

# INITIATION OF ANTIRETROVIRAL THERAPY

Updated: September 25, 2025

Reviewed: September 25, 2025

Panel's Recommendations
<ul style="list-style-type: none"><li>• The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends antiretroviral therapy (ART) for all people with HIV to reduce morbidity and mortality <b>(AI)</b> and to prevent transmission of HIV to others <b>(AI)</b>.</li><li>• The Panel recommends initiating ART immediately (or as soon as possible) after HIV diagnosis in order to increase the uptake of ART and linkage to care, decrease the time to viral suppression for individual patients, and improve the rate of virologic suppression among people with HIV <b>(AII)</b>.</li><li>• When initiating ART, people with HIV should be counseled on the benefits, <b>lifelong need, and importance of adherence to ART</b>; clinicians should also <b>identify and address barriers</b> to care engagement and <b>ART adherence (AIII)</b>.</li></ul>
<p><b>Rating of Recommendations:</b> A = Strong; B = Moderate; C = Weak</p> <p><b>Rating of Evidence:</b> 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</p>

## Introduction

The primary goals of antiretroviral therapy (ART) are to prevent HIV-associated morbidity and mortality and to prevent transmission of HIV to others. These goals are accomplished by using effective ART to achieve and maintain plasma HIV-1 RNA levels (viral load) below the quantification limits of commercially available assays. Durable viral suppression lowers the risk of both AIDS-defining and other HIV-related complications, improves immune function and overall health, and allows people with HIV to live a lifespan approaching that of people without HIV.<sup>1,2</sup> High plasma viral load is a major risk factor for HIV transmission; effective ART suppresses viremia and, consequently, substantially reduces the risk of sexual<sup>3-7</sup> and perinatal HIV transmission.<sup>8,9</sup> Modeling studies and ecological studies of populations with high ART uptake and high viral suppression rates suggest that expanded use of ART lowers the incidence of HIV and, eventually, the prevalence of HIV on a community or population level.<sup>10-12</sup>

Early clinical trials of combination ART focused on people with advanced HIV and low CD4 T lymphocyte (CD4) cell counts.<sup>13-15</sup> Consequently, treatment guidelines at that time recommended the initiation of ART based on CD4 count thresholds or the development of AIDS-defining conditions. The benefits of ART for people with high CD4 counts were unclear, along with concerns about the toxicities of some antiretroviral (ARV) drugs. However, two large randomized controlled trials, START<sup>16</sup> and TEMPRANO<sup>17</sup>, both published in 2015, addressed the optimal time to initiate ART. Both studies demonstrated reductions in morbidity and mortality among people with HIV who had CD4 counts >500 cells/mm<sup>3</sup> and who initiated ART immediately when compared with people who delayed initiation of ART.

Deferring ART until CD4 counts decline puts people with HIV at risk of both AIDS-defining conditions and certain serious non-AIDS-defining conditions. Furthermore, the magnitude of CD4 recovery is directly correlated with CD4 count at ART initiation. Consequently, some individuals who start treatment with CD4 counts <350 cells/mm<sup>3</sup> do not achieve CD4 counts >500 cells/mm<sup>3</sup> after up to

10 years on ART,<sup>18,19</sup> and they have a shorter life expectancy than those who initiated therapy at higher CD4 count thresholds.<sup>18-20</sup>

Fundamental to the recommendation for earlier initiation of ART is the assumption that HIV will be diagnosed early in the course of the disease. The Centers for Disease Control and Prevention (CDC) recommends HIV screening to be performed for all people aged 13 to 64 years, including during pregnancy, using an opt-out screening approach.<sup>21</sup> More frequent HIV screening is recommended for certain populations with higher HIV prevalence.<sup>22</sup> The U.S. Preventive Services Task Force (USPSTF) also recommends HIV testing for people aged 15 to 65 years and for all pregnant women. This recommendation has been designated a Grade A recommendation by the USPSTF, meaning that third-party payers should cover this service without cost to patients.<sup>23</sup> HIV testing should also be performed for people younger than 15 and older than 65 years of age when indicated or requested.

