



Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

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Initiation of Antiretroviral Therapy (Last updated October 17, 2017; last reviewed October 17, 2017)

Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all individuals with HIV, regardless of CD4 T lymphocyte cell count, to reduce the morbidity and mortality associated with HIV infection (**AI**).
- ART is also recommended for individuals with HIV to prevent HIV transmission (**AI**).
- When initiating ART, it is important to educate patients regarding the benefits and considerations of ART, and to address strategies to optimize adherence. On a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors, but therapy should be initiated as soon as possible.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Introduction

Without antiretroviral therapy (ART), most individuals with HIV will eventually develop progressive immunodeficiency marked by CD4 T lymphocyte (CD4) cell depletion and leading to AIDS-defining illnesses and premature death. The primary goal of ART is to prevent HIV-associated morbidity and mortality. This goal is best accomplished by using effective ART to maximally inhibit HIV replication to sustain plasma HIV-1 RNA (viral load) below limits of quantification by commercially available assays. Durable viral suppression improves immune function and overall quality of life, lowers the risk of both AIDS-defining and non-AIDS-defining complications, and prolongs life.

Furthermore, high plasma HIV-1 RNA is a major risk factor for HIV transmission; effective ART can reduce both viremia and transmission of HIV to sexual partners.^{1,2} Modelling studies suggest that expanded use of ART may lower incidence and, eventually, prevalence of HIV on a community or population level.³ Thus, a secondary goal of ART is to reduce the risk of HIV transmission.

Historically, individuals with HIV have had low CD4 counts at presentation to care.⁴ However, there have been concerted efforts to increase testing of at-risk individuals and to link individuals with HIV to medical care before they have advanced HIV disease. Deferring ART until CD4 counts decline puts individuals with HIV at risk of both AIDS-defining and certain serious non-AIDS conditions. Furthermore, the magnitude of CD4 recovery is directly correlated with CD4 count at ART initiation. Consequently, many individuals who start treatment with CD4 counts <350 cells/mm³ never achieve CD4 counts >500 cells/mm³ after up to 10 years on ART^{5,6} and have a shorter life expectancy than those initiating therapy at higher CD4 count thresholds.⁵⁻⁷

Two large, randomized controlled trials that addressed the optimal time to initiate ART—START⁸ and TEMPRANO⁹—demonstrated approximately a 50% reduction in morbidity and mortality among individuals with HIV who had CD4 counts >500 cells/mm³ and who were randomized to receive ART immediately versus delaying initiation of ART (described in more detail below). The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) therefore recommends immediate initiation of ART for all people living with HIV, regardless of CD4 count (**AI**). Prompt initiation of ART is particularly important for patients with certain clinical conditions, as discussed below.

The decision to initiate ART should always include consideration of a patient's comorbid conditions and his or her willingness and readiness to initiate therapy. Thus, on a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors; however, therapy should be initiated as soon as possible.

Panel's Recommendations

ART is recommended for all individuals with HIV, regardless of CD4 cell count, to reduce the morbidity and

mortality associated with HIV infection (AI). ART is also recommended for individuals with HIV to prevent HIV transmission (AI). When initiating ART, it is important to educate patients about the benefits of ART, and to address barriers to adherence and recommend strategies to optimize adherence. On a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors; however, therapy should be initiated as soon as possible. Patients should also understand that currently available ART does not cure HIV. To improve and maintain immunologic function and maintain viral suppression, ART should be continued indefinitely.

