Perspective

Antiretroviral Therapy for HIV Infection: When to Initiate Therapy, Which Regimen to Use, and How to Monitor Patients on Therapy

Antiretroviral therapy is recommended for all patients with HIV infection. The benefit of immediate antiretroviral therapy was confirmed by results from the START (Strategic Timing of Antiretroviral Treatment) trial, which showed a 57% reduction in risk for the composite end point of AIDS-related events, serious non–AIDS-related events, or death from any cause with immediate treatment in antiretroviral therapy–naive participants with CD4+ cell counts above 500/µL. Other changes in HIV care include the widespread adoption of integrase strand transfer inhibitor–based regimens. Considerations regarding when to initiate antiretroviral therapy, which initial regimens to use, and appropriate monitoring of individuals taking antiretroviral therapy are discussed. This article summarizes an IAS–USA continuing education webinar presented by Steven C. Johnson, MD, in July 2015.

Keywords: HIV, antiretroviral therapy, START trial, HIV treatment guidelines, antiretroviral therapy recommendations, monitoring

When to Initiate Antiretroviral Therapy

Most current guidelines on antiretroviral therapy recommend antiretroviral therapy for all HIV-infected individuals to reduce the risk of disease progression and to prevent transmission of HIV.[1-3] Results from 2 recently reported randomized trials—START (Strategic Timing of Antiretroviral Treatment) and TEMPRANO (Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults)—provide definitive support for early initiation of antiretroviral therapy.[4,5]

From its inception, the START trial was somewhat controversial in terms of whether a large randomized trial of early antiretroviral therapy was necessary given other available clinical data and in light of the remarkable benefit of therapy in preventing HIV transmission. In the trial, antiretroviral therapy–naive participants from around the world who had CD4+ cell counts above 500/µL were randomly assigned to receive immediate (n = 2326) or deferred (n = 2359) treatment (deferred until CD4+ count declined to less than 350/µL or until the development of AIDS).[4] The study required use of an approved combination of antiretroviral medications from the US Department of Health and Human Services (DHHS) guidelines. The predominant regimen was a nucleos(t)ide analogue reverse transcriptase inhibitor (nRTI) backbone of tenofovir disoproxil fumarate (TDF) and emtricitabine plus efavirenz. Some protease inhibitors (PIs) were used, and relatively few integrase strand transfer inhibitors (InSTIs) were used. As announced in a National Institutes of Health press release in May 2015, the data and safety monitoring board for the trial recommended that participants in the deferred-initiation arm be offered antiretroviral therapy on the basis of superiority of immediate treatment.[6]

The primary end point of the START trial was a composite of AIDS-related events (plus Hodgkin disease), serious non–AIDS-related events (cardiovascular disease, end-stage renal disease, non–AIDS-related cancer), or death by any cause. Figure 1 shows time to first primary end point event in the immediate-treatment group and the deferred-treatment group (hazard ratio [HR], 0.43; $P < .001$); HRs for the various end point components were 0.28 ($P < .001$) for serious AIDS-related events, 0.61 ($P = .04$) for serious non–AIDS-related events, and 0.58 ($P = .13$) for death by any cause. Immediate treatment was associated with a significantly reduced risk for tuberculosis (HR, 0.29; $P = .008$) and Kaposi sarcoma (HR, 0.09; $P = .02$) and a numerically reduced risk for malignant lymphoma (HR, 0.30; $P = .07$), non–AIDS-defining cancers (HR, 0.50; $P = .09$), and cardiovascular disease (HR, 0.84, $P = .65$). Subgroup analyses showed that HRs for the primary end point always favored immediate

