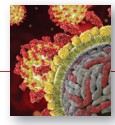

Treatment Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents: An Update

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Important changes to the guidelines clarify the use of antiretroviral therapies and the treatment options for patients who experience virologic failure to first- and second-line regimen failures.

On April 8, 2015, HSS released updated HIV treatment guidelines.[1] The original 1998 guidelines for the use of antiretroviral agents for treating adults and adolescents infected with HIV emphasized the benefit of potent combination antiretroviral therapies (ARTs) that included protease inhibitors (PIs).[2,3] Since then there have been more than 25 HSS guidelines focusing primarily on when to initiate ART and which ART to prescribe. The question of when to start ART had been controversial, but the most recently issued guidelines have addressed this question. For the first time, HSS recommends ART for all individuals infected with HIV regardless of CD4+ T-cell count.[1] The timely initiation of effective ART with an associated reduction in HIV viremia benefits patients infected with HIV and substantially decreases transmission of HIV to uninfected sexual partners.[3]

Three large, international randomized placebo-controlled studies conducted between 2002 and 2015 provide evidence that the benefits of ART outweigh the potential deleterious effects of long-term ART. The Strategies for Management of Antiretroviral Therapy (SMART) was the first published study in this trifecta.[4,5] Given concern about the adverse effects (AEs) of ART, particularly PIs, this study was designed to investigate whether long-term ART was associated with more toxicities than was deferred therapy, determined by CD4+ cell counts. The study was halted prematurely, because the risk of death or grade-4 toxicity was statistically greater among those receiving episodic ART than among those on continuous therapy. The SMART trial demonstrated that ART therapy was beneficial, but it did not determine when to initiate ART, particularly in asymptomatic persons.[5]

It was thought that the risk of transmission of HIV through sexual contact or shared drug paraphernalia was significantly lower for patients on ART who achieve viral suppression compared with those with uncontrolled viremia. The HIV Prevention Trials Network study enrolled HIV-serodiscordant couples to examine transmission of HIV. The trial compared HIV-positive patients who initiated ART when their CD4+ cell count was between 350 to 550 cells/mm^3 with patients who began therapy when their CD4+ cell count was < 250 cells/mm^3 or when an AIDS-defining illness was diagnosed. The difference in the rate of transmission to a HIV-negative partner was dramatic. The rate was 96% less among those in the early-therapy group vs those in the deferred-therapy group. In addition, there was a 40% reduction in the progression of HIV-related disease in the participants randomized to the early-therapy group.[6]

In March 2011, the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), which conducted SMART, initiated the Strategic Timing of AntiRetroviral Treatment (START) study to define the optimal time to begin ART among asymptomatic patients with a CD4+ count of > 350 cells/mm^3. Patients with a CD4+ cell count of > 500 cells/mm^3 were randomized to either initiate ART, or defer ART until the CD4+ cell count fell to

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Table 1. Recommended and Alternative ART Regimen Options for Treatment-Naïve Patients

Recommended Regimen Options[a,b]	
INSTI-based regimens	DTG/ABC/3TC (Triumeq): **AI** Patients must be HLA-B*5701 negative DTG + TDF/FTC (Truvada): **AI** EVG/c/TDF/FTC (Stribild): **AI** Only for patients with pretreatment CrCl > 70 mL/min RAL + TDF/FTC: **AI** EVG/c/TAF/FTC (Genvoya) Only for patients with pretreatment CrCl > 30 mL/min[c]
PI/r-based regimen	DRV/r + TDF/FTC: **AI**
Alternative Regimen Options	
NNRTI-based regimens	Efavirenz/TDF/FTC (Atripla): **BI** Rilpivirine/TDF/FTC (Complera): **BI** Only for patients with HIV RNA < 100,000 copies/mL and CD4+ > 200 cells/mm^3
PI-based regimens	ATV/c + TDF/FTC: **BI** Only for patients with a pretreatment CrCl > 70 mL/min ATV/r + TDF/FTC: **BI** DRV/c (Prezcobix): **BIII** or DVR/r (BII) + ABC/3TC: **BII** patients must be HLA-B*5701 negative DRV/c + TDF/FTC: **BII** Only for patients with a pretreatment CrCl > 70 mL/min

Abbreviations: 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; c, cobicistat; CrCl, creatinine clearance; DRV, darunavir; DTG, dolutegravir; EVG , Elvitegravir; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; r, ritonavir; RAL, raltegravir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.
[a]Rating of recommendations: A = strong; B = moderate; C = optional.
[b]Quality of evidence for recommendation: I: Randomized trials with clinical endpoints and/or validated lab endpoints; II: Well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III: Expert opinion.
[c]FDA approved in November 2015; not included in guidelines.