While ART is recommended for all patients, the following conditions increase the urgency to initiate therapy:

- Pregnancy (refer to the [Perinatal Guidelines](#) for more detailed recommendations on the management of pregnant women with HIV)¹⁰
- AIDS-defining conditions, including HIV-associated dementia (HAD) and AIDS-associated malignancies
- Acute opportunistic infections (OIs) (see discussion below)
- Lower CD4 counts (e.g., <200 cells/mm³)
- HIV-associated nephropathy (HIVAN)
- Acute/early infection (see discussion in the [Acute/Early Infection](#) section)
- HIV/hepatitis B virus coinfection
- HIV/hepatitis C virus coinfection

Acute Opportunistic Infections and Malignancies

In patients who have AIDS-associated opportunistic diseases for which there is no effective therapy (e.g., cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy), improvement of immune function with ART may improve disease outcomes, thus ART should be started as soon as possible. For patients with mild to moderate cutaneous Kaposi's sarcoma (KS), prompt initiation of ART alone without chemotherapy has been associated with improvement of the KS lesions, even though initial transient progression of KS lesions as a manifestation of immune reconstitution inflammatory syndrome (IRIS) can also occur.¹¹ Similarly, although an IRIS-like presentation of non-Hodgkin's lymphoma after initiation of ART has been described,¹² greater ART-mediated viral suppression is also associated with longer survival among individuals undergoing treatment for AIDS lymphoma.¹³ Drug interactions should be considered when selecting ART given the potential for significant interactions between chemotherapeutic agents and some antiretroviral drugs (particularly some non-nucleoside reverse transcriptase inhibitors [NNRTIs] and ritonavir- or cobicistat-boosted regimens). However, a diagnosis of malignancy should not delay initiation of ART nor should initiation of ART delay treatment for the malignancy.

In the setting of some OIs, such as cryptococcal and tuberculous meningitis, for which immediate ART may increase the risk of serious IRIS, a short delay before initiating ART may be warranted.¹⁴⁻¹⁷ When ART is initiated in a patient with an intracranial infection, the patient should be closely monitored for signs and symptoms associated with IRIS. In the setting of other OIs, such as *Pneumocystis jirovecii* pneumonia, early initiation of ART is associated with increased survival;¹⁸ therefore, ART should not be delayed.

In patients who have active non-meningeal tuberculosis, initiating ART during treatment for tuberculosis confers a significant survival advantage;¹⁹⁻²³ therefore, ART should be initiated as recommended in [Mycobacterium Tuberculosis Disease with HIV Coinfection](#).

Clinicians should refer to the [Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents](#)¹¹ for more detailed discussion on when to initiate ART in the setting of a specific OI.

The Need for Early Diagnosis of HIV

Fundamental to the earlier initiation of ART recommended in these guidelines is the assumption that HIV will be diagnosed early in the course of the disease. Unfortunately, in some patients, HIV infection is not diagnosed until the later stages of the disease. Despite the recommendations for routine, opt-out HIV screening in the health care setting regardless of perceptions about a patient's risk of infection²⁴ and the gradual increase in CD4 counts at first presentation to care, the median CD4 count of newly diagnosed patients remains below 350 cells/mm³.⁴ Diagnosis of HIV infection is delayed more often in nonwhites, those who use injection drugs, and older adults than in other populations, and many individuals in these groups develop AIDS-defining illnesses within 1 year of diagnosis.²⁵⁻²⁷ Therefore, to ensure that the current treatment guidelines have maximum impact, routine HIV screening per current Centers for Disease Control and Prevention recommendations is essential. It is also critical that all patients who receive an HIV diagnosis are educated about HIV disease and linked to care for full evaluation, follow-up, and management as soon as possible. Once patients are in care, focused effort is required to initiate ART and retain them in the health care system so that both the individuals with HIV and their sexual partners can fully benefit from early diagnosis and treatment (see [Adherence to the Continuum of Care](#)).