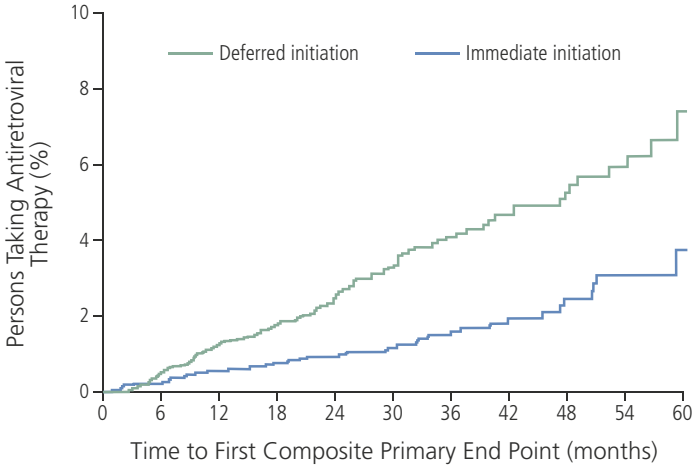

Figure 1. Time to first primary end point (serious AIDS-related or non–AIDS-related event, including death) in individuals who received immediate versus deferred antiretroviral therapy in the START (Strategic Timing of Antiretroviral Treatment) trial. Adapted from Lundgren et al.[4]

Dr Johnson is Director of the University of Colorado HIV/AIDS Clinical Program and Professor of Medicine at the University of Colorado School of Medicine in Aurora, Colorado.

Table 1. Subgroup Analysis for Primary End Point in the START Trial

Subgroup	Percentage in Group	Immediate Initiation of ART N (rate[a])	Deferred Initiation of ART N (rate[a])	Hazard Ratio	P Value
Age					0.98
≤35 y	48.8	15 (0.43)	31 (0.91)	0.47	
>35 y	51.2	27 (0.78)	65 (1.85)	0.42	
Sex					0.38
Male	73.2	35 (0.66)	74 (1.40)	0.47	
Female	26.8	7 (0.42)	22 (1.34)	0.31	
Race					0.65
Black	30.1	15 (0.82)	28 (1.52)	0.57	
White	44.5	21 (0.63)	53 (1.54)	0.40	
Other	25.4	6 (0.34)	15 (0.91)	0.37	
Region					0.55
High income	46.0	20 (0.56)	51 (1.42)	0.39	
Low or moderate income	54.0	22 (0.65)	45 (1.35)	0.48	
CD4+ cell count (baseline)					0.71
<600/μL	31.5	10 (0.44)	35 (1.54)	0.28	
600/μL-800/μL	48.6	24 (0.70)	46 (1.38)	0.50	
>800/μL	19.9	8 (0.63)	15 (1.14)	0.56	
HIV RNA level (baseline)					0.25
<5000 copies/mL	31.8	12 (0.56)	18 (0.83)	0.66	
5000-30,000 copies/mL	35.5	13 (0.53)	36 (1.41)	0.38	
>30,000 copies/mL	32.5	17 (0.72)	42 (1.92)	0.37	
Current smoker					0.93
Yes	31.9	18 (0.78)	43 (1.81)	0.43	
No	68.1	24 (0.52)	53 (1.16)	0.44	
10-year CVD risk score[b]					0.56
<0.8	32.7	8 (0.35)	17 (0.77)	0.46	
0.8-3.6	32.3	11 (0.48)	27 (1.23)	0.39	
>3.6	33.5	23 (1.00)	50 (2.05)	0.50	

Abbreviations: ART, antiretroviral therapy; CVD, cardiovascular disease; START, Strategic Timing of Antiretroviral Treatment. Adapted from Lundgren et al.[4]
[a]Rate per 100 person-years.
[b]Risk calculated using information from the Framingham Heart Study.

antiretroviral therapy, with the effect being statistically significant in nearly all subgroups examined (Table 1).

Safety has been an issue in the debate over when to initiate antiretroviral therapy. In START, immediate and deferred therapy had similar safety profiles: symptomatic grade 4 adverse events occurred in 73 participants each in the groups that received immediate therapy and deferred therapy, unscheduled hospitalizations occurred in 262 and 287 participants, respectively, and the rate of bacterial infections was lower in the group that received immediate therapy. Of note, the antiretroviral regimens used in the trial tended to be older regimens with relatively little use of integrase strand transfer inhibitors and may therefore have been associated with more frequent adverse events.