< 350 cells/mm^3 or until an AIDS-defining illness occurred.[7] On May 15, 2015, the study was terminated early. Based on an interim analysis, the data safety and monitoring board announced that the risk for a serious AIDS-related event, serious non-AIDS-related event, or death from any cause was 57% less in the early treatment group. When compared with patients who delayed ART, for those on ART, serious AIDS-related events were reduced 72%, and serious non-AIDS events were reduced 39%.[8] A similar study conducted in the Ivory Coast from March 2008 to January 2015 also favored early rather than deferred ART.[9]

Experience in clinical practice, these landmark clinical trials, and several cohort studies served as the basis of the changes in the new HSS guidelines that endorse ART for all HIV-infected persons. The World Health Organization (WHO) has recently published similar guidelines.[10] It is yet to be determined whether the guidelines have been implemented successfully. Nonetheless, for both the clinician and the patient where access to ongoing care and ART are available, the new guidelines greatly simplify the treatment choices.

WHAT'S NEW IN THE GUIDELINES?

The *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* presents significant changes in several of the tables that are most clinically useful, including Tables 6, 7, and 8.[1] Table 6 presents recommended, alternative, and other antiretroviral regimen options. The guidelines also added new tables describing antiretroviral regimen considerations for initial therapy and the mechanisms of antiretroviral-associated drug interactions.

Initial Combination Regimens for the Antiretroviral-Naïve Patient

Five regimens are now recommended for ART-naïve patients: 4 are integrase strand transfer inhibitor-based regimens, and 1 is a ritonavir-boosted PI-based regimen (Table 1). A nonnucleoside reverse transcriptase inhibitor-based regimen is no longer recommended. The guidelines include regimens that are now considered less favorable for a variety of reasons, including reduced virologic activity and greater risk of toxicities, higher pill burden, and more potential drug interactions. Several regimens that have been widely used are now included in this latter option, in particular efavirenz plus abacavir/lamivudine (3TC), lopinavir/

ritonavir plus abacavir (ABC)/3TC, and tenofovir fumarate (TDF)/emtricitabine (FTC).

The most significant change in the guideline is the reclassification of efavirenz from a recommended to an alternative therapy. The principal reasons for this change are central nervous system (CNS) AEs, which can include depression and a reported 2-fold increase in the risk of suicide or suicidal ideation.[11]

In November 2015, the FDA approved Genvoya, a once-daily, fixed-dose combination tablet containing elvitegravir, cobicistat, FTC, and tenofovir alafenamide (TAF).[12] With this approval, there are now 5 once-daily HIV treatment options. This new drug is similar to elvitegravir/cobicistat/TDF/FTC, but it substitutes TAF for TDF. The benefits of this substitution include less bone loss and decreased renal toxicity.[13-15] Genvoya may be prescribed in patients with a 30 mL/min creatinine clearance. The TAF-containing once-daily formulation achieves higher intracellular levels and lower blood levels of TAF. Therefore, the cholesterol-lowering benefits are less than those of the TDF-containing alternative.

In the 2015 guidelines, Table 7 provides concise guidance on the selection of an ART regimen based on patient and regimen characteristics, including food-based AEs; the presence of other medical and/or psychiatric conditions; and the presence of co-infections, including hepatitis B virus (HBV), hepatitis C virus (HCV), and tuberculosis.[1] In addition, Table 8 outlines the advantages and disadvantages of the different classes of ART.[1] For example, dolutegravir may have a higher barrier to resistance than that of elvitegravir or raltegravir.[16]

It is now possible for those living with HIV to have ongoing viral suppression, which will not only improve their lives, but also decrease the risk of HIV transmission to sexual partners. Starting from the time of diagnosis, achieving viral suppression is dependent on a link to care with initiation of ART and retention in care. The 5 once-daily options should improve adherence. The infrastructure to ensure lifelong retention in care, medication availability, and adherence still poses many challenges.

