Antiretroviral Medications and Initial Therapy

Background

The availability of highly effective antiretroviral therapy in the mid-1990s transformed HIV from a fatal infection to a manageable, chronic disease. Persons with HIV who take modern combination antiretroviral therapy significantly reduce their morbidity and mortality associated with HIV infection, as well as lower their risk of transmitting HIV to others. The United States Food and Drug Administration (FDA) has approved medications in five different classes to treat HIV infection: entry inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), and protease inhibitors (PIs). This Topic Review will summarize the mechanism of action of antiretroviral medications, indications for antiretroviral therapy, and recommended antiretroviral regimens for treatment-naïve individuals. Separate Topic Reviews will address issues related to antiretroviral therapy, including adverse effects, drug interactions, simplification or switching therapy, assessment of drug resistance, and management of virologic failure. In addition, detailed information for each antiretroviral medication and for all fixed-dose combinations is available in the Antiretroviral Medication section of this web site.
HIV Life Cycle and Antiretroviral Drug Targets

Understanding the basic HIV life cycle is the foundation for understanding the mechanism of action of the different classes of antiretroviral medications. The following discussion will focus on key HIV enzymes and relevant steps in the HIV life cycle related to HIV antiretroviral therapy. The Howard Hughes Medical Institute has produced an excellent HIV Life Cycle video (below) that summarizes the key steps in the HIV life cycle.

HIV Entry and Entry Inhibitors

HIV Envelope

The initial step in the HIV life cycle involves a complex interaction between HIV envelope spikes and host surface proteins. The HIV envelope consists of two structural components: surface envelope glycoprotein (gp120) and transmembrane envelope glycoprotein (gp41) (Figure 2).[9] The surface of HIV is studded with approximately 14 envelope spikes, with each spike consisting of a trimer of three gp120 and gp41 subunits (Figure 3).[10,11] Both gp120 and gp41 play an essential role in HIV entry into the host cell.

- **gp120**: The gp120 subunit is the component of the envelope that interacts with the host receptors and coreceptors; these interactions involve the gp120 CD4 binding site on the outermost surface of gp120 and the more internal variable 3 (V3) region of gp120. The gp120 V3 region plays a major role in determining the coreceptor tropism of HIV.
- **gp41**: The gp41 subunit consists of three domains: ectodomain (in the extracellular region), the transmembrane domain (spans the HIV membrane), and the cytoplasmic tail (inside the HIV membrane).[12,13,14] The gp41 ectodomain has several functional components that include the N-terminal hydrophobic region (functions as the fusion peptide) and the N-terminal heptad repeat region 1 (HR1) and the heptad repeat region 2 (HR2). Prior to cell binding, the HIV gp41 exist in a conformation in which the gp41 is folded back on itself in an energy loaded state.

HIV Entry

The HIV entry process involves a sequential and coordinated interaction between the virus and the host cell that includes three key steps: (1) attachment of HIV gp120 with the host CD4 receptor, (2) HIV gp120-host chemokine coreceptor binding, and (3) gp41-mediated fusion of HIV with the host surface membrane.[9,15]

- **Attachment**: After initial nonspecific interactions between HIV and the host cell, the HIV gp120 attaches to the host CD4 receptor, with binding occurring at the CD4 binding pocket on HIV gp120 and the extracellular domain 1 (D1) of the CD4 receptor.[16]
- **Coreceptor Binding**: Following the initial gp120-CD4 receptor attachment, the HIV gp120 undergoes rearrangement, with formation of a bridging sheet and repositioning of the V3 loop. This rearrangement allows the HIV gp120 V3 loop to interact with a host chemokine coreceptor (CC)—either the CCR5 or CXCR4 coreceptor (Figure 4). The HIV coreceptor binding (CCR5 or CXCR4) depends on the HIV subtype (R5 or X4), which is determined primarily by the HIV gp120 V3 region.
- **Fusion**: The HIV gp120-coreceptor interaction is believed to activate the gp41 fusion machinery, which triggers the unfolding of the gp41, with the insertion of the distal end of gp41 (gp41 fusion peptide) into the host cell membrane.[9,16] Next, each of the three gp41 then undergo a hairpin-like fold, resulting in the formation of a six-bundle helix central coil in which the HR1 and HR2 domains mesh along a series of grooves. In the process of forming this hairpin-like coiled bundle, the HIV and host membranes are pulled toward each other, generating the necessary momentum for the formation of a fusion pore and HIV-host cell membrane fusion.[9,16]