The TEMPRANO trial examined early antiretroviral therapy and isoniazid preventive treatment in African individuals with CD4+ counts below 800/μL who did not meet then-current World Health Organization guidelines for antiretroviral therapy.[5] A total of 2056 participants were randomly assigned to receive deferred or immediate antiretroviral treatment with or without isoniazid. Overall, 41% of participants had CD4+ cell counts of 500/μL or higher. As shown in Figure 2, risk of death or severe HIV-related illness, the primary end point, was reduced with early antiretroviral therapy with or without isoniazid preventive treatment among those with CD4+ cell counts of 500/μL or higher.

The benefits of immediate antiretroviral therapy have now been demonstrated in large, randomized, international trials. The data supporting a benefit to personal health are now as strong as the data supporting treatment as prevention. Country-specific and global guidelines on when to initiate antiretroviral therapy should soon be harmonized. It is sobering that only an estimated 41% of the world's 36.9 million persons with HIV infection are currently taking antiretroviral therapy.[7] A statement from the DHHS on July 28 indicated that in light of the findings of the START and TEMPRANO trials, the recommendation for initiating therapy in all patients regardless of pretreatment CD4+ cell count remains the same, with the strength of the recommendation upgraded to A1 for all HIV-infected persons.[8] Among individuals with acute HIV infection, potential benefits of immediate antiretroviral therapy include improved laboratory markers of

disease progression, reduced severity of acute infection, reduced viral replication and better preservation of immune function, reduced size of the latent viral reservoir, and reduced risk of HIV transmission with reduction in viral load. Individuals with elite control of HIV infection—those who have a high CD4+ cell count and a low or undetectable viral load without antiretroviral treatment—may also benefit from antiretroviral therapy, as they still have chronic inflammation caused by HIV infection that may increase their risk for comorbid conditions. In a recent study, after adjustment for demographic and clinical factors, individuals with elite control of HIV infection had higher rates of all-cause, cardiovascular, and psychiatric hospitalizations than persons with HIV infection controlled with antiretroviral therapy.[9]

Which Initial Antiretroviral Regimen to Use

Initial antiretroviral therapy typically consists of a 2-nRTI backbone with a third component of a nonnucleoside analogue reverse transcriptase inhibitor (NNRTI), a PI, or an InSTI. Options include once-daily therapy, and different combinations are available that can help with adherence issues or insurance copays.

A number of recent trials have compared standard regimens. One of these, the AIDS Clinical Trials Group (ACTG) 5257 trial, was an open-label trial that compared ritonavir-boosted atazanavir, ritonavir-boosted darunavir, and raltegravir, each with TDF and emtricitabine in approximately 1800 individuals who were naive to antiretroviral therapy.[9] At 96 weeks, the group receiving raltegravir had superior outcomes compared with the other 2 groups, based on composite virologic and tolerability end points. Virologic failure occurred in 9% of the group receiving raltegravir, 15% of the group receiving darunavir, and 13% of the group receiving atazanavir, and tolerability failure occurred in 1%, 5%, and 14%, respectively. Improved tolerability, as well as efficacy, has contributed to the wide adoption of InSTI-based regimens.

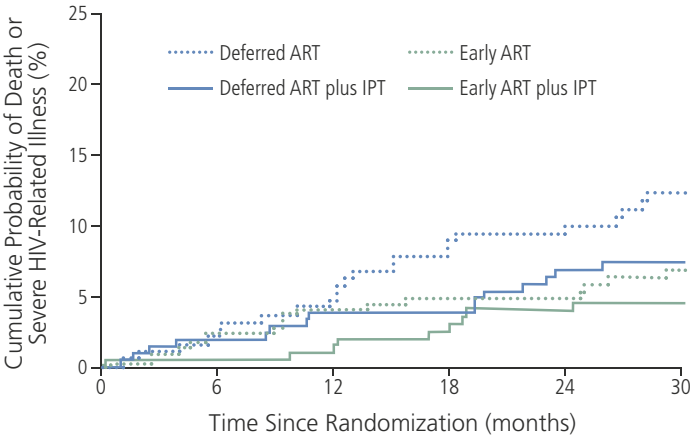

Figure 2. Risk for primary end point in individuals with a baseline CD4+ cell count of 500/μL or higher in the TEMPRANO (Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults) trial. ART indicates antiretroviral therapy; IPT, isoniazid preventive therapy. Adapted from Danel et al.[5]

