the ART regimen change. The patient underwent head magnetic resonance imaging and was found to have a tuberculosis located in the middle of the medulla that was causing the nystagmus. The patient was treated with low-dose prednisone, with resolution of the tuberculosis and nystagmus.

A 33-year-old patient with tuberculosis (TB) with lung infiltrates and mediastinal lymphadenopathy, CD4+ cell count of 10/µL, HIV RNA level of 1.1 million copies/mL, HBsAg+ status, and hepatitis B virus (HBV) viral load of 165,000 copies/mL was started on antiretroviral therapy (ART) with efavirenz, emtricitabine, and tenofovir disoproxil fumarate, RIPE (rifampicin, isoniazid, pyrazinamide, and ethambutol), and trimethoprim/sulfamethoxazole. The patient developed a drug reaction with eosinophilia and systemic symptoms (DRESS) from rifampicin and TB treatment was switched to isoniazid, ethambutol, and moxifloxacin. Clinical improvement was observed, the CD4+ cell count increased to 84/µL, and the HIV RNA level decreased to less than 40 copies/mL. However, the patient complained of blurred vision and was found to have continuous vertical nystagmus that did not improve with focusing. The patient underwent head magnetic resonance imaging and was found to have a tuberculoma and nystagmus. The patient was indeed subsequently found to have converted to HBeAg-negative status.
after starting ART. The onset of IRIS does not require achieving of high CD4+ cell counts; in fact, the syndrome can be observed in the absence of any marked increase after starting ART. All ART regimens have been associated with IRIS; early indications of a lower risk with HIV integrase strand transfer inhibitors have not been borne out in clinical trial populations.

The Occam’s razor “law of parsimony” does not apply in HIV-late presenters within HIV infection; as such, IRIS—patients may have 2 or more infectious states that may account for findings and all need to be addressed. It is also important to note that IRIS can occur in individuals who do not have HIV infection for reasons other than the initiation of ART. The syndrome has been observed in patients with disseminated mycobacterial infection who have received a transplant for primary immune deficiency, in patients with PML after natalizumab treatment, in TB monoinfected patients who can experience paradoxical worsening after initiation of TB medications, and in other settings in which immune suppression is followed by immune recovery.

Clinical management of IRIS includes observation or symptomatic relief in mild cases. In more severe cases, drug treatment includes nonsteroidal antiinflammatory drugs and corticosteroids. Lymph node drainage and use of a lumbar drain (in cases of cryptococcal meningitis) may be necessary. As noted, it is crucial that cryptococcal meningitis be diagnosed early and that it be treated until CSF is sterile. To prevent unmasking IRIS, cryptococcal antigen (CRAg) and acid-fast bacillus (AFB) screening should be performed in patients in high-prevalence areas. ART should be continued during management.

An example of the benefit of early prednisone treatment in IRIS is provided by a trial in which patients who rapidly developed mild to moderate symptomatic TB IRIS after starting ART were randomly assigned to prednisone (n=54) or placebo (n=48). At 4 weeks after starting ART, symptom relief was observed in 80% vs 56% of patients (P=.03), with 7% vs 13% patients being converted to open-label treatment within 2 weeks.16

Another, more recent, study showed that prophylactic prednisone was associated with significant reduction in risk for paradoxical TB-IRIS (Figure 5). In the trial, patients with TB and with CD4+ counts less than 100/µL were randomly assigned to receive prophylactic prednisone at 40 mg for 2 weeks after starting ART, and then 20 mg for 2 weeks (n=120) or placebo (n=120). The cumulative incidence of TB-associated IRIS at 12 weeks was 32.5% vs 46.7% (relative risk, 0.70; P= .02; overall hazard ratio, 0.61; P=.03).17 It should be noted that the trial was performed in outpatients with overall milder cases of TB.

Conclusions

Opportunistic infections remain a reality in regions with high prevalence of HIV. IRIS is an inflammatory reaction that can be managed with maintenance of ART, but may require immune suppression with corticosteroid treatment in patients who are already very ill. Management of immunosuppressed HIV patients should include screening for opportunistic infections. In cases of cryptococcal meningitis, it is crucial to sterilize CSF before starting ART. It is important to note that unmasking cryptococcal meningitis-associated IRIS may increase in frequency with test and treat roll-out in high-prevalence areas. Prednisone can be effective in prevention and early treatment of TB-associated IRIS in select patients (ie, in non-hospitalized, non-critically ill patients).  

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References


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