HIV Entry Inhibitors

The FDA-approved HIV entry inhibitors includes three subclasses: (1) CD4 postattachment inhibitor, (2) CCR5
coreceptor antagonists, and (3) fusion inhibitors; each one of these subclasses of entry inhibitors has one FDA-approved drug.[17,18]

- **Attachment Inhibitor**: The early interaction of HIV and the host cell involves binding of the host CD4 receptor and the binding site of the HIV gp120 envelope protein. The attachment inhibitor fostemsavir is an oral prodrug that is hydrolyzed to the active form temsavir, which binds to the HIV gp120 envelope adjacent to the gp120-CD4 binding site.[19,20] The binding of temsavir prevents the gp120 conformational change required for normal attachment to the CD4 receptor (Figure 5).[19]

- **Postattachment Inhibitor**: The early interaction of HIV and the host cell involves binding of the host CD4 receptor and the HIV gp120 envelope. The initial attachment occurs with the domain 1 region of the host CD4 receptor and the HIV gp120 binding site. The humanized monoclonal antibody ibalizumab binds to the domain 2 region of the host CD4 receptor and through steric hindrance it prevents the normal structural shifts that occur in gp120 that result in gp120-coreceptor binding (Figure 6); the net effect of ibalizumab is prevention of viral entry.[21,22] Ibalizumab does not block the initial attachment of CD4 domain 1 and HIV gp120. In addition, ibalizumab is not thought to interfere with CD4-mediated immune function since it does not interfere with CD4 binding of MCH class II molecules, which occurs at the CD4 domain 1 region.

- **CCR5 Receptor Antagonists**: The appropriate use of CCR5 antagonists depends on knowledge of the person’s HIV subtype. There are three HIV subtypes related to the host coreceptor binding: R5 HIV (binds only to the CCR5 coreceptor); X4 HIV (binds only to the CXCR4 coreceptor); dual-tropic HIV (binds to either the CCR5 or CXCR4 coreceptor).[23,24] Individuals with a mixture of R5 HIV and X4 HIV have mixed-tropic HIV. The CCR5 antagonists bind to the CCR5 coreceptor, causing a conformational change in the coreceptor that prevents HIV gp120 from binding to the CCR5 coreceptor (Figure 7).[23,25] The CCR5 antagonists do not effectively block the entry of X4, dual tropic, or mixed tropic HIV. The drug maraviroc is the only FDA-approved CCR5 antagonist, and it is recommended for use in antiretroviral treatment-experienced individuals only if they have documented pure R5 HIV. Thus, prior to starting maraviroc, an HIV coreceptor tropism assay must be performed; these assays reports provide information on the presence of R5, X4, and dual/mixed (the reports do not differentiate dual and mixed isolates).[23,25,26].

- **Fusion Inhibitor**: In the normal fusion process, the HIV gp41 heptad repeat region 2 folds back on the heptad repeat region 1, in essence zipping up the gp41. This process pulls the HIV and host membranes together and results in the fusion of the viral and host membranes. The fusion inhibitor enfuvirtide is a 36-amino-acid synthetic peptide that corresponds to a 36-amino-acid segment in the HIV gp41 heptad repeat region 2 (Figure 8); the enfuvirtide peptide binds to the heptad repeat region 1 of gp41, thus preventing the normal interaction and folding of the gp41 heptad repeat regions 1 and 2.[24,27,28] Enfuvirtide is the only FDA-approved fusion inhibitor. Unique among the antiretroviral agents, the route of enfuvirtide delivery is subcutaneous injection.