Table 2. Recommended and Alternative Regimens for Initial Antiretroviral Therapy From the US Department of Health and Human Services

Recommended Regimens
InSTI-based regimens
– Dolutegravir, abacavir, and lamivudine[a] (only for individuals who test negative for the HLA-B*5701 allele)
– Dolutegravir plus TDF and emtricitabine[a]
– Cobicistat-boosted elvitegravir, TDF, and emtricitabine[a] (only for individuals with a pretreatment estimated CrCl ≥70 mL/min)
– Cobicistat-boosted elvitegravir, TAF, and emtricitabine[a]
– Raltegravir plus TDF and emtricitabine[a]
PI-based regimen
– Ritonavir-boosted darunavir plus TDF and emtricitabine[a]
Alternative Regimens
NNRTI-based regimens
– Efavirenz, TDF, and emtricitabine[a]
– Rilpivirine, TDF, and emtricitabine[a] (only for individuals with a pretreatment HIV RNA level <100,000 copies/mL and a CD4+ cell count >200 cells/μL)
PI-based regimens
– Cobicistat-boosted atazanavir plus TDF and emtricitabine[a] (only for individuals with a pretreatment estimated CrCl ≥70 mL/min)
– Ritonavir-boosted atazanavir plus TDF and emtricitabine[a]
– Cobicistat- or ritonavir-boosted darunavir plus abacavir and lamivudine[a] (only for individuals who test negative for the HLA-B*5701 allele)
– Efavirenz, TDF, and emtricitabine[a]

Abbreviations: CrCl, creatinine clearance; InSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate. Adapted from US Department of Health and Human Services.[1]

[a]Lamivudine and emtricitabine may be substituted for one another.

Current DHHS recommendations for initial antiretroviral therapy are shown in Table 2 and include 5 InSTI-based regimens. Although there are guidelines for initiation of antiretroviral therapy, choices should be tailored to the individual.

Table 3 shows some of the advantages and disadvantages of nRTIs, InSTIs, PIs, and NNRTIs in approved regimens. Of the 2 recommended nRTI backbones, TDF and emtricitabine have activity against hepatitis B virus, and some data indicate that this combination produces higher virologic response rates than abacavir and lamivudine when combined with ritonavir-boosted atazanavir or efavirenz in individuals with a baseline HIV RNA level of 100,000 copies/mL or higher. TDF and emtricitabine are available in a single-pill formulation with efavirenz, rilpivirine, or cobicistat-boosted elvitegravir, and abacavir and lamivudine are available in a single-pill formulation with dolutegravir. In 2015, a coformulation of a new form of tenofovir (tenofovir alafenamide [TAF]) with emtricitabine and cobicistat-boosted elvitegravir was approved by the US Food and Drug Administration (FDA).

Nephrotoxic effects are a concern with tenofovir use. In a recently reported retrospective analysis of the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) cohort, cumulative exposure to TDF as well as to ritonavir-boosted atazanavir or ritonavir-boosted lopinavir was associated with

