EDITORIAL

2018 IAS-USA Recommendations for the Use of Antiretroviral Therapy for HIV
Building on Decades of Progress

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Soon after HIV was first identified as the cause of AIDS in the early 1980s, it became clear that antiretroviral treatments were needed to prevent the development of opportunistic infections and malignancies that were often fatal. Over the next decade into the 1990s, several therapies rapidly became available, including zidovudine and protease inhibitors such as saquinavir and indinavir. As these medications were developed, investigators learned that combinations of these drugs were needed to successfully inhibit viral replication, prevent resistance from developing, and extend life expectancy.

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The culmination of this early research led to the first guidelines from the International AIDS Society–USA panel, published in *JAMA* in 1996.[1] These guidelines were designed to summarize the most important and timely clinical studies and synthesize recommendations for clinicians caring for patients with HIV infection to provide the best treatment possible. Over the 22 years since the initial guidelines were published, many new antiretroviral treatments have been developed and much has been learned about the biology of HIV infection, which has led to improved treatment strategies and a significant decrease in mortality, transforming AIDS into a chronic, manageable disease in many countries of the world. In this issue of *JAMA*, the International Antiviral Society–USA (IAS-USA) panel provides a 2018 update to these guidelines, which have evolved considerably over the years.[2] This iteration reports several important changes in recommendations made since the last guidelines were published in 2016.[3]

It has been well established that all patients diagnosed with HIV infection should receive antiretroviral therapy (ART) as soon as possible, with very few exceptions. In these updated guidelines, this concept is developed further to support immediate treatment when feasible. This recommendation is based on the accumulation of data from studies performed both in the United States and internationally. In a study performed in San Francisco, 37 of 39 eligible patients with CD4 cell counts less than 200/μL or with recently contracted HIV infection (within 6 months) began ART under the RAPID (Rapid ART Program for Individuals With an HIV Diagnosis) protocol within 24 hours of HIV diagnosis.[4] Among these patients, time to virologic suppression (<200 HIV RNA copies/mL) was significantly shorter (median, 1.8 months)than for patients who had been treated in the same clinic under previous recommendations for universal ART (4.3 months; $P = .0001$). Similarly, a study performed in Lesotho in sub-Saharan Africa evaluated the efficacy of home HIV testing combined with immediate initiation of ART before a standard outpatient clinic visit.[5] When compared with 137 patients randomized to receive usual care, 134 patients who received immediate treatment were more likely to become linked to care at 3 months (68% vs 43%) and have viral suppression at 12 months (50% vs 34%) ($P = .007$).

Based on these studies and others, the time at which ART is recommended to be started has become as soon as is feasible based on availability of medication without waiting for results of supporting laboratory tests, including resistance testing. Exceptions include patients not ready to start treatment or those at risk for immune reconstitution inflammatory syndrome in the setting of active tuberculosis infection, cryptococcal meningitis, or certain other opportunistic infections.[6]

As new, high-potency, single-tablet ART regimens have been developed over the past 6 years, the recommendations for initial treatment have changed. Integrase single-strand transfer inhibitors (InSTIs) in combination with 2 nucleoside reverse transcriptase inhibitors are preferred in most circumstances. InSTIs are potent and have few adverse effects, which makes these medications attractive for initial therapy. In addition, agents such as dolutegravir and bictegravir have a high genetic barrier to resistance and few drug-drug interactions.[7] As a result, bictegravir- and dolutegravir-based regimens are now preferred, because these medications can be coformulated into single-tablet regimens and can be taken with or without food. The combination of bictegravir, tenofovir alafenamide, and emtricitabine is particularly well suited for rapid initiation of therapy because it is a single-tablet regimen, contains a high-potency InSTI, and is likely to remain active in the setting of commonly transmitted drug-resistance mutations such as M184V and K103N.[8] Because raltegravir has a higher pill burden, is not coformulated, and has a lower barrier to resistance, this medication is now considered an alternative. Similarly, elvitegravir is now considered an alternative because it has a lower genetic barrier to resistance and has more drug-drug interactions because of cytochrome P450 metabolism. Because of a preliminary report from a study in Botswana suggesting that dolutegravir may be linked to neural tube defects, it is now recommended that this drug be avoided in pregnancy if possible.[9]