Evidence Supporting Benefits of Antiretroviral Therapy to Prevent Morbidity and Mortality

Although observational studies had been inconsistent in defining the optimal time to initiate ART,²⁸⁻³¹ randomized controlled trials now definitively demonstrate that ART should be initiated in all patients with HIV, regardless of disease stage. The urgency to initiate ART is greatest for patients at lower CD4 counts, where the absolute risk of OIs, non-AIDS morbidity, and death is highest. Randomized controlled trials have long shown that ART improves survival and delays disease progression in patients with CD4 counts <200 cells/mm³ and/or history of AIDS-defining conditions.^{18,32} Additionally, a randomized controlled trial conducted in Haiti showed that patients who started ART with CD4 counts between 200 to 350 cells/mm³ survived longer than those who deferred ART until their CD4 counts fell below 200 cells/mm³.³³ Most recently, the published START and TEMPRANO trials provide the evidence for the Panel's recommendation to initiate ART in all patients regardless of CD4 cell count **(AI)**. The results of these two studies are summarized below.

The START trial is a large, multi-national, randomized controlled clinical trial designed to evaluate the role of early ART in asymptomatic patients with HIV in reducing a composite clinical endpoint of AIDS-defining illnesses, serious non-AIDS events, or death. In this study, ART-naïve adults (aged >18 years) with CD4 counts >500 cells/mm³ were randomized to initiate ART soon after randomization (immediate-initiation arm) or to wait to initiate ART until their CD4 counts declined to <350 cells/mm³ or until they developed a clinical indication for therapy (deferred-initiation arm). The study enrolled 4,685 participants, with a mean follow-up of 3 years. When the randomized arms of the study were closed, the primary endpoint of serious AIDS or non-AIDS events was reported in 42 participants (1.8%, or 0.60 events/100 person-years) in the immediate ART arm and 96 participants (4.1%, or 1.38 events/100 person-years) in the deferred ART arm (hazard ratio [HR] 0.43, favoring early ART [95% confidence interval (CI), 0.30–0.62, $P < .001$]). The most common clinical events reported were tuberculosis and AIDS and non-AIDS malignancies. The majority (59%) of clinical events in the deferred ART arm occurred in participants whose CD4 counts were still above 500 cells/mm³, evidence for a benefit of immediate ART even before CD4 count declines below this threshold. Furthermore, the benefit of immediate ART was evident across all participant subgroups examined, including men and women, older and younger participants, individuals with high and low plasma HIV RNA levels, and participants living in high-income and low/middle-income countries. Although START was not sufficiently powered to examine the benefit of immediate ART for each category of clinical events, the benefit of immediate ART appeared to be particularly strong for AIDS events (HR 0.28, [95% CI, 0.15–0.50, $P < .001$]), tuberculosis (HR 0.29, [95% CI, 0.12–0.73, $P = .008$]), and malignancies (HR 0.36, [95% CI, 0.19 to 0.66; $P = .001$]). Importantly, immediate ART also significantly reduced the rate of pooled serious non-AIDS events (HR 0.61, [95% CI, 0.38–0.97, $P = 0.04$]).⁸

The TEMPRANO ANRS 12136 study was a randomized controlled trial conducted in Cote d'Ivoire. Using a two-by-two factorial design, participants with HIV who had CD4 counts <800 cells/mm³ were randomized

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to either immediate ART or deferred ART (based on the national guidelines criteria for starting treatment); half of the participants in each group received isoniazid for prevention of tuberculosis for 6 months and half did not. The primary study endpoint was a combination of all-cause deaths, AIDS diseases, non-AIDS malignancies, and non-AIDS invasive bacterial diseases. More than 2,000 participants enrolled in the trial, with a median follow-up of 30 months. Among the 849 participants who had baseline CD4 counts >500 cells/mm³, 68 primary outcome events were reported in 61 patients. The risk of primary events was lower with immediate ART than with deferred ART, with a hazard ratio of 0.56 in favor of early ART (CI, 0.33–0.94). On the basis of these results, the study team concluded that early ART is beneficial in reducing the rate of these clinical events.⁹

The TEMPRANO and START trials had very similar estimates of the protective effect of immediate ART among individuals with HIV who had CD4 counts >500 cells/mm³, further strengthening the Panel's recommendation that ART be initiated in all patients regardless of CD4 cell count.