Table 3. Advantages and Disadvantages of Antiretroviral Drugs

Drug Class/Name	Advantages	Disadvantages
nRTIs		
TDF and emtricitabine	Coformulated with efavirenz, rilpivirine, or cobicistat-boosted elvitegravir in single-tablet regimens Activity against hepatitis B virus Better virologic responses than abacavir and lamivudine with baseline HIV RNA level of ≥100,000 copies/mL when combined with ritonavir-boosted atazanavir or efavirenz	Nephrotoxic effects Decreases bone mineral density more than other regimens
TAF and emtricitabine	Rates of renal insufficiency and decreased bone mineral density seen with TAF are less than those observed with TDF	
Abacavir and lamivudine	Coformulated with dolutegravir in a single-tablet regimen	Cardiovascular risk in some studies Hypersensitivity in individuals who test positive for the HLA-B*5701 allele
InSTIs		
Dolutegravir	Once-daily dosing May have a higher barrier to resistance than elvitegravir or raltegravir Coformulated with abacavir and lamivudine No food requirement No interactions with cytochrome P450 3A4	Inhibits renal tubular secretion of creatinine and can increase serum creatinine without affecting glomerular function
Cobicistat-boosted elvitegravir	Coformulated as a single-tablet regimen with TDF or TAF and emtricitabine Once-daily dosing	Cobicistat inhibits active tubular secretion of creatinine and can increase serum creatinine without affecting glomerular function Drug-drug interactions
Raltegravir	Compared with other InSTIs, has longest postmarketing experience No food requirement No interactions with cytochrome P450 3A4	Twice-daily dosing May have a lower genetic barrier to resistance than regimens that contain boosted PIs or dolutegravir
PIs		
Ritonavir- or cobicistat-boosted atazanavir	Once-daily dosing Boosted PI with a higher barrier to resistance Atazanavir is coformulated with cobicistat	Indirect hyperbilirubinemia Food requirement Nephrolithiasis and cholelithiasis Drug-drug interactions
Ritonavir- or cobicistat-boosted darunavir	Once-daily dosing Boosted PI with a higher barrier to resistance Darunavir is coformulated with cobicistat	Food requirement Gastrointestinal adverse effects Drug-drug interactions
Ritonavir-boosted lopinavir	Only PI coformulated with ritonavir Once- or twice-daily dosing No food requirement	Requires 200 mg of ritonavir daily Possible increased risk of myocardial infarction Drug-drug interactions
NNRTIs		
Efavirenz	Once-daily dosing Coformulated with TDF and emtricitabine Long-term clinical experience Efavirenz-based regimens (except for efavirenz plus abacavir and lamivudine) have well-documented efficacy in individuals with high HIV RNA levels	Transmitted drug resistance more common than with PIs or InSTIs CNS-related adverse effects, including depression and suicidality (in some studies) Lower barrier to resistance than PIs or InSTIs Drug-drug interactions
Rilpivirine	Once-daily dosing Coformulated with TDF and emtricitabine Compared with efavirenz, fewer discontinuations for CNS-related adverse effects, fewer lipid-related effects, and fewer rashes	Not recommended for individuals with pretreatment HIV RNA levels >100,000 copies/mL or CD4+ cell counts <200/μL Transmitted drug resistance more common than with PIs or InSTIs Food requirement Drug-drug interactions

Abbreviations: CNS, central nervous system; InSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; nRTI, nucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate. Adapted from US Department of Health and Human Services.[1]

risk of chronic kidney disease, although risk decreased over time when TDF was stopped.[10] The new formulation of TAF has been associated with a lower rate of chronic kidney disease and loss of bone density when compared with TDF.[11]

Increased cardiovascular risk has been observed in some studies of abacavir and lamivudine. A recent report from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) showed an increased risk of myocardial infarction when abacavir had been recently used.[12] Individuals who test positive for the HLA-B*5701 allele have an approximately 50% risk of having a hypersensitivity reaction to abacavir.

Among InSTIs, now the most common class of drugs used with an NRTI backbone for initial antiretroviral therapy, dolutegravir and elvitegravir have the advantage of once-daily dosing, with raltegravir being dosed twice daily. Cobicistat, a boosting agent currently available in a single-tablet formulation with elvitegravir, and dolutegravir can inhibit renal tubular secretion of creatinine, resulting in elevation of serum creatinine without any effect on glomerular function. This effect should not be confused with the nephrotoxic effects observed with TDF use, for example.