Unfortunately, in some individuals, the diagnosis of HIV is not made until the later stages of the disease. In a survey conducted between 2016 and 2017, it was noted that fewer than 40% of American adults had ever had an HIV test.<sup>24</sup> Delayed diagnosis of HIV has been reported more often in people who inject drugs, people who live in rural communities, older adults, and among Black and Hispanic persons.<sup>25-27</sup> Many people with HIV access health care years before their HIV diagnosis but are not offered HIV testing.<sup>28</sup>

To ensure that the current treatment guidelines have maximum impact, routine HIV screening per current CDC or USPSTF recommendations is essential.<sup>23,29</sup> Early diagnosis also has clinical and economic benefits, including prolonging life, improving the quality of life, and decreasing the costs related to the management of AIDS and its comorbidities.<sup>30,31</sup> Additionally, HIV screening is a key step in the Ending the HIV Epidemic initiative to prevent the transmission of HIV to others.<sup>32</sup> It is critical that everyone who receives an HIV diagnosis be educated about HIV disease; initiated on ART; and linked to care for full evaluation, follow-up, and management as soon as possible. In order for people with HIV and their sexual partners to fully benefit from early diagnosis, clinicians should initiate ART as soon as possible and provide support to enhance engagement in care and full ART adherence (see [Adherence to the Continuum of Care](#) and [Treatment as Prevention](#)).

## Initiating Antiretroviral Therapy

The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends ART for all people with HIV to reduce the morbidity and mortality associated with HIV infection **(AI)** and to prevent HIV transmission to sexual partners and infants **(AI)**. ART should be initiated as soon as possible after HIV diagnosis **(AII)**. Clinicians should refer to [What to Start](#) for guidance on ART regimen selection for all adults and adolescents with HIV, including those who received pre-exposure prophylaxis (PrEP) before HIV diagnosis; the [Perinatal Guidelines](#) provide guidance on ART regimen selection during pregnancy. When initiating ART, people with HIV should be counseled on the benefits, lifelong need, and importance of adherence to ART; clinicians should also identify and address barriers to care engagement and ART adherence **(AIII)**. People with HIV should also understand that the currently available ART does not cure HIV. To improve and maintain immunologic function and maintain viral suppression, ART should be continued indefinitely without interruption. Initiating ART as soon as possible is particularly important for people with AIDS-defining conditions, those with acute or recent HIV infection, and during pregnancy. Delaying therapy in these subpopulations may increase risks for morbidity, mortality, and HIV transmission. [Laboratory Testing for Initial Assessment and Monitoring of People With HIV Receiving Antiretroviral Therapy](#) provides recommendations for baseline and follow-up laboratory monitoring for people starting ART.

## Early (Acute/Recent) HIV Infection

The term “early HIV” refers to both acute and recent infection. “Acute HIV” occurs soon after transmission (onset of symptoms typically within 2–4 weeks after infection) and is characterized by the presence of HIV RNA alone or with positive p24 antigen and nonreactive or indeterminate HIV antibody results on the confirmatory immunoassay. “Recent HIV” refers to the first 6 months after infection, during which anti-HIV antibodies and HIV RNA become detectable.<sup>33,34</sup> Detailed discussion on the diagnosis of acute HIV can be found in [Early \(Acute and Recent\) HIV Infection](#).

Early HIV is considered a period of high infectivity,<sup>35</sup> and early ART substantially reduces the risk of HIV transmission.<sup>4-7</sup> Additionally, clinical trial data indicate that individuals who are treated during early HIV may experience immunologic and virologic benefits.<sup>36-41</sup> Therefore, ART should be initiated as soon as possible after a positive qualitative test result or a quantitative HIV RNA test result (**All**). Before starting ART, and without delaying its initiation, a blood sample should be sent for genotypic resistance testing (see [Drug Resistance Testing](#) and [What to Start](#)). Same-day or rapid ART initiation in people with acute HIV has been shown to be safe, acceptable, and effective.<sup>42</sup> When initiating ART, clinicians should identify and address barriers to ART adherence and engagement in care for each person with HIV (see [Adherence to the Continuum of Care](#)).

To verify the diagnosis of acute HIV, a new blood specimen should be collected for a confirmatory HIV antibody test and a quantitative plasma HIV RNA test. Given the sensitivity of current HIV RNA assays,<sup>43</sup> a positive result by quantitative or qualitative plasma HIV RNA testing in the setting of a negative or indeterminate antibody test result indicates that acute HIV infection is highly likely. If acute HIV is highly suspected, ART should be initiated without delay while awaiting confirmation of diagnosis<sup>44</sup>; if the pending test results later rule out HIV infection, then ART for the treatment of HIV should be discontinued. People who tested negative but remain at risk of sexual HIV transmission should be offered ARV PrEP per [recommendations from the CDC](#).

Some individuals with early HIV may decline ART initially. Individuals who do not begin ART immediately should be maintained in care, and every effort should be made to initiate therapy as soon as they are ready.