Theoretical Continued Benefit of Early Antiretroviral Therapy Initiation Long After Viral Suppression is Achieved

While the START and TEMPRANO studies demonstrated a clear benefit of immediate ART initiation in individuals with CD4 cell counts >500 cells/mm³, it is plausible that the benefits of early ART initiation continue long after viral suppression is achieved. As detailed in the [Poor CD4 Cell Recovery and Persistent Inflammation](#) section, persistently low CD4 counts and abnormally high levels of immune activation and inflammation despite suppressive ART predict an increased risk of not only AIDS events, but also non-AIDS events including kidney disease, liver disease, cardiovascular disease, neurologic complications, and malignancies. Earlier ART initiation appears to increase the probability of restoring normal CD4 counts, a normal CD4/CD8 ratio, and lower levels of immune activation and inflammation.^{34–39} Individuals initiating ART very early (i.e., during the first 6 months after infection) also appear to achieve lower immune activation levels and better immune function (as assessed by vaccine responsiveness) during ART-mediated viral suppression than those who delay therapy for a few years or more.^{40–42} Thus, while these questions have yet to be addressed in definitive randomized controlled trials, earlier ART initiation may result in less residual immune dysfunction during treatment, which theoretically may result in reduced risk of disease for decades to come.

Evidence Supporting the Use of Antiretroviral Therapy to Prevent HIV Transmission

Prevention of Sexual Transmission

A number of investigations, including biological, ecological, and epidemiological studies and one randomized clinical trial, provide strong evidence that treatment of individuals with HIV can significantly reduce sexual transmission of HIV. Lower plasma HIV RNA levels are associated with decreases in the concentration of the virus in genital secretions.^{43,44} Studies of HIV-serodiscordant heterosexual couples have demonstrated a relationship between level of plasma viremia and risk of HIV transmission—when plasma HIV RNA levels are lower, transmission events are less common.^{1,2}

Most significantly, the multi-continental HPTN 052 trial enrolled 1,763 HIV-serodiscordant couples in which the partner with HIV was ART naive with a CD4 count of 350 to 550 cells/mm³ at enrollment to compare the effect of immediate ART versus delayed therapy (not started until CD4 count <250 cells/mm³) on HIV transmission to the partner who did not have HIV.⁴⁵ At study entry, 97% of the participants reported to be in a heterosexual monogamous relationship. All study participants were counseled on behavioral modification and condom use. The interim results reported 28 linked HIV transmission events during the study period, with only one event in the early therapy arm. This 96% reduction in transmission associated with early ART was statistically significant (HR 0.04; 95% CI, 0.01–0.27; *P* < 0.001). The final results of this study showed a sustained 93% reduction of HIV transmission within couples when the partner with HIV was taking ART as prescribed and viral load was suppressed.² Notably, there were only eight cases of HIV transmission within couples after the partner with HIV started ART; four transmissions occurred before the partner with HIV

was virologically suppressed and four other transmissions occurred during virologic failure. These results provide evidence that suppressive ART is more effective at preventing transmission of HIV than all other behavioral and biomedical prevention interventions studied. This study, as well as other observational studies and modeling analyses showing a decreased rate of HIV transmission among serodiscordant heterosexual couples following the introduction of ART, demonstrate that suppression of viremia in ART-adherent patients with no concomitant sexually transmitted infections (STIs) substantially reduces the risk of HIV transmission.^{3,46-49} HPTN 052 was conducted in heterosexual couples and not in populations at risk of HIV transmission via male-to-male sexual contact or needle sharing. In addition, in this clinical trial, adherence to ART was excellent. However, the prevention benefits of effective ART observed in HPTN 052 can reasonably be presumed to apply broadly. Therefore, the Panel recommends that ART be offered to individuals who are at risk of transmitting HIV to sexual partners (**AI**). Clinicians should discuss with patients the potential individual and public health benefits of therapy and the need for adherence to the prescribed regimen. Clinicians should also stress that ART is not a substitute for condom use and behavioral modification and that ART does not protect against other STIs.