### Reverse Transcription and Reverse Transcriptase Inhibitors

#### HIV Reverse Transcriptase

The HIV reverse transcriptase enzyme is the enzyme involved in the critical HIV reverse transcription process. The HIV reverse transcriptase enzyme is a heterodimer consisting of the p66 and p51 subunits; the p66 and p51 subunit are 560 and 440 amino acids in length respectively, with the 440 amino acids of p51 overlapping with the first 440 amino acids of the p66 subunit (Figure 9).[29] The p66 subunit, which primarily has a catalytic role, consists of the polymerase and RNase H domains. Conceptually, the polymerase domain is structurally analogous to a human right hand, with specific regions corresponding to fingers, palm, and thumb. The p51 subunit functions have a structural role, and it is very closely related to, but not identical with, the polymerase domain of the p66 subunit. Each HIV-1 virion contains approximately 50 reverse transcriptase enzymes.[29]

#### Reverse Transcription
The HIV reverse transcription process is a multistep process that results in a copy of linear, double-strand HIV DNA being generated from single strand HIV RNA. Each HIV-1 virion contains two copies of plus-stranded genomic RNA. Conceptually, the key steps in reverse transcription are the conversion of single strand HIV RNA to a single strand of HIV DNA, followed by digestion of the HIV RNA, and finishing with the formation of double-strand HIV DNA from the single strand of HIV DNA. The HIV reverse transcriptase enzyme plays a central role during reverse transcription and the enzymatic activities that occur involve the polymerase and RNase H active sites, which are both located in the p66 subunit. During this process, the HIV reverse transcriptase polymerase domain functions to add host nucleotides to the expanding strand of DNA whereas the RNase H is digesting unwanted fragments of HIV RNA and HIV DNA. During this process of DNA synthesis, the HIV reverse transcriptase incorporates host nucleotides into the elongating primer strand, which is forming opposite to the HIV template strand (Figure 10).[29]

**Reverse Transcriptase Inhibitors**

The HIV reverse transcriptase inhibitors include two classes of antiretroviral medications: the nucleoside reverse transcriptase inhibitors (NRTIs) and the non-nucleoside reverse transcriptase inhibitors (NNRTIs). Mechanistically, the fundamental difference between these classes is that the NRTIs act as host nucleotide decoys and cause termination of the elongating HIV DNA chain whereas the NNRTIs bind directly to the HIV reverse transcriptase enzyme and inhibit the function of the enzyme.

- **Nucleoside Reverse Transcriptase Inhibitors**: The NRTIs require intracellular phosphorylation to obtain an active state. Once in a triphosphorylated state, the NRTIs mimic human nucleotides and can be interchangeably taken up by reverse transcriptase. Unlike the human nucleotides, the NRTI medications do not have a 3'-hydroxyl group and additional nucleotides cannot be added to the NRTI drug, hence the name chain terminator (Figure 11).

- **Non-nucleoside Reverse Transcriptase Inhibitors**: The NNRTIs bind to a hydrophobic pocket in the p66 subunit, which is close to the active polymerase site (Figure 12).[30, 31] Binding of the NNRTI causes hyperextension of the reverse transcriptase thumb region, which causes a conformational change in this polymerase domain, thereby blocking the process of DNA polymerization, a critical step in HIV reverse transcription.[30, 32] The NNRTI hydrophobic binding pocket region is predominantly lined by amino acid codons 98 to 108 and 179 to 190.[33]

**HIV Integration and Integrase Strand Transfer Inhibitors**

**HIV Integrase**

The HIV integrase enzyme is a 288 amino-acid protein that consists of three distinct structural domains: the amino (N)-terminal domain, the catalytic core domain, and the carboxy (C)-terminal domain; the catalytic core domain contains a trio of amino acids that coordinate binding with a divalent metal cofactor (either Mg2+ or Mn2+) and this region forms the active catalytic site (Figure 13).[34, 35, 36]. The HIV integrase enzyme can exist in the form of a monomer, dimer, tetramer, and possibly higher order forms, such as octamers. Each HIV-1 virion has an estimated 40 to 100 integrase enzymes.[36]

