Initiation of Antiretroviral Therapy (Last updated December 18, 2019; last reviewed December 18, 2019)

Panel's Recommendations
• Antiretroviral therapy (ART) is recommended for all persons with HIV to reduce morbidity and mortality **(AI)** and to prevent the transmission of HIV to others **(AI)**.
• The Panel on Antiretroviral Guidelines for Adults and Adolescents 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 persons with HIV **(AII)**.
• When initiating ART, it is important to educate patients regarding the benefits of ART and to deploy strategies to optimize care engagement and treatment adherence **(AIII)**.
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

The primary goal of antiretroviral therapy (ART) is to prevent HIV-associated morbidity and mortality. This goal is accomplished by using effective ART to achieve and maintain a plasma HIV-1 RNA (viral load) below the quantification limits of 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 allows persons with HIV to live a lifespan approaching that of persons without HIV.[1]

Another goal of ART is to reduce the risk of HIV transmission to sexual partners and to infants born to persons with HIV. High plasma HIV RNA levels are a major risk factor for HIV transmission; effective ART can reduce both viremia and the risk of transmission of HIV to sexual partners[2-6] and prevent perinatal transmission.[7,8] Modelling studies and ecological studies of populations with high ART uptake and high viral suppression rates suggest that expanded use of ART may lower the incidence of HIV and, eventually, the prevalence of HIV on a community or population level.[9-11]

Two large, randomized controlled trials addressed the optimal time to initiate ART—START[12] and TEMPRANO.[13] Both studies demonstrated reductions in morbidity and mortality among individuals with HIV who had CD4 T lymphocyte (CD4) cell counts >500 cells/mm^3 and who were randomized to receive ART immediately when compared to individuals who delayed initiation of ART.

Deferring ART until CD4 counts decline puts individuals 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, many individuals who start treatment with CD4 counts <350 cells/mm^3 do not achieve CD4 counts >500 cells/mm^3 after up to 10 years on ART,[14,15] and they have a shorter life expectancy than those who initiated therapy at higher CD4 count thresholds.[14-16]

Fundamental to the recommendation for earlier initiation of ART in these guidelines is the assumption that HIV will be diagnosed early in the course of the disease. 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.[17] Evidence shows that many people with HIV access health care years before their HIV diagnosis but are not offered HIV testing despite recommendations from the Centers for Disease Control and Prevention (CDC) for routine testing for everyone aged 13 to 64 years.[18,19] There are also economic benefits to early diagnosis, including prolonging life, improving the quality of life, and decreasing the costs related to the management of AIDS and its co-morbidities.[20,21] Additionally, HIV screening is a key step in the Ending the HIV Epidemic initiative to prevent the transmission of HIV to others.[22]

Diagnosis of HIV is delayed more often in nonwhite individuals, those who inject drugs, those who live in rural communities, and older adults, and many individuals in these groups develop AIDS-defining illnesses within 1 year of diagnosis.[23-25] Therefore, to ensure that the current treatment guidelines have maximum impact, routine HIV screening per current CDC recommendations is essential. The U.S. Preventative Services Task Force recommends HIV testing for persons aged 15 to 65 years and for all pregnant individuals. HIV testing should also be performed for younger and older persons when indicated. This recommendation has been designated a Grade A recommendation by the U.S. Preventative Services Task Force, meaning that third-party payers should cover this service without cost to patients.[26] It is critical that everyone who receives an HIV diagnosis be educated about HIV disease and linked to care for full evaluation, follow-up, and management as soon as possible. In order for both individuals 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 retention in care and ART adherence (see Adherence to the Continuum of Care).

Initiating Antiretroviral Therapy

ART is recommended for all individuals 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)**. When initiating ART, it is important to educate patients about the goals and benefits of ART and to identify and address barriers to care engagement and treatment adherence **(AIII)**. 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 without interruption. Initiating ART early is particularly important for patients with AIDS-defining conditions, those with acute or recent HIV infection, and individuals who are pregnant; delaying therapy in these subpopulations has been associated with high risks of morbidity, mortality, and HIV transmission.