Prevention of Perinatal Transmission

As noted above, effective ART reduces transmission of HIV. The most dramatic and well-established example of this effect is the use of ART in pregnant women to prevent perinatal transmission of HIV. Effective suppression of HIV replication is a key determinant in reducing perinatal transmission. In the setting of maternal viral load suppressed to <50 copies/mL near delivery, use of combination ART during pregnancy has reduced the rate of perinatal transmission of HIV from approximately 20% to 30% to 0.1% to 0.5%.^{50,51} ART is thus recommended for all pregnant women with HIV, for both maternal health and for prevention of HIV transmission to the newborn. In ART-naïve pregnant women ART should be initiated as soon as possible, with the goal of suppressing plasma viremia throughout pregnancy (see [Perinatal Guidelines](#)).

Considerations When Initiating Antiretroviral Therapy

ART regimens for treatment-naïve patients currently recommended in this guideline (see [What to Start](#)) can suppress and sustain viral loads below the level of quantification in most patients who adhere to their regimens. Most of the recommended regimens have low pill burden and are well tolerated. Once started on treatment, patients must continue ART indefinitely.

Optimizing Adherence and Retention in Care

The key to successful ART in maintaining viral suppression is adherence to the prescribed regimen. Treatment failure and resultant emergence of drug resistance mutations may compromise future treatment options. While optimizing adherence and linkage to care are critical regardless of the timing of ART initiation, the evidence thus far indicates that drug resistance occurs more frequently in individuals who initiate therapy later in the course of infection than in those who initiate ART earlier.⁵² In both the START⁸ and TEMPRANO⁹ trials, participants randomized to immediate ART achieved higher rates of viral suppression than those randomized to delayed ART. Nevertheless, it is important to discuss strategies to optimize adherence and retention in care with patients before ART initiation.

Several clinical, behavioral, and social factors have been associated with poor adherence. These factors include untreated major psychiatric disorders, neurocognitive impairment, active substance abuse, unstable housing, other unfavorable social circumstances, patient concerns about side effects, and poor adherence to clinic visits. Clinicians should identify areas where additional intervention is needed to improve adherence both before and after initiation of therapy. Some strategies to improve adherence are discussed in [Adherence to the Continuum of Care](#). Nevertheless, clinicians are often inaccurate in predicting ART adherence and ART reduces morbidity and mortality even in patients with relatively poor adherence and established drug resistance. Thus, mental illness, substance abuse, and psychosocial challenges are not reasons to withhold ART from a patient. Rather, these issues indicate the need for additional interventions to support adherence

and possibly the type of ART regimen to recommend (see [What to Start](#)).

Immediate Antiretroviral Therapy Initiation on the Day of HIV Diagnosis

Since many individuals may fail to engage in care during the delay between initial HIV diagnosis (or first clinic visit) and the time ART is prescribed, some groups have proposed rapid ART initiation on the same day of HIV diagnosis as a strategy to increase engagement in care and increase the proportion of individuals who achieve and maintain ART-mediated viral suppression. This strategy was recently tested in a randomized controlled trial of 377 individuals in South Africa who had recently received HIV diagnoses. Those randomized to receive immediate ART on the day of diagnosis were significantly more likely than those randomized to usual care (three to five additional visits with adherence counseling over 2 to 4 weeks prior to ART initiation) to be virally suppressed at 10 months (64% vs. 51%).⁵³ Similar improvements in both the proportion of participants retained in care achieving viral suppression and survival at the end of 1 year were recently reported in a randomized controlled trial of same-day ART initiation conducted in Haiti.⁵⁴ While there are many differences between the health care systems, structural barriers to engagement in care, and underlying HIV and TB epidemics in South Africa and Haiti that limit the generalizability of these findings to the United States, these studies suggested that same-day initiation of ART may be feasible and could potentially improve clinical outcomes. While no randomized controlled trials have been performed in the United States, a recent pilot study of 39 individuals in San Francisco suggested that initiating ART on the same day of HIV diagnosis might modestly shorten the time to achieving viral suppression.⁵⁵ It should be emphasized, however, that ART initiation on the same day of HIV diagnosis is resource-intensive, requiring “on-call” clinicians, nurses, social workers, and laboratory staff to coordinate the patient transportation, clinical evaluation, counseling, accelerated insurance coverage, required intake laboratory testing, and systems in place to assure linkage to ongoing care. As these resources may not be available in all settings and the long-term clinical benefits of same-day ART initiation have yet to be proven in the United States, this approach remains investigational.