Additional studies published since the last IAS-USA guidelines support the use of 2-drug regimens previously considered investigational. The combination of dolutegravir and rilpivirine has now been approved by the US Food and Drug Administration for switch therapy (changing from one successful antiretroviral regimen to a new regimen) for patients who achieve viral suppression and do not have prior resistance mutations to either agent. However, rilpivirine must be taken with a meal, which is a limitation for some individuals, and cannot be taken with acid-suppressing medications (such as proton pump inhibitors or H_2 blockers). In addition, in the pivotal phase 3 trial, more patients in the dolutegravir-rilpivirine group (3% [17/516]) discontinued treatment because of adverse events compared with patients who continued their 3-drug regimen (<1% [3/512]).[10] Other 2-drug strategies, such as the combination of lamivudine and dolutegravir, have been shown to be efficacious in smaller studies. In a retrospective cohort of 94 patients with virologic suppression who switched to a combination of lamivudine and dolutegravir dual therapy, no virologic failures (defined as viral load >50 copies/mL) or virologic blips (defined as viral load >50 copies/mL after virologic suppression, followed by a return to virologic suppression) occurred up to 24 weeks.[11]

In contrast, in an AIDS Clinical Trials Group pilot study involving 120 patients who received lamivudine and dolutegravir as initial therapy, virologic failure occurred in 12 patients, including 1 patient who developed significant resistance mutations.[12] Therefore, 2-drug strategies should currently be avoided if possible as initial therapy but appear to be safer for switch therapy. Because these regimens do not contain 2 drugs active against hepatitis B virus, these drugs should be avoided in this population of co-infected patients, and monotherapy also continues to not be recommended.

HIV prevention and linkage to care remain a prominent part of the IAS-USA guidelines. Major challenges to controlling the HIV epidemic have not changed over the years. It has remained difficult to diagnose HIV in all patients early in the course of infection and then effectively maintain viral suppression in all patients. Viral suppression is important because it not only leads to the improved health of individual patients but also prevents HIV transmission to others. Despite the availability of highly potent, single-tablet antiretroviral medications and a sophisticated medical infrastructure, in 2014 the Centers for Disease Control and Prevention estimated that only 49% of the approximately 1.1 million people living with HIV in the United States were virologically suppressed.[13] Therefore, it is clear that new strategies are needed to reach HIV-infected individuals who are not receiving effective treatment.

The IAS-USA panel recommended discouraging the use of cash transfers to promote adherence in the United States because it judged these incentives to be inconsistently effective. In a study performed at 11 hospitals in the United States, patients with substance use disorders and HIV infection were randomly assigned to different interventions, including 271 patients who received an intervention comprising assistance with health care system navigation and a financial incentive.[14] No difference in viral suppression was identified in any of the groups compared with usual care when evaluated at 6 and 12 months. However, these strategies have been found to be beneficial in other settings. In the HPTN 065 trial, 18 community HIV clinics were randomized to provide cash incentives in an attempt to link patients to care and maintain viral suppression and were compared with clinics that simply provided usual care.[15] In that study, linkage to care was not affected; however, there was a 3.8% proportionate higher rate of viral suppression in 1047 patients (at the peak of intervention) in the cash incentive group compared with 809 patients in the usual care group (P = .01). Therefore, it appears that cash incentives may be effective for some groups but not others.

Since the initial IAS-USA guidelines for HIV treatment were published in 1996, much has changed in the way the medical community provides care for persons infected with HIV. Over time, patients have ultimately benefited from single-tablet regimens that are highly potent, have a high genetic barrier to resistance, and are associated with fewer adverse effects than drugs first developed in the late 1980s. It also is now recognized that starting treatment as early as possible is beneficial for individual patients and for the broader community at large to prevent HIV transmission. Guidelines serve an important purpose to summarize and interpret the most important recent advances and disseminate this information as efficiently as possible to a wide audience so that best practices can be observed across diverse care settings. However, guidelines serve only as a starting point, as evidenced by the fact that implementation has proved to be much more challenging. It is now clear that to effectively address the HIV epidemic, a multipronged approach is needed that includes new HIV prevention strategies (HIV preexposure prophylaxis, education regarding condom use), expanded HIV testing, rapid and immediate linkage to care when possible, viral suppression for persons who are HIV infected, and strategies to enhance adherence to therapy and retention in care.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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