Immediate Antiretroviral Therapy Initiation on the Day of HIV Diagnosis

Since individuals may fail to engage in care between the 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 ART uptake and engagement in care and to accelerate the time to ART-mediated viral suppression. Rapid ART initiation also has the potential to reduce the time during which people with newly diagnosed HIV can transmit HIV. The rapid ART initiation strategy is supported by randomized controlled trials that were performed in resource-limited settings outside of the United States[27-29] and observational trials in the United States that included both immediate initiation of ART (on the day of diagnosis)[30-32] and rapid ART initiation (within days or weeks of diagnosis).[32,33] The results from some of these studies are discussed below.

A randomized controlled trial conducted in South Africa enrolled 377 individuals who had recently received HIV diagnoses (median CD4 count was 210 cells/mm^3). Participants were randomized to receive ART on the day of diagnosis or to receive the usual care (three to five additional visits over 2–4 weeks before ART initiation). Those who received immediate ART were significantly more likely to be virally suppressed at 10 months (64% vs. 51% of patients achieved viral suppression, respectively).[27] In another randomized controlled trial conducted in Haiti, a higher proportion of participants who were randomized to receive same-day ART initiation were retained in care and had viral suppression at the end of 1 year than those who initiated ART at the standard time (3 weeks after HIV testing); survival was also higher in the same-day ART initiation group.[28] A novel randomized controlled trial in Lesotho compared same-day, home-based ART to usual care and standard clinic referral (which involved a minimum of two counseling sessions prior to ART initiation). Participants randomized to receive same-day ART initiation were significantly more likely to achieve linkage to care within 90 days after enrollment (68.6% vs. 43.1%) and virologic suppression at

approximately 12 months (50.4% vs. 34.3%).[29]

There are many differences between health care in southern Africa and Haiti and in the United States—including differences in the health care systems, structural barriers to engagement in care, underlying HIV and tuberculosis (TB) epidemics, and ART regimens used—that limit the generalizability of the findings of the results from the studies described above. These studies, however, suggest that same-day initiation of ART is feasible and could potentially improve clinical outcomes.

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 showed a median time from HIV diagnosis to ART start of 0 days (with a range of 0–56 days) and a median time from ART initiation to viral suppression (defined as <200 copies/mL) of 41 days. Over a median follow-up of 1.09 years (range 0–3.92 years), 92.1% of patients achieved virologic suppression. The RAPID study included a diverse and traditionally marginalized population, with a substantial proportion of participants having a major substance use disorder (51.4%), a major mental health disorder (48.1%), or unstable housing (30.6%).[31]

Whether rapid ART initiation improves long-term care engagement and virologic suppression is not yet known. One cohort study from France, however, found that earlier initiation of ART was negatively associated with care engagement at 1 year.[34] It should be emphasized that ART initiation on the same day of HIV diagnosis is resource intensive, and 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.[31] While the infrastructure and resources necessary to implement an immediate ART program may not be available in all health care settings, removing structural barriers in order to facilitate rapid ART initiation may improve outcomes in the United States. The Panel on Antiretroviral Guidelines for Adults and Adolescents (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 among individuals who have recently received HIV diagnoses **(AII)**. This rating for this recommendation reflects the fact that only observational trials have been conducted in the United States or other highly resourced countries, where health systems and socioeconomic contexts differ substantially from those in the countries where randomized trials were conducted.

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 is a list of important factors to consider when initiating ART in these situations.

- **When no effective therapy exists for the OI (e.g., cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy):** In these situations, ART may be the only treatment that can improve immune function and clinical outcomes. ART should be initiated without delay in these patients (see the Adult and Adolescent Opportunistic Infection Guidelines for more information).
- **Concerns regarding immune reconstitution inflammatory syndrome (IRIS):** For some OIs, such as cryptococcal and TB meningitis, immediate ART initiation may increase the risk of serious IRIS. A short delay before initiating ART may be warranted.[35-38] After ART initation, the patient should be closely monitored for signs and symptoms associated with IRIS.
- **Non-meningeal TB:** In these patients, initiating ART during treatment for TB confers a significant survival advantage;[39-43] therefore, ART should be initiated as recommended in Tuberculosis/HIV Coinfection.
- **For patients 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.[44]

- **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,[45] ART-mediated viral suppression is associated with longer survival among individuals undergoing treatment for AIDS-related lymphoma.[46]
  - Drug interactions should be considered when selecting ART, as there is the potential for significant interactions between chemotherapeutic agents and some antiretroviral drugs (particularly some ritonavir-boosted or cobicistat-boosted regimens).