Considerations for Special Populations

Elite HIV Controllers

A small subset of individuals with HIV maintains plasma HIV-1 RNA levels below level of quantification for years without ART. These individuals are often referred to as “elite HIV controllers.”^{56,57} There are limited data on the role of ART in these individuals. Given the clear benefit of ART regardless of CD4 count from the START and TEMPRANO studies, delaying ART to see if a patient becomes an elite controller after initial diagnosis is strongly discouraged. Nevertheless, significant uncertainty remains about the optimal management of elite controllers who have maintained undetectable viremia in the absence of ART for years. Given that ongoing HIV replication occurs even in elite controllers, ART is clearly recommended for controllers with evidence of HIV disease progression, as defined by declining CD4 counts or development of HIV-related complications. Nonetheless, even elite controllers with normal CD4 counts also have evidence of abnormally high immune activation and surrogate markers of atherosclerosis, which may contribute to an increased risk of non-AIDS related diseases.^{56,58-60} One observational study suggests that elite controllers are hospitalized more often for cardiovascular and respiratory disease than patients from the general population and ART-treated patients.⁶¹ Moreover, elite controllers with preserved CD4 counts appear to experience a decline in immune activation after ART initiation, suggesting that treatment may be beneficial.⁶² Whether this potential immunologic benefit of ART in elite controllers outweighs potential ART toxicity and results in clinical benefit is unclear. Unfortunately, randomized controlled trials to address this question are unlikely, given the very low prevalence of elite controllers. Although the START study included a number of participants with very low viral loads and demonstrated the benefit of immediate ART regardless of the extent of viremia, the study did not include a sufficient number of controllers to definitively determine the clinical impact of ART in this specific population. Nevertheless, there is a clear theoretical rationale for prescribing ART to HIV controllers even in the absence of detectable plasma HIV RNA levels. If ART is withheld, elite controllers should be followed closely, as some may experience CD4 cell decline, loss of viral control, or complications related to HIV infection.

Adolescents with HIV

Neither the START trial nor the TEMPRANO trial included adolescents. The Panel's recommendation to initiate ART in all patients is extrapolated to adolescents based on the expectation that they will derive benefits from early ART similar to those observed in adults. Historically, compared to adults, youth have demonstrated significantly lower levels of ART adherence and viral suppression, and higher rates of viral rebound following initial viral suppression.⁶³ Because youth often face multiple psychosocial and other barriers to adherence, their ability to adhere to therapy should be carefully considered when making decisions about ART initiation. Although some adolescents may not be ready to initiate therapy, clinicians should offer ART while providing effective interventions to assess and address barriers to accepting and adhering to therapy. To optimize the benefits of ART for youth, a multidisciplinary care team should provide psychosocial and adherence support (see [Adolescents with HIV](#)).⁶⁴

Conclusion

The results of definitive randomized controlled trials support the Panel's recommendation to initiate ART to all individuals with HIV, regardless of CD4 cell count. Early diagnosis of HIV infection, followed by prompt ART initiation, has clear clinical benefits in reducing morbidity and mortality for patients with HIV and decreasing HIV transmission to their sexual partners. Although there are certain clinical and psychosocial factors that may occasionally necessitate a brief delay in ART, ART should be started as soon as possible. Clinicians should educate patients on the benefits and risks of ART and the importance of adherence.

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