## Immediate Antiretroviral Therapy Initiation on the Day of HIV Diagnosis

ART initiation on the same day of HIV diagnosis in the outpatient setting may be used as a strategy to increase ART uptake and engagement in care, to accelerate the time to ART-mediated viral suppression, and, consequently, to reduce the potential for HIV transmission. Benefits of rapid ART initiation are supported by randomized controlled trials that were performed in resource-limited settings outside of the United States<sup>45-47</sup> and observational trials in the United States that included both immediate initiation of ART (on the day of diagnosis)<sup>48-50</sup> and rapid ART initiation (within days or weeks of diagnosis).<sup>50,51</sup> Two randomized trials were performed in South Africa (n = 377)<sup>45</sup> and Haiti (n = 703).<sup>46</sup> In these trials, same-day ART initiation increased the proportion of participants who had suppressed viral loads about a year after HIV diagnosis compared with those who initiated ART between 3 weeks and 3 months after diagnosis. In addition, these studies demonstrated that rapid ART initiation can be feasible and beneficial in resource-limited settings. While no randomized controlled trials have been conducted in the United States, several prospective observational studies have demonstrated the feasibility of same-day ART initiation. City-wide implementation of the San Francisco RAPID program among 225 patients who were newly diagnosed with HIV resulted in ART initiation on the day of diagnosis for more than half of the patients and a median time from ART initiation to viral suppression (defined as <200 copies/mL) of 41 days. Over a median follow-up of 1.1 years (range 0–3.9 years), 92.1% of patients achieved virologic suppression. In the RAPID

study, a substantial proportion of participants had a major substance use disorder (51.4%), a major mental health disorder (48.1%), or unstable housing (30.6%).<sup>49</sup>

It should be emphasized that ART initiation on the same day of HIV diagnosis can be resource intensive. This strategy may require additional staff, multidisciplinary coordination, provision of ART starter packs, and consolidation of “usual care” patient services (e.g., clinical evaluation, education, counseling, initiation or optimization of insurance coverage, intake laboratory testing) into a 2- or 3-hour visit.<sup>49</sup> While the infrastructure and resources necessary to implement an immediate ART program may not be available in all health care settings, facilitating rapid ART initiation may improve treatment outcomes. The Panel recommends initiating ART at the time of diagnosis (when possible) or soon afterwards to increase the uptake of ART, decrease the time required to achieve linkage to care and virologic suppression, and improve the rate of virologic suppression **(AII)**. The rating for this recommendation reflects the fact that randomized trials have only been conducted in low-resource countries, while evidence for benefit in the United States **is based** on observational studies.

## Antiretroviral Therapy for Persons With Acute Opportunistic Infections and Malignancies

Initiation of ART in the setting of an acute, AIDS-associated opportunistic infection (OI) or malignancy can improve immune function and potentially enhance treatment success for the OI. Clinicians should refer to the [Adult and Adolescent Opportunistic Infection Guidelines](#) for a more in-depth discussion on specific OIs. Below are some important factors to consider when initiating ART in these situations.

- **When no effective therapy exists for the treatment of the OI (e.g., cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy):** In these situations, ART is the only treatment that can improve immune function and clinical outcomes. ART should be initiated without delay.
- **Concerns about immune reconstitution inflammatory syndrome (IRIS):** For some OIs, such as cryptococcal and tuberculosis (TB) meningitis, immediate ART initiation may increase the risk of serious IRIS. A short delay before initiating ART may be warranted.<sup>52-55</sup> After ART initiation, the patient should be closely monitored for signs and symptoms associated with IRIS.
- **Nonmeningeal TB:** In these patients, initiating ART during treatment for TB confers a significant survival advantage<sup>56-60</sup>; therefore, ART should be initiated as recommended in [Tuberculosis/HIV Coinfection](#).
- **For people with mild to moderate cutaneous Kaposi sarcoma:** Prompt initiation of ART alone without chemotherapy has been associated with improvement of cutaneous Kaposi sarcoma lesions, even though initial transient progression of Kaposi sarcoma lesions as a manifestation of IRIS can also occur.<sup>61</sup>
- **For people with other OIs:** After starting treatment for the OI, ART should be initiated as soon as feasible to improve immune function.
- **For patients with malignancies that require chemotherapy:**
  - A diagnosis of malignancy should not delay initiation of ART, nor should initiation of ART delay treatment for the malignancy.
  - Although an IRIS-like presentation of non-Hodgkin’s lymphoma after initiation of ART has been described,<sup>62</sup> ART-mediated viral suppression is associated with longer survival among individuals undergoing treatment for AIDS-related lymphoma.<sup>63</sup>

Importantly, drug interactions should be considered when selecting ART, as there is the potential for significant interactions between some ARV drugs (particularly ritonavir- or cobicistat-boosted regimens) and drugs for treatment of OIs (particularly with rifamycins and azole antifungal drugs) and chemotherapy drugs.