**HIV Integration**

For replications, retroviruses must integrate the linear, double-stranded HIV DNA formed by reverse transcription into the host DNA. The integration of HIV DNA into host DNA is a multistep process and the HIV enzyme integrase performs two key catalytic reactions: 3' processing of the HIV DNA and strand transfer of the HIV DNA into the host DNA.[35, 36, 37] Initially, the HIV integrase (most likely in the dimer form) binds to each end of the newly formed HIV DNA as part of an intracellular nucleoprotein particle known as the preintegration complex (Figure 14).[35] The DNA-bound integrase removes two nucleotides on the 3'-ends of the DNA, forming sticky ends that are capable of inserting into the host DNA.[37] The preintegration complex then migrates into the nucleus of the host cell through a nuclear pore. Inside the nucleus, the host protein lens epithelium-derived growth factor (LEDGF)/p75 binds to the preintegration complex and the host DNA,
serving as a tethering protein (or bridge) between the preintegration complex and the host DNA.\[35,38\] Next, the strand transfer reaction occurs when the integrase enzyme catalyzes the HIV DNA 3′-hydroxyl group attack on the host DNA and the HIV DNA is then inserted into the host DNA. In the final step, cellular enzymes perform DNA gap repair, which smooth over the HIV-host DNA junctions.\[37\]

**Integrase Strand Transfer Inhibitors**

Multiple potential sites of inhibition exist with the HIV integration process. Currently, available HIV integrase inhibitors utilize multiple mechanisms to block the integrase strand transfer step and are thus referred to as integrase strand transfer inhibitors (INSTIs) [39,40]. The INSTIs only bind to the integrase enzyme when the integrase enzyme is attached to the viral DNA.\[41\] The diketo acid group of the INSTIs binds to the magnesium ions in the active site of HIV integrase, thereby inhibiting the active site (Figure 15).\[35\] In addition, upon binding to the magnesium ions, the INSTIs displace the HIV DNA 3′-hydroxyl ends, which interrupts the integration process since the 3′-hydroxyl ends are the critical nucleophiles during the transfer of the strand of HIV DNA into the host DNA.\[41\] Further, binding of the INSTI to the integrase enzyme prevents the HIV complex from integrating into the host DNA. When the HIV integration process is blocked, the HIV DNA becomes a substrate for host repair enzymes that subsequently convert the HIV DNA complex into byproduct 2-long terminal repeat (2-LTR) circles.\[37\]

**HIV Protein Processing and HIV Protease inhibitors**

**HIV Protease**

The HIV protease enzyme is a 99-amino-acid dimer made up of two identical subunits (Figure 16). This enzyme has a key role in post-transcriptional processing of the Gag (Pr55) and Gag-Pol (Pr160) polyproteins.\[42\] The HIV protease has three major conformational forms: open, semi-open, and closed (Figure 17). The protease enzyme has an active site near the center of the heterodimer and the active site includes two opposed aspartic acid (Asp) residues. Movement from the open to closed causes the flap ends to overlap and functionally act as a molecular scissor.

**Polyprotein Processing and Maturation**

The protease-related polyprotein processing occurs in a consistent sequential pattern. The Gag polyprotein contains four structural proteins: matrix (p17), capsid (p24), nucleocapsid (p7), and p6 proteins. In addition, two spacer peptides (p2 and p1) are part of Gag. During approximately 5 to 10% of the Gag translation events, a ribosomal frameshift occurs that results in translation of the Gag-Pol polyprotein.\[43\] The Gag-Pol polyprotein includes the same structural Gag proteins, with the addition of the Pol functional enzymes (protease, reverse transcriptase, and integrase). Each virion contains approximately 5,000 Gag polyproteins.\[44\] The HIV protease initially catalyzes its own release from the Gag-Pol polyprotein strand. Once the HIV protease is untethered, it processes both the Gag-Pol and the Gag polyproteins. The HIV protease polyprotein processing of the Gag protein occurs in a predictable sequential cascade (Figure 18).\[43,45,46\] The timing of the polyprotein processing occurs late in the HIV replication cycle, typically during and shortly after the virus release from the host cell. The processing of the Gag and Gag-Pol polyproteins results in release of the matrix, capsid, nucleocapsid, p6, protease, reverse transcriptase, and integrase proteins.\[45\] The HIV protease enzyme is not involved in the processing of the gp160 envelope protein, which is the precursor glycoprotein for the gp120 and gp41 envelope glycoproteins.