PI-based regimens are now used less frequently, although cobicistat is available in coformulations with darunavir and atazanavir. NNRTI-based regimens are available in single-tablet formulations. However, efavirenz is associated with higher rates of transmitted drug resistance than PI- or InSTI-based regimens and is also associated with central nervous system–related adverse effects.

Risk of transmitted drug resistance should be considered when selecting initial antiretroviral therapy. A study sponsored by the Centers for Disease Control and Prevention assessed the prevalence of drug resistance in cases of newly diagnosed HIV infection from 2007 to 2010 in 10 surveillance areas: Chicago, Illinois; Colorado; Florida; Los Angeles, California; Louisiana; Michigan; New York; Seattle, Washington; South Carolina; and Texas.[13] Infections were classified as recent or established based on serologic techniques. Among 3904 recent cases, any transmitted drug resistance was found in 17.9%, NNRTI-associated resistance in 10.5%, nRTI-associated resistance in 7.0%, and PI-associated resistance in 4.5%. Among 11,963 established cases, any transmitted drug resistance was found in 15.5%, and NNRTI-, nRTI-, and PI-associated resistance were found in 7.3%, 6.5%, and 4.4%, respectively.

In a study that examined baseline clinical samples from studies of antiretroviral therapy–naive participants predominantly in the United States and Western Europe in 2000, 2003, and 2013, NNRTI-associated resistance increased from 1.9% to 7.8% and nRTI-associated resistance declined slightly from 2.7% to 2.2%.[14] Thus far, InSTI-associated resistance has been infrequent; in the samples from 2013, drug resistance–associated mutations were found in only 1 of 1617 samples.

Data from New York State indicate an increase in the rate of any transmitted drug resistance from 17% in 2006 to 24% in 2013.[15] Data from San Diego, California, for 1996 to 2013 indicate an overall prevalence of transmitted drug resistance of 16.2%, consisting of predominantly NNRTI-associated resistance (10.1%), with prevalence increasing over time.[16] Rates of resistance to PIs and nRTIs have remained relatively unchanged. Resistance to 2 and 3 drug classes has been seen in 4.8% and 0.9% of individuals, respectively.

Promising new antiretroviral drugs include TAF, a tenofovir prodrug associated with lower risk of bone loss and nephrotoxic effects than the current TDF formulation. As mentioned above, the first coformulation with TAF was recently approved by the FDA. Additional coformulations with TAF are likely to be approved in the near future. The investigational, once-daily, NNRTI doravirine is effective against virus with the K103N NNRTI resistance–associated mutation. A coformulation of the investigational InSTI cabotegravir and the NNRTI rilpivirine in long-acting parenteral form is currently being evaluated in clinical trials. Individuals initially receive a 3-drug combination that includes cabotegravir and rilpivirine in oral form, which is then simplified to only these 2 drugs for individuals with an undetectable viral load; those with maintained viral suppression are then randomly assigned to receive a monthly injection of these 2 drugs in parenteral form. Newer classes of antiretroviral drugs in development include the investigational attachment inhibitor fostemsavir and the investigational maturation inhibitor BMS-955176.

Monitoring of Individuals Taking Antiretroviral Therapy

DHHS recommendations for monitoring of viral load and CD4+ cell count are shown in Table 4. Viral load should be monitored at time of entry into care, 2 weeks to 4 weeks after initiation of antiretroviral therapy, and then every 4 weeks to 8 weeks until viral load is undetectable. Thereafter, monitoring is recommended every 3 months to 4 months during the first 2 years of antiretroviral therapy and then every 6 months if viral load remains consistently suppressed. However, monitoring should be conducted more frequently (ie, every 3 months) if there is a change in clinical status in individuals with maintained viral suppression (eg, new HIV clinical symptoms or treatment with systemic corticosteroids or antineoplastic therapy).