## Antiretroviral Therapy Initiation in Hospitalized People With HIV

Some people receive their first HIV diagnosis while hospitalized for HIV-related or unrelated conditions.<sup>64</sup> The test-and-treat concept of initiating ART has been successful in the outpatient setting as described above; however, newly diagnosed people with HIV who are hospitalized seldom start ART before hospital discharge.<sup>65</sup> Some concerns about initiating ART during hospitalization include the potential for drug–drug interactions or ART-related adverse effects that may complicate management of the acute condition that prompted hospitalization, the risk of paradoxical or unmasking IRIS in the context of OIs, and limited HIV care experience among hospital staff. Additionally, securing ART prescription coverage for a person with newly diagnosed HIV requires a multidisciplinary approach, including coordination with social workers/case managers to navigate through some complex insurance/patient assistance programs. As a result, some clinicians prefer to leave this task to the primary HIV clinic.

Although receiving an HIV diagnosis during an acute illness can be overwhelming, several reasons make this an opportune time to initiate ART. For example, being hospitalized allows more time for the person with HIV to receive education and ask questions about HIV and treatment goals and to receive ART-related counseling. Upon patient approval, having family or caregivers participate in these discussions will allow them to assist with adherence to ART (and concomitant medications) and clinic follow-up after discharge. Administering the first doses of ART during hospitalization allows clinicians to assess ART tolerance while under observation. Using a multidisciplinary team approach (e.g., HIV specialists, pharmacists, social workers) during the hospital stay to assist with ART initiation can facilitate transition to outpatient care. Clinical pharmacists can assess for potential drug–drug and drug–nutrient interactions and provide counseling on ART and adherence. Social workers/patient navigators can assist with exploring options for outpatient ARV coverage and facilitate linkage to HIV primary care. A multicenter study that enrolled hospitalized people with HIV from 2012 to 2014 demonstrated that starting ART in hospitalized patients who had a recent history of substance use was associated with shorter time to linkage to their first HIV clinical appointment after discharge and more clinic visits in the first 12 months after ART initiation than those who were not started on ART before discharge; however, no difference was observed in the rate of viral suppression and retention in care over 12 months.<sup>66</sup>

Certain situations, such as in the setting of TB meningitis or cryptococcal meningitis, may warrant a short delay in ART initiation due to concerns of severe consequences related to paradoxical IRIS; however, in most other situations, the benefits of starting ART during hospitalization outweigh the concerns listed above. Therefore, the Panel recommends initiating ART during hospitalization whenever possible **(BIII)**.

Before starting ART, and without delaying its initiation, a blood sample should be sent for genotypic resistance testing (see [Drug Resistance Testing](#) and [What to Start](#)). If the resistance testing results are not available before hospital discharge, they should be forwarded to the outpatient HIV provider as soon as they become available. If ART is initiated before hospital discharge, clinicians should coordinate with their multidisciplinary team to ensure sufficient ART supply (e.g., at least 2–4 weeks'

supply) is available until the outpatient clinic appointment. See [Adherence to the Continuum of Care](#) for more discussions on the transition of care between different health care settings.

## Evidence Supporting the Benefits of Antiretroviral Therapy in Preventing Morbidity and Mortality

### Randomized Controlled Trials of Early Versus Deferred Antiretroviral Therapy

Two large randomized controlled trials, START and TEMPRANO, published in 2015, provided the evidence for the Panel's recommendation to initiate ART in all patients regardless of CD4 count **(AI)**. The results of these two studies are summarized below.

START was a large, multinational, randomized controlled clinical trial designed to evaluate the role of early ART initiation in asymptomatic adults with high CD4 counts in reducing AIDS-defining illnesses, serious non-AIDS events, or death. In this study, ART-naive adults (aged >18 years) with CD4 counts >500 cells/mm<sup>3</sup> were randomized to initiate ART at randomization (immediate arm) or to wait to initiate ART until their CD4 counts declined to <350 cells/mm<sup>3</sup> or until they developed a clinical indication for therapy (deferred arm).