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

Randomized Controlled Trials of Early vs. Deferred Antiretroviral Therapy

Two large randomized controlled trials, START and TEMPRANO, provide 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, multi-national, randomized controlled clinical trial designed to evaluate the role of early ART initiation in asymptomatic patients with HIV in reducing a composite clinical endpoint of AIDS-defining illnesses, serious non-AIDS events, or death. The study began at a time when initiating ART was not recommended until an individual's CD4 count fell below 350 cells/mm^3. In this study, ART-naive adults (aged >18 years) with CD4 counts >500 cells/mm^3 were randomized to initiate ART at randomization (early initiation arm) or to wait to initiate ART until their CD4 counts declined to <350 cells/mm^3 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. 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) who were randomized to initiate ART early, 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 most common clinical events reported were TB and malignancies (including both AIDS and non-AIDS malignancies). The majority of clinical events (59%) in the deferred ART arm occurred in participants whose CD4 counts were still above 500 cells/mm^3, evidence for a benefit of initiating ART even before CD4 count declines below this threshold. Furthermore, the benefit of early ART was consistent across all participant subgroups, including gender, age, plasma HIV RNA levels, and income level of country. Although START was not sufficiently powered to compare the benefits of early ART initiation and deferred ART initiation for each category of clinical events, 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. Importantly, early ART initiation also significantly reduced the rate of pooled serious non-AIDS events (HR 0.61).[12,47]

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^3 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^3, 68 primary outcome events were reported in 61 patients. The risk of primary events was lower among those who were randomized to start ART early than among those in the deferred arm, with an HR of 0.56 in favor of early ART (95% CI, 0.33–0.94). On the basis of these results, the study team concluded that early ART initiation is beneficial in reducing the rate of these clinical events.[13]

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^3, further supporting the Panel's recommendation that ART be initiated in all patients regardless of CD4 count.

Use of Antiretroviral Therapy to Prevent HIV Transmission

Prevention of Sexual Transmission

A randomized clinical trial[3] and several large observational cohort studies[4-6] 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 persons 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 their partners **(AII)**. Patients 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.

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% to 30% to 0.1% to 0.5%.[7,8] ART is thus recommended for all pregnant individuals with HIV, for both maternal health and for the prevention of HIV transmission to the newborn. In ART-naive pregnant individuals, ART should be initiated as soon as possible, with the goal of suppressing plasma viremia throughout pregnancy. All pregnant individuals should be tested for HIV upon confirmation of pregnancy, with testing repeated throughout pregnancy as needed for those at risk of HIV acquisition (see Maternal HIV Testing and Identification of Perinatal 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 patients who adhere to their regimens. Most of the recommended regimens have a low pill burden and are well tolerated. Once started on treatment, patients must continue ART indefinitely.

Optimizing Adherence, Antiretroviral Therapy Access, and Care Engagement

The key to successfully maintaining viral suppression is continuous access to ART and 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.[48] 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 major psychiatric disorders, neurocognitive impairment, substance use disorder, unstable housing, 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. 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 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.[49,50] There are limited data on the benefits of initiating ART in these individuals. The START and TEMPRANO studies demonstrated that initiating ART is clearly beneficial for the patient regardless of CD4 count; therefore, delaying ART to see if a patient becomes an elite controller 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 strongly recommended for controllers with evidence of HIV disease progression, which is defined by declining CD4 counts or the development of HIV-related complications **(AIII)**. Nonetheless, even elite controllers with normal CD4 counts show evidence of abnormally high immune activation and surrogate markers of atherosclerosis, which may contribute to an increased risk of non-AIDS–related diseases.[49,51-53] One observational study suggested that elite controllers are hospitalized more often for cardiovascular and respiratory disease than patients from the general population and ART-treated patients.[54] Moreover, elite controllers with preserved CD4 counts appear to experience a decline in immune activation after ART initiation, suggesting that treatment may be beneficial.[55] Whether this potential immunologic benefit of ART in elite controllers outweighs the potential risks of ART toxicity and results in clinical benefit is unclear. Unfortunately, it is unlikely that randomized controlled trials will be able to address this question, 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 initiation 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.[56] Nevertheless, there is a clear rationale for prescribing ART to elite 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 initiation that are similar to those observed in adults. 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.[57] In recent years, more adolescents have been prescribed once-daily regimens, which has increased the rate of viral suppression in this population, even though there has been no significant difference in treatment adherence.[58] 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 may not be ready to initiate therapy, clinicians should offer ART while providing effective interventions to assess and address barriers to receiving care and to adherence. To optimize the benefits of ART for youth, a multidisciplinary care team should provide psychosocial and adherence support to adolescent patients (see Adolescents and Young Adults with HIV).[59]