TREATMENT-EXPERIENCED PATIENTS

The guidelines were updated to include more direction on virologic failure to a first-line regimen as well as a second-line regimen failure or beyond. It includes a discussion of treatment options for achieving full virologic suppression. There also are treatment recommendations for patients with multidrug viral resistance in whom maximal viral suppression may not be achieved. For such patients, ART should be continued to preserve immunologic function, lessen clinical progression, and minimize resistance to drug classes that could include new efficacious drugs.[17,18]

Table 2. CDC Steps to Achieve Viral Suppression

Step 1: HIV testing and diagnosis
Step 2: Getting and keeping people living with HIV in medical care
Step 3: Prescribing HIV medications
Step 4: Helping patients achieve viral suppression

There is also a discussion in the guidelines of the issues surrounding isolated CNS virologic failure and the onset of new neurologic symptoms. With CNS virologic failure, magnetic resonance brain imaging may be abnormal with a lymphocytic pleocytosis in the cerebrospinal fluid (CSF). If available to guide therapy, CSF HIV RNA should be measured, and HIV drug resistance in the CSF should be tested. Central nervous system viral escape should be differentiated from other CNS conditions, such as herpes zoster infection; incidental mild CSF HIV RNA increases; or the now relatively common but chronic neurocognitive impairment seen with HIV infection.[19,20]

Poor CD4+ Recovery and Persistent Inflammation Despite Viral Suppression

For patients on ART who achieve viral suppression but fail to have a significant increase in CD4+ cell count over time (particularly for the patient with a CD4+ cell count < 200 cells/mm^3), the guidelines do not endorse additional ARTs or switching the regimen. However, there may be an increased risk of non-AIDS mortality and morbidity, including cardiovascular disease. For such patients, interleukin-2 adjunctive therapy has no demonstrated clinical benefit.[21] Interleukin-7 and recombinant human growth hormone should be used only as part of a clinical trial.

It is now evident that immune activation and inflammation, although lessened, persist despite ART-mediated viral suppression.[22,23] There is no recommendation to monitor markers of immune activation and inflammation. Efforts should focus on risk factor

modifications, such as smoking cessation, improved diet, treatment of alcohol abuse and dependence, regular exercise, and maintenance of appropriate weight. Emphasis should be on treating chronic comorbidities, such as hypertension, diabetes, osteoporosis, and hyperlipidemia.

HIV/HCV Co-infection

According to the WHO, 130 to 150 million people worldwide have chronic HCV infection.[24] In the U.S., it is estimated that up to one-quarter of HIV-infected persons have HCV co-infection.[25] With the currently available oral direct-acting agents (DAAs) for the treatment of chronic HCV infection in patients with HIV/HCV co-infection, rates of sustained virologic response to treatment are comparable in patients with HIV/HCV co-infection with those of patients with HCV mono-infection.[26] Accordingly, all HIV-infected patients should be screened for HCV infection, and HIV ART should not be deferred for most patients.

For patients with a CD4+ cell count of < 200 cells/mm^3, treatment of HCV should be deferred until the patients are on a stable and effective ART regimen. Whereas for those with a CD4+ cell count > 500 cells/mm^3, HCV can be treated before initiating HIV ART. When initiating HCV therapy, clinicians must pay attention to drug-drug interactions. Patients with cirrhosis are particularly at risk. The most recent guidelines for the treatment of HCV co-infection should be reviewed when selecting a DAA to treat HCV.[27] Many patients are now being treated successfully for HCV co-infection. Extending such therapy to all patients with HIV/HCV co-infection for whom treatment is appropriate should be a priority for clinicians, insurance providers, and policy makers.