**Protease Inhibitors**

The HIV protease inhibitors are structurally complex molecules that bind to the active site of HIV protease and inhibit the protease enzyme activity (Figure 19).\[42,43\] The HIV protease inhibitors disrupt the normal Gag and Gag-Pol polyprotein processing, causing arrest of the normal maturation process, which thereby prevents infection of new cells. The protease inhibitors do not have an impact on cells already infected with HIV (those with proviral DNA integrated into the host DNA).
**When to Initiate Antiretroviral Therapy**

**Recommendations for Initiation of Antiretroviral Therapy**

The Adult and Adolescent ART Guidelines recommend initiation of antiretroviral therapy for all persons with HIV to reduce morbidity and mortality associated with HIV infection and to prevent HIV transmission to others [Table]. Panel's Recommendations for Initiating Antiretroviral Therapy in Treatment-Naive Patients.[47] In addition, antiretroviral therapy should be started immediately, or as soon as possible, after the HIV diagnosis.[47]

**Data for Clinical Benefit of Antiretroviral Therapy**

The Adult and Adolescent ART Guidelines recommendation to initiate antiretroviral therapy in all persons living with HIV to reduce morbidity and mortality is based on multiple cohort studies and clinical trials, as outlined below, that have shown a clear benefit of starting antiretroviral therapy earlier in the course of HIV disease progression.

- **ART Cohort Collaboration:** The ART Cohort Collaboration (ART-CC) followed 12,574 treatment-naïve adults with HIV who started 3-drug antiretroviral therapy and investigators identified baseline CD4 cell count when starting antiretroviral therapy as the most important prognostic factor for new AIDS-defining illness or death (Figure 20).[48] Although the initial ART-CC used a CD4 count of 350 cells/mm$^3$ or greater as the highest CD4 category, follow-up analysis with this cohort further stratified the data in the higher CD4 categories and reported a higher rate of progression to AIDS and/or death in patients who deferred therapy in the CD4 count range of 251-350 cells/mm$^3$ compared with those who initiated therapy with a CD4 count between 351-500 cells/mm$^3$.[49]

- **CIPRA HT-001:** In the CIPRA HT-001 clinical trial conducted in Haiti, investigators randomized participants to start antiretroviral therapy at a CD4 count of 200-350 cells/mm$^3$, or to defer treatment until either their CD4 count decreased to less than 200 cells/mm$^3$ or they developed an AIDS-defining condition.[50] In an interim analysis of the study, participants who began antiretroviral therapy with CD4 counts of 200-350 cells/mm$^3$ had a lower mortality rate and lower incidence of tuberculosis than participants who deferred therapy (Figure 21).[50]

- **Johns Hopkins Cohort:** A study from Johns Hopkins found that among 1,173 adults with HIV treated with antiretroviral therapy, those with a baseline CD4 count less than 200 cells/mm$^3$ had a more rapid 3-year disease progression than those who had a baseline of 201 to 350 cells/mm$^3$, even when obtaining comparable durable virologic suppression (Figure 22).[51]

- **NA-ACCORD:** The North American AIDS Cohort Collaborative Collaboration on Research and Design (NA-ACCORD), an observational analysis including more than 17,000 patients, showed that adults with a CD4 count of 351 to 500 cells/mm$^3$ who deferred antiretroviral therapy until the CD4 count declined to 350 cells/mm$^3$ or lower had a 69% increased risk of death when compared with those who did not defer antiretroviral therapy.[2] In this same study, a parallel analysis involving adults with a CD4 count greater than 500 cells/mm$^3$ found that deferral of therapy until the CD4 count declined to 500 cells/mm$^3$ or lower was associated with a 94% increased risk of death when compared with earlier initiation of antiretroviral therapy.[2]

- **SMART:** The multinational Strategies for Management of Antiretroviral Therapy (SMART) trial randomized more than 5,400 participants with CD4 counts greater than 350 cells/mm$^3$ to receive continuous antiretroviral therapy or to interrupt treatment until the CD4 count decreased to less than 250 cell/mm$^3$.[52] A subgroup analysis, which involved the 249 treatment-naïve participants at enrollment, found a trend of lower risk of serious AIDS- and non-AIDS-related events in the group who initiated therapy immediately when compared with those who deferred therapy until the CD4 count decreased to less than 250 cells/mm$^3$.[52]