The study enrolled 4,685 participants. Initial results were unblinded early (after a mean follow-up of 3 years) because of the superiority of the immediate ART strategy. The primary endpoint of serious AIDS or non-AIDS events was reported in 42 participants (1.8%, or 0.60 events per 100 person-years) in the immediate ART arm and 96 participants (4.1%, or 1.38 events per 100 person-years) in the deferred ART arm (hazard ratio [HR] 0.43, favoring early ART; 95% confidence interval [CI], 0.30–0.62,  $P < 0.001$ ). The majority of clinical events (59%) in the deferred ART arm occurred in participants whose CD4 counts were still above 500 cells/mm<sup>3</sup>, evidence for a benefit of initiating ART even before CD4 count declines below this threshold. Furthermore, the benefit of immediate ART was consistent across all participant subgroups, including sex, age, plasma HIV RNA levels, and country income level. The benefit appeared to be particularly strong for AIDS events (HR 0.28), TB (HR 0.29), malignancies (HR 0.36), and severe bacterial infections (HR 0.39). The benefit at lower CD4 counts was primarily a reduction in the number of AIDS events, while the benefit at higher CD4 counts was primarily a reduction in the number of serious non-AIDS events. In addition to AIDS-related events, early ART initiation also significantly reduced the rate of pooled serious non-AIDS events (HR 0.61).<sup>16,67</sup>

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/mm<sup>3</sup> and who did not meet the criteria for starting ART according to World Health Organization guidelines at that time were randomized to start ART early (upon enrollment) or defer ART based on the national guidelines criteria for starting treatment. Half of the participants in each group received isoniazid for prevention of TB 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/mm<sup>3</sup>, early ART reduced the rate of primary events compared with deferred ART, with an HR of 0.56 (95% CI, 0.33–0.94).<sup>17</sup>

The TEMPRANO and START trials had very similar estimates for the protective effect of ART among individuals with HIV who had CD4 counts >500 cells/mm<sup>3</sup>. Guidelines around the world now recommend starting ART irrespective of CD4 count at the time or soon after HIV diagnosis.

# Use of Antiretroviral Therapy to Prevent HIV Transmission

## Prevention of Sexual Transmission

A randomized clinical trial<sup>4</sup> and several large observational cohort studies<sup>5-7</sup> have provided strong evidence that achieving sustained viral suppression prevents sexual transmission of HIV. Thus, a key goal of ART is to prevent transmission of HIV to seronegative sexual partners **(AI)**. All people with HIV should be informed that maintaining a plasma HIV RNA (viral load) of <200 copies/mL (including any measurable value below this threshold value) with ART prevents sexual transmission of HIV to partners **(AII)**. People with HIV may recognize this concept as Undetectable = Untransmittable, or U=U. The results of these studies are summarized in [Antiretroviral Therapy to Prevent Sexual Transmission of HIV](#). Clinicians should also discuss with these individuals the potential harm of non-adherence to ART, including that it can lead to viremia, which may affect their own health, lead to drug resistance, and potentially transmission to sexual partners.

## Prevention of Perinatal Transmission

The first well-established example of ART reducing the risk of HIV transmission is the use of ART during pregnancy to prevent perinatal transmission of HIV. Effective suppression of HIV replication is a key determinant in reducing the risk of perinatal transmission. In the setting of maternal viral load suppressed to <50 copies/mL near delivery, the use of combination ART during pregnancy has reduced the rate of perinatal HIV transmission from approximately 20%–30% to 0.1%–0.5%.<sup>8,9</sup> ART is thus recommended during all pregnancies in the context of HIV, for both maternal health and for the 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. HIV testing should be performed upon confirmation of pregnancy, with testing repeated throughout pregnancy as needed for those at risk of HIV acquisition (see [Pregnancy and Postpartum HIV Testing and Identification of Perinatal and Postnatal HIV Exposure](#) in the [Perinatal Guidelines](#)).

## Considerations When Initiating Antiretroviral Therapy

The ART regimens that are currently recommended as initial therapy in these guidelines (see [What to Start](#)) can suppress and maintain viral loads below the level of quantification in most people who fully adhere to their regimens. Most of the recommended regimens have a low pill burden (one or two pills once daily) and are well tolerated. People with HIV should be assessed for coexisting medical conditions and medications that may influence the selection of ART regimens or require dose adjustments or additional monitoring (see [What to Start](#)). Once started on treatment, patients must continue ART indefinitely, although future switches to alternative ART regimens may occur due to adverse events, drug–drug or drug–food interactions, cost, regimen simplification, or other reasons.