CD4+ cell count should be monitored at time of entry to care, 3 months after initiation of antiretroviral therapy, and every 3 months to 6 months during the first 2 years of therapy. In some cases, it may be helpful to measure CD4+ cell count 1 month after initiation of antiretroviral therapy, as the initial increase may be reassuring and may serve to support adherence to treatment. After the first 2 years, CD4+ cell count can be measured every 12 months in virologically suppressed individuals with counts of 300/μL to 500/μL. A relatively new recommendation is that measuring of CD4+ cell count is optional for individuals with consistent virologic suppression after 2 years of antiretroviral therapy and with CD4+ cell counts greater than 500/μL. With reassurance and education, patients have been generally accepting of this approach.

Table 4. Recommendations on the Frequency of Viral Load and CD4+ Cell Count Monitoring

Clinical Scenario	Viral Load Monitoring	CD4+ Cell Count Monitoring
Before initiation of antiretroviral therapy	At time of entry into care	At time of entry into care
After initiation of antiretroviral therapy	After 2-4 wk of therapy; every 4-8 wk until viral load is undetectable	3 mo after initiation of therapy
During the first 2 years of antiretroviral therapy	Every 3-4 mo	Every 3-6 mo
After 2 years of antiretroviral therapy, consistently virologically suppressed, with CD4+ cell count of 300/µL-500/µL	Every 6 mo	Every 12 mo
After 2 years of antiretroviral therapy, consistently virologically suppressed, CD4+ cell count of >500/µL	Every 6 mo	Optional
Change in clinical status (eg, new HIV clinical symptom or initiation of treatment with interferon alfa, chronic systemic corticosteroids, or antineoplastic therapy)	Every 3 mo	Perform CD4+ cell count and repeat as clinically indicated

Adapted from US Department of Health and Human Services.[1]

There are a number of important points to remember when monitoring viral load and CD4+ cell count. The DHHS guidelines use an HIV RNA of less than 200 copies/mL to indicate virologic response; virologic failure is a confirmed HIV RNA level greater than 200 copies/mL. The significance of low-level viremia (HIV RNA level <200 copies/mL but quantifiable) is unclear, with some studies demonstrating risk of virologic failure and others not finding such risk. From a practical standpoint, a detectable HIV RNA level of less than 200 copies/mL should not prompt a change in antiretroviral regimen. Blips under this threshold may represent transient viremia, and such increases can be used to discuss with individuals the importance of adherence to antiretroviral treatment without raising concern about clinical implications. Also, there is substantial laboratory variation in HIV RNA levels—the minimum fold change that should be considered clinically significant is 3 or 0.5 $\log_{10}$ (eg, a change in HIV RNA level from 40,000 copies/mL to 20,000 copies/mL is not clinically significant).

With regard to measurement of CD4+ cell count, counts vary by time of day. In one study, CD4+ cell count was 59/µL higher at 10:00 PM than at 8:00 AM. Variation in CD4+ cell count is also observed between and likely within laboratories. CD4+ cell count may increase by 2-fold after a splenectomy, with such an increase representing a lack of improvement in immune function. Lower CD4+ cell count despite viral suppression has been associated with older age and with lower counts at the time of initiation of antiretroviral therapy. Individuals taking suppressive antiretroviral therapy who do not develop high CD4+ cell counts can be reassured that disease progression is much less likely than for those with similar CD4+ cell counts who are not taking antiretroviral therapy. In addition, whereas HIV infection results in a reduced number and percentage of CD4+ cells, factors that cause a more global lymphocytopenia can result in a lower number of CD4+ cells without affecting percentage (eg, therapy with interferon alfa, chemotherapy, acute HIV infection).

In addition to monitoring of viral load and CD4+ cell count, primary care and comorbidity management should address the frequency and timing of patient follow-up. Factors that must also be taken into account include depression, bipolar disorder or other mental illness, alcohol use, tobacco use, recreational drug use, hepatitis B virus infection, hepatitis C virus infection, human papillomavirus infection, heart disease, hyperlipidemia, diabetes, hypertension, and aging.