- **START:** The Strategic Timing of Antiretroviral Therapy (START) study was a multicenter international trial that examined the benefits and risks of initiating antiretroviral therapy in asymptomatic individuals with HIV who had a CD4 count greater than 350 cells/mm$^3$.[1] Investigators randomized
4,685 adults with HIV to one of two arms: 1) start antiretroviral therapy immediately (immediate-initiation group) or 2) defer antiretroviral therapy until the CD4 count decreased to 350 cells/mm$^3$ or development of an AIDS-related condition (or another condition) that warranted the use of antiretroviral therapy (deferred-initiation group). Comparing the immediate-initiation group with the deferred-initiation group, the hazard ratio for a serious AIDS-related event was 0.28, for a serious non-AIDS event was 0.61, and 0.58 for death from any cause (Figure 23).[1]

- **Swiss HIV Cohort Study**: In the Swiss HIV Cohort Study, investigators compared early initiation of antiretroviral therapy (adults with CD4 counts greater than 350 cells/mm$^3$) versus deferred therapy (adults monitored without therapy) and found an approximate 5-fold decrease in disease progression to AIDS in the subsequent 3-year period among those who initiated therapy (Figure 24).[53]

### Data for Antiretroviral Therapy Reducing HIV Transmission

The Adult and Adolescent ART Guidelines recommendation regarding use of antiretroviral therapy to prevent HIV transmission is based on multiple studies that indicate antiretroviral therapy dramatically lowers the risk of perinatal transmission of HIV and sexual transmission of HIV.

- **PACTG 076**: In the Pediatric AIDS Clinical Trials Group study (PACTG) 076, zidovudine given during pregnancy, labor, and to the infant for 6 weeks reduced mother-to-child transmission of HIV by nearly 70%.[54] This landmark trial established that perinatal HIV transmission could be markedly reduced with antiretroviral therapy. Multiple other studies have confirmed the overwhelming benefit of providing antiretroviral therapy to pregnant and breastfeeding women to prevent vertical transmission of HIV.

- **HPTN 052**: The most notable treatment-as-prevention trial, HPTN-052, enrolled 1,763 serodifferent (mostly heterosexual) couples from 9 countries and demonstrated that early initiation of antiretroviral therapy (prior to a decline in CD4 count or the onset of HIV-related symptoms) reduced rates of sexual transmission of HIV to the HIV-negative partner by 93% when compared with persons who deferred antiretroviral therapy.[4]

- **PARTNER-1 Study**: In the first phase of the European PARTNER (Partners of People on ART—A New Evaluation of the Risks) study, investigators at 75 sites in 14 European countries evaluated the impact of antiretroviral therapy on HIV transmission risk in 888 HIV-serodifferent couples engaging in condomless sex, including 548 heterosexual couples and 340 gay male couples.[6] The eligibility for enrollment required the partner with HIV to be taking antiretroviral therapy and have an HIV RNA level less than 200 copies/mL.[6] Enrollment took place during September 2010 to May 2014 and during this time there were zero phylogenetically linked HIV transmissions that occurred in these couples, with an estimated 58,000 condomless sex acts (22,000 in gay male couples and 36,000 in heterosexual couples).[6] There were 11 new HIV infections during the study period, but none of these were phylogenetically linked.