References:

1. Antiretroviral Therapy Cohort C. Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. *Lancet HIV*. 2017;4(8):e349-e356. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28501495.
2. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med*. 2000;342(13):921-929. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10738050.
3. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. *N Engl J Med*. 2016;375(9):830-839. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27424812.
4. Bavinton BR, Pinto AN, Phanuphak N, et al. Viral suppression and HIV transmission in serodiscordant male couples: an international, prospective, observational, cohort study. *Lancet HIV*. 2018;5(8):e438-e447. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30025681.
5. Rodger AJ, Cambiano V, Bruun T, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. *JAMA*. 2016;316(2):171-181. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27404185.
6. Rodger AJ, Cambiano V, Bruun T, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. *Lancet*. 2019;393(10189):2428-2438. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31056293.
7. Tubiana R, Le Chenadec J, Rouzioux C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis*. 2010;50(4):585-596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20070234.
8. Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS*. 2008;22(8):973-981. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18453857.
9. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet*. 2009;373(9657):48-57. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19038438.
10. Das M, Chu PL, Santos GM, et al. Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. *PLoS One*. 2010;5(6):e11068. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20548786.
11. Montaner JS, Lima VD, Harrigan PR, et al. Expansion of HAART coverage is associated with sustained decreases in HIV/AIDS morbidity, mortality and HIV transmission: the "HIV Treatment as Prevention" experience in a Canadian setting. *PLoS One*. 2014;9(2):e87872. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24533061.
12. INSIGHT START Study Group, Lundgren JD, Babiker AG, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*. 2015;373(9):795-807. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26192873.
13. TEMPRANO ANRS Study Group, Danel C, Moh R, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med*. 2015;373(9):808-822. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26193126.
14. Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis*. 2007;44(3):441-446. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17205456.
15. Palella FJJ, Armon C, Chmiel JS, et al. CD4 cell count at initiation of ART, long-term likelihood of achieving CD4 >750 cells/mm^3 and mortality risk. *J Antimicrob Chemother*. 2016;71(9):2654-2662. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27330061.
16. Samji H, Cescon A, Hogg RS, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS One*. 2013;8(12):e81355. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24367482.
17. Pitasi MA, Delaney KP, Brooks JT, DiNenno EA, Johnson SD, Prejean J. HIV Testing in 50 local jurisdictions accounting for the majority of new HIV diagnoses and seven states with disproportionate occurrence of HIV in rural areas, 2016–2017. *MMWR Morb Mortal Wkly Rep*. 2019;68(25):561-567. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31246940.