Drug Interactions

Given the availability of numerous once-daily ART regimens, prescribing ART has been greatly simplified. Nonetheless, there are many pharmacokinetic drug-drug interactions between antiretroviral drugs and concomitant medications. When changing either the ART or adding or changing other medications, the clinician must always pay attention to potential drug-drug interactions. Consideration must be given to the interaction with drugs that affect antiretroviral absorption—particularly, acid-reducing agents and products that contain polyvalent cations, including calcium and magnesium.

When antiretrovirals that undergo hepatic metabolism are given with other drugs that also are metabolized by the cytochrome P450 enzyme system or other hepatic enzymes, the levels of antiretrovirals or other drug may be significantly increased or decreased.[1] The 2 boosters—cobicistat and ritonavir—used to increase certain antiretrovirals levels also may alter the metabolism of other drugs.[28,29] The new guidelines contain updated and detailed tables on drug-drug interactions. Given the comorbid conditions, particularly among those aging with HIV, polypharmacy is an increasingly common concern. It is essential for clinicians to work with knowledgeable HIV pharmacists to ensure the correct and safe prescribing of all medications.

HIV/AIDS DEMOGRAPHICS IN U.S.

Of the more than 1.2 million people aged > 13 years in the U.S. living with HIV, about 1 in 8 are unaware of their infection.[30] The Centers for Disease Control and Prevention (CDC) estimates that about 50,000 people are newly infected every year.[31] Men who have sex with men (MSM) are the group most impacted by HIV, and African American MSM are disproportionately represented. Although MSM were only about 4% of the U.S. male population in 2010, 78% of the newly diagnosed HIV infections among males were in MSM (63% of all new HIV infections).[32,33] The groups at greatest risk of HIV infection are now young black and Latino MSM aged 13 to 24 years.[33] Decreasing the rate of new HIV infections in this high-risk population remains challenging.

Across the U.S., the HIV epidemic continues to disproportionately impact southern states. An estimated 44% of all people living with HIV in the U.S. reside in the District of Columbia and in 16 southern states.[34] Among the 10 states with the highest death rate for persons diagnosed with HIV, 7 are southern states–Louisiana, Alabama, Mississippi, South Carolina, Kentucky, and Maryland.[35,36] The HIV epidemic in southern states is not confined to urban centers but instead extends across rural areas that have limited access to adequate health care and high rates of poverty.[37]

HIV Care Continuum

In July 2013, President Obama established the HIV Continuum Care Initiative directing federal departments to accelerate efforts and direct resources to increase the proportion of HIV-infected persons successfully receiving care in each stage of the continuum

as part of the National HIV/AIDS Strategy.[38,39] In November 2014, the CDC released a report on HIV in the U.S. that found about 14% of those with HIV infection have never been diagnosed, and only 40% are receiving HIV medical care.[40] Despite the much improved and simplified ART regimens, only 30% of those living with HIV infection in the U.S. have achieved viral suppression. The CDC has outlined 4 steps for achieving viral suppression, the ultimate goal of all HIV treatment (Table 2).[41]

In the U.S. and Canada, a person diagnosed with HIV aged 20 years who adheres to a HIV ART regimen has a life expectancy of 71 years. The same person not taking ART has a dramatically shortened life expectancy of 32 years.[42] The successful implementation of ART can help those living with HIV to enjoy an average life expectancy no different from that of persons without HIV infection.

THE FUTURE OF THE HIV/AIDS EPIDEMIC

In 2014, the Joint United Nations Program on HIV/AIDS estimated that 35 million people were living with HIV/AIDS and that 13 million were receiving ART globally. Three of 5 people with HIV infection, about 22 million, did not have access to ART. Less than one-quarter of HIV-infected children are on ART.[43]

Changing the course of the HIV/AIDS pandemic in the U.S. and worldwide is within reach, and the new HSS and WHO guidelines provide an evidence-based framework to alter this course. Significantly expanding screening for HIV and ensuring treatment access for all persons diagnosed with HIV as well as appropriate provision of pre-exposure prophylaxis would irrevocably alter the lives of the millions of people living with HIV/AIDS and others in their communities. It remains to be seen whether the goal to eliminate AIDS by 2020, set in both the National HIV/AIDS Strategy and the UN global commitment will be achieved. ●

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