## Optimizing Adherence, Antiretroviral Therapy Access, and Care Engagement

The key to successfully maintaining viral suppression is continuous access to ART and full adherence to the prescribed regimen. Lack of adherence or intermittent access to ART can result in treatment failure and the emergence of drug resistance mutations that may compromise future treatment options. While optimizing adherence and linkage to care and ensuring continuous access

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.<sup>68-70</sup> It is important to discuss strategies to optimize adherence, care engagement, and ART access with all patients.

Several clinical, behavioral, and social factors have been associated with poor adherence. These factors include untreated psychiatric disorders, neurocognitive impairment, substance use disorder, unstable housing, patient concerns about side effects, difficulty remembering, demanding or irregular daily routines, experiences of HIV-related stigma, and ongoing adjustment to HIV diagnosis. Clinicians should identify areas in which 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](#). However, mental illness, substance use disorder, 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 they may influence the ART regimen that is recommended (see [What to Start](#)).

## Considerations for Special Populations

### Elite HIV Controllers

A small subset of people with HIV maintains plasma viral load below the level of quantification for years without ART. These individuals are often referred to as elite HIV controllers.<sup>71,72</sup> **Data on the role of ART** and the optimal management of elite controllers are sparse, and clinicians should engage in shared decision-making with the elite controller.

Despite the absence of detectable viremia, ongoing HIV replication occurs even in HIV elite controllers. In addition, even with normal CD4 counts, elite controllers show evidence of abnormally high immune activation, **chronic inflammation, immune aging**, and surrogate markers of atherosclerosis, which may contribute to an increased risk of non-AIDS–related diseases.<sup>71,73-77</sup> One observational multisite study in the United States suggested that elite controllers not receiving ART are hospitalized more often for cardiovascular and psychiatric disease than well-controlled patients on ART.<sup>78</sup> **A subsequent observational study did not show an increase in the incidence of hospitalization, but the study population was younger and had a lower incidence of hepatitis C virus (HCV) coinfection than that of the previous study.**<sup>79</sup> In additional cohort studies of HIV elite controllers, **loss of viral control, older age, and HCV coinfection were independently associated with a higher incidence of non-AIDS–defining events.**<sup>79-82</sup>

Elite controllers with preserved CD4 counts appear to experience a decline in immune activation **and the size of the HIV reservoir** after ART initiation, suggesting that treatment may be beneficial.<sup>77,83</sup> Whether this potential immunologic benefit of ART in elite controllers outweighs the potential risks of ART-associated adverse effects is unclear.<sup>77</sup> Unfortunately, given the very low prevalence of elite controllers, it is unlikely that randomized controlled trials will be able to address this question.<sup>84</sup> Nevertheless, there is a clear rationale for prescribing ART to some elite controllers even in the absence of detectable plasma viral load.

**Based on discussions above, the Panel strongly recommends ART for elite controllers with evidence of HIV-related complications, declining CD4 counts, intermittent detectable viral load, or comorbidities (e.g., cardiovascular disease, cancer, hepatitis B virus/HCV coinfection), or for those who are pregnant (AIII). The Panel also recommends initiation of ART for all other HIV elite controllers (BII). If**

ART is deferred, elite controllers should be followed closely, as some may experience CD4 count decline, loss of viral control, or complications related to HIV infection.

## Adolescents and Young Adults With HIV

Neither the START trial nor the TEMPRANO trial included adolescents aged <18 years. The Panel's recommendation to initiate ART in all people with HIV is extrapolated to adolescents based on the expectation that they will derive benefits from early ART initiation similar to those observed in adults. However, adolescence is marked by socioemotional, cognitive, and developmental changes that can increase the risk of treatment nonengagement. Compared with adults, adolescents have demonstrated significantly lower levels of ART adherence and viral suppression, as well as higher rates of viral rebound following initial viral suppression.<sup>85</sup> In recent years, more adolescents have been prescribed once-daily regimens, which has increased the rate of viral suppression in this population.<sup>86</sup> Because youth often face 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 and young adults may not be immediately ready to initiate therapy, clinicians should offer ART, preferably fixed-dose, once-daily regimens with a high barrier to drug resistance, alongside effective interventions to assess and address existing and potential barriers to care and adherence. To optimize the benefits of ART for youths, multidisciplinary care teams should individualize psychosocial and adherence support to adolescents and young adults (see [Adolescents and Young Adults With HIV](#)).<sup>87</sup>

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