Summary

Antiretroviral therapy is recommended for all persons living with HIV infection. Data from the START trial should remove any remaining doubt about the remarkable benefits of antiretroviral therapy for all HIV-infected individuals. The choice of antiretroviral regimen should be based on the results of these randomized clinical trials and on patient-specific factors. Recent guidelines suggest that monitoring may occur less frequently for individuals who respond well to treatment.

Presented by Dr Johnson in July 2015. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Johnson in January 2016.

Financial affiliations in the past 12 months: Dr Johnson has served as a consultant to ViiV Healthcare and has received payment for development of educational presentations from Clinical Care Options.

References

1. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed on January 21, 2016.
2. Gunthard HF, Aberg JA, Eron JJ, et al. Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society–USA panel. *JAMA*. 2014;312(4):410-425.
3. European AIDS Clinical Society. European guidelines for clinical management and treatment of HIV-infected adults in Europe. http://www.eacsociety.org/files/guidelines-7.1-english.pdf. Accessed on January 21, 2016.
4. Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV Infection. *N Engl J Med*. 2015;373(9):795-807.

5. Danel C, Moh R, Gabillard D, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med.* 2015; 373(9):808-822.
6. National Institutes of Health. Starting antiretroviral treatment early improves outcomes for HIV-infected individuals. http://www.nih.gov/news-events/news-releases/starting-antiretroviral-treatment-early-improves-outcomes-hiv-infected-individuals. Accessed on January 21, 2016.
7. UNAIDS. Fact sheet 2015. http://www.unaids.org/en/resources/campaigns/HowAIDSchangedeverything/factsheet. Accessed on January 28, 2016.
8. Department of Health and Human Services. Statement by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents regarding results from the START and TEMPRANO trials. https://aidsinfo.nih.gov/news/1592/statement-from-adult-arv-guideline-panel-start-and-temprano-trials. Accessed on January 21, 2016.
9. Lennox JL, Landovitz RJ, Ribaudo HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naive volunteers infected with HIV-1: a randomized, controlled equivalence trial. *Ann Intern Med.* 2014;161(7):461-471.
10. Mocroft A, Lundberg GD, Ross M, et al. Exposure to antiretrovirals and development of chronic kidney disease-D:A:D Study Group [Abstract 142]. Conference on Retroviruses and Opportunistic Infections. February 23-26, 2015; Seattle, Washington.
11. Sax PE, Saag MS, Yin MT, et al. Renal and bone safety of tenofovir alafenamide vs tenofovir disoproxil fumarate [CROI Abstract 143LB]. In Special Issue: Abstracts From the 2015 Conference on Retroviruses and Opportunistic Infections. *Top Antivir Med.* 2015; 23(e-1):58.
12. Palella FJ, Althoff KN, Moore R, et al. Abacavir use and risk for myocardial infarction in the NA-ACCORD [Abstract 749LB]. Conference on Retroviruses and Opportunistic Infections. February 23-26, 2015; Seattle, Washington.
13. Kim D, Ziebell R, Saduvala KR, et al. Trend in transmitted HIV-1 antiretroviral drug resistance-associated mutations, 10 HIV surveillance areas, United States, 2007-2010. [Abstract 149]. Conference on Retroviruses and Opportunistic Infections. March 3-6, 2013; Atlanta, Georgia.
14. Margot NA, Martin R, Miller MD, Callebaut C. Drug resistance mutations in treatment-naive HIV-infected patients 2000-2013. [Abstract 578]. Conference on Retroviruses and Opportunistic Infections. March 3-6, 2014; Boston, Massachusetts.
15. Wang Z, Walits E, Gordon DE, et al. Transmitted drug resistance and time of HIV infection, New York State, 2006-2013. [Abstract 599]. Conference on Retroviruses and Opportunistic Infections. February 23-26, 2015; Seattle, Washington.
16. Panichsillapakit T, Smith DM, Wertheim J et al. Transmitted HIV drug resistance among early infected persons in San Diego, California. [Abstract 600]. Conference on Retroviruses and Opportunistic Infections. February 23-26, 2015; Seattle, Washington.

Top Antivir Med. 2016;23(5):161-167.