18. Wejnert C, Prejean J, Hoots B, et al. Prevalence of missed opportunities for HIV testing among persons unaware of their infection. *JAMA*. 2018;319(24):2555-2557. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29946714.
19. Hall HI, Tang T, Johnson AS, Espinoza L, Harris N, McCray E. Timing of linkage to care after HIV diagnosis and time to viral suppression. *J Acquir Immune Defic Syndr*. 2016;72(2):e57-60. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26977745.
20. Schackman BR, Metsch LR, Colfax GN, et al. The cost-effectiveness of rapid HIV testing in substance abuse treatment: results of a randomized trial. *Drug Alcohol Depend*. 2013;128(1-2):90-97. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22971593.
21. Fleishman JA, Yehia BR, Moore RD, Gebo KA, Network HIVR. The economic burden of late entry into medical care for patients with HIV infection. *Med Care.* 2010;48(12):1071-1079. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21063228.
22. Fauci AS, Redfield RR, Sigounas G, Weahkee MD, Giroir BP. Ending the HIV epidemic: a plan for the United States. *JAMA*. 2019;321(9):844-845. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30730529.
23. O'Connell S, Enkelmann J, Sadlier C, Bergin C. Late HIV presentation - missed opportunities and factors associated with a changing pattern over time. *Int J STD AIDS*. 2017;28(8):814-821. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27707954.
24. Lopes BLW, Eron JJ, Jr., Mugavero MJ, Miller WC, Napravnik S. HIV care initiation delay among rural residents in the Southeastern United States, 1996 to 2012. *J Acquir Immune Defic Syndr*. 2017;76(2):171-176. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28639994.
25. Centers for Disease Control and Prevention. HIV and older americans. 2019. Available at: https://www.cdc.gov/hiv/group/age/olderamericans/index.html.
26. Force USPST, Owens DK, Davidson KW, et al. Screening for HIV infection: U.S. Preventive Services Task Force recommendation statement. *JAMA*. 2019;321(23):2326-2336. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31184701.
27. Rosen S, Maskew M, Fox MP, et al. Initiating antiretroviral therapy for HIV at a patient's first clinic visit: The RapIT randomized controlled trial. *PLoS Med*. 2016;13(5):e1002015. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27163694.
28. Koenig SP, Dorvil N, Devieux JG, et al. Same-day HIV testing with initiation of antiretroviral therapy versus standard care for persons living with HIV: A randomized unblinded trial. *PLoS Med*. 2017;14(7):e1002357. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28742880.
29. Labhardt ND, Ringera I, Lejone TI, et al. Effect of offering same-day ART vs usual health facility referral during home-based HIV testing on linkage to care and viral suppression among adults with HIV in Lesotho: The CASCADE Randomized Clinical Trial. *JAMA*. 2018;319(11):1103-1112. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29509839.
30. Pilcher CD, Ospina-Norvell C, Dasgupta A, et al. The effect of same-day observed initiation of antiretroviral therapy on HIV viral load and treatment outcomes in a U.S. public health setting. *J Acquir Immune Defic Syndr*. 2017;74(1):44-51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27434707.
31. Coffey S, Bacchetti P, Sachdev D, et al. RAPID antiretroviral therapy: high virologic suppression rates with immediate antiretroviral therapy initiation in a vulnerable urban clinic population. *AIDS*. 2019;33(5):825-832. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30882490.
32. Colasanti J, Sumitani J, Mehta CC, et al. Implementation of a rapid entry program decreases time to viral suppression among vulnerable persons living with HIV in the Southern United States. *Open Forum Infect Dis*. 2018;5(6):ofy104. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29992172.
33. Hoenigl M, Chaillon A, Moore DJ, et al. Rapid HIV viral load suppression in those initiating antiretroviral therapy at first visit after HIV diagnosis. *Sci Rep.* 2016;6:32947. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27597312.
34. Cuzin L, Cotte L, Delpierre C, et al. Too fast to stay on track? Shorter time to first anti-retroviral regimen is not associated with better retention in care in the French Dat'AIDS cohort. *PLoS One*. 2019;14(9):e0222067. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31490985.
35. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)-associated tuberculous meningitis. *Clin Infect Dis*. 2011;52(11):1374-1383. Available at: https://www.ncbi.nlm.nih.gov/

pubmed/21596680.

36. Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med*. 2014;370(26):2487-2498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24963568.
37. Phillips P, Bonner S, Gataric N, et al. Nontuberculous mycobacterial immune reconstitution syndrome in HIV-infected patients: spectrum of disease and long-term follow-up. *Clin Infect Dis*. 2005;41(10):1483-1497. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16231262.
38. Bicanic T, Meintjes G, Rebe K, et al. Immune reconstitution inflammatory syndrome in HIV-associated cryptococcal meningitis: a prospective study. *J Acquir Immune Defic Syndr*. 2009;51(2):130-134. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19365271.
39. Velasco M, Castilla V, Sanz J, et al. Effect of simultaneous use of highly active antiretroviral therapy on survival of HIV patients with tuberculosis. *J Acquir Immune Defic Syndr*. 2009;50(2):148-152. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19131895.
40. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. 2010;362(8):697-706. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20181971.
41. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med*. 2011;365(16):1492-1501. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22010915.
42. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med*. 2011;365(16):1471-1481. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22010913.
43. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med*. 2011;365(16):1482-1491. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22010914.
44. Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. 2018. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.
45. Gopal S, Patel MR, Achenbach CJ, et al. Lymphoma immune reconstitution inflammatory syndrome in the center for AIDS research network of integrated clinical systems cohort. *Clin Infect Dis*. 2014;59(2):279-286. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24755860.
46. Gopal S, Patel MR, Yanik EL, et al. Association of early HIV viremia with mortality after HIV-associated lymphoma. *AIDS*. 2013;27(15):2365-2373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23736149.
47. O'Connor J, Vjecha MJ, Phillips AN, et al. Effect of immediate initiation of antiretroviral therapy on risk of severe bacterial infections in HIV-positive people with CD4 cell counts of more than 500 cells per muL: secondary outcome results from a randomised controlled trial. *Lancet HIV*. 2017;4(3):e105-e112. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28063815.
48. Uy J, Armon C, Buchacz K, Wood K, Brooks JT. Initiation of HAART at higher CD4 cell counts is associated with a lower frequency of antiretroviral drug resistance mutations at virologic failure. *J Acquir Immune Defic Syndr*. 2009;51(4):450-453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19474757.
49. Hunt PW, Brenchley J, Sinclair E, et al. Relationship between T cell activation and CD4+ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy. *J Infect Dis*. 2008;197(1):126-133. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18171295.
50. Choudhary SK, Vrisekoop N, Jansen CA, et al. Low immune activation despite high levels of pathogenic human immunodeficiency virus type 1 results in long-term asymptomatic disease. *J Virol*. 2007;81(16):8838-8842. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17537849.
51. Pereyra F, Lo J, Triant VA, et al. Increased coronary atherosclerosis and immune activation in HIV-1 elite controllers. *AIDS*. 2012;26(18):2409-2412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23032411.
52. Hsue PY, Hunt PW, Schnell A, et al. Role of viral replication, antiretroviral therapy, and immunodeficiency in HIV-associated atherosclerosis. *AIDS*. 2009;23(9):1059-1067. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19390417.
53. Krishnan S, Wilson EM, Sheikh V, et al. Evidence for innate immune system activation in HIV type 1-infected elite controllers. *J Infect Dis*. 2014;209(6):931-939. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24185941.
54. Crowell TA, Gebo KA, Blankson JN, et al. Hospitalization rates and reasons among HIV elite controllers and persons with medically controlled HIV infection. *J Infect Dis*. 2015;211(11):1692-1702. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25512624.
55. Hatano H, Yukl SA, Ferre AL, et al. Prospective antiretroviral treatment of asymptomatic, HIV-1 infected controllers. *PLoS*

Pathog. 2013;9(10):e1003691. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24130489.

56. Sereti I, Gulick RM, Krishnan S, et al. ART in HIV-positive persons with low pretreatment viremia: results from the START Trial. *J Acquir Immune Defic Syndr*. 2019;81(4):456-462. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31241541.
57. Ryscavage P, Anderson EJ, Sutton SH, Reddy S, Taiwo B. Clinical outcomes of adolescents and young adults in adult HIV care. *J Acquir Immune Defic Syndr*. 2011;58(2):193-197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21826014.
58. Beer L, Mattson CL, Bradley H, Shouse RL, Medical Monitoring P. Trends in ART prescription and viral suppression among HIV-positive young adults in care in the United States, 2009–2013. *J Acquir Immune Defic Syndr*. 2017;76(1):e1-e6. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28489729.
59. Rudy BJ, Murphy DA, Harris DR, Muenz L, Ellen J, Adolescent Trials Network for HIVAI. Patient-related risks for nonadherence to antiretroviral therapy among HIV-infected youth in the United States: a study of prevalence and interactions. *AIDS Patient Care STDS*. 2009;23(3):185-194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19866536.