- **PARTNER-2 Study**: In the second phase of the European PARTNER (Partners of People on ART—A New Evaluation of the Risks) study, investigators at the same 75 sites in 14 European countries continued the PARTNER study, but additional enrollment was open only for serodifferent gay men.[55] The extended enrollment included a total of 972 serodifferent gay male couples.[55] The design to include only serodifferent gay male couples was to make up for some of the imbalance of the predominantly heterosexual serodifferent couples enrolled in the PARTNER-1 trial. As with PARTNER-1, the eligibility for enrollment required the partner with HIV to be taking antiretroviral therapy and have an HIV RNA level less than 200 copies/mL. During the study, the serodifferent gay male couples reported condomless anal sex a total of 76,088 times and there were zero phylogenetically-linked transmissions.[55] There were, however, 15 new HIV infections during the study period, but none of these were phylogenetically linked.[55]

- **Opposites Attract**: The Opposites Attract trial was conducted from 2012-2016 and enrolled 358 HIV-serodifferent gay male couples in Thailand, Brazil, and Australia.[56] Of the 358 couples that enrolled, 343 had at least one follow-up visit and 75% (258 of 343) of the HIV-positive partners had an HIV RNA level less than 200 copies/mL.[56] There were zero phylogenetically-linked cases of HIV transmission from among 12,447 sex acts that involved (1) condomless anal intercourse, (2) the partner with HIV...
taking antiretroviral therapy and having an HIV RNA less than 200 copies/mL, and (3) the partner without HIV not taking preexposure prophylaxis.\cite{56} There were three new HIV infections during the study period, but none were phylogenetically linked.\cite{56}

**Recommendations for Elite and Viremic Controllers**

**Definition of Elite and Viremic Controllers**

A small percentage of persons naturally control their HIV without medications and are considered "elite controllers" of HIV. These individuals have a unique immunologic response to HIV that results in persistent control of plasma HIV RNA levels to levels consistently below the limit of quantitation. These individuals also usually maintain long-term control of CD4 cell count levels above 500 cells/mm$^3$.\cite{57} Similarly, a larger, but still small subset of individuals with HIV, referred to as "viremic controllers", have the ability to naturally maintain plasma HIV RNA at very low, but not undetectable, levels.\cite{57} The viremic controllers also usually have high CD4 cell counts, but typically have less stable and lower CD4 cell counts than elite controllers.\cite{58}

**Management of Elite and Viremic Controllers**

The optimal antiretroviral management of elite controllers and viremic controllers has generated controversy since, without antiretroviral therapy, these individuals naturally control HIV RNA levels and theoretically would pose minimal risk of transmitting HIV to others. These individuals, however, may still have increased risk of non-AIDS-related morbidity from immune activation and a significant proportion will eventually lose their immunologic control of HIV and have disease progression.\cite{57,59,60} The Adult and Adolescent ART Guidelines make the following key recommendations for "elite controllers":\cite{47}

- Antiretroviral therapy is clearly recommended for elite controllers if they have evidence of HIV disease progression.
- The clinical benefit of antiretroviral therapy in elite controllers who do not have HIV disease progression remains uncertain.
- Elite controllers have increased immune activation and markers for increased risk of atherosclerosis.
- There is a theoretical benefit of giving antiretroviral therapy to elite controllers to reduce immune activation and potential non-AIDS morbidity.
- If antiretroviral therapy is not given to elite controllers, close follow-up should occur since some of these individuals lose their natural control of HIV.
Antiretroviral Regimens for Initial Therapy

The Adult and Adolescent ART Guidelines stratify antiretroviral regimens for initial therapy as (1) **Recommended for Most People with HIV**, (2) **Recommended in Certain Clinical Situations**, and (3) **Not Recommended as Initial Therapy**. The category **Recommended for Most People with HIV** is further sub-divided into (1) recommendations for people who do not have a history of receiving long-acting cabotegravir as HIV preexposure prophylaxis (PrEP) and (2) recommendations for people diagnosed with HIV who have a history of using long-acting cabotegravir for PrEP.[61]

### Recommended Initial Regimens for Most People with HIV

#### For People Who Have Not Received Long-Acting Cabotegravir for PrEP

The Adult and Adolescent ART Guidelines regimens listed as **Recommended Initial Regimens for Most People with HIV**, in the setting of no history of receiving long-acting cabotegravir as PrEP prior to HIV diagnosis, include an INSTI anchor drug in combination with at least one NRTI (Table 2).[61] The choice of the specific first-line antiretroviral regimen depends on multiple factors, including medical comorbidities, potential drug interactions, and patient preferences (pill burden, frequency of dosing, and food requirements. All of these regimens can be dosed once daily. Note that dolutegravir-lamivudine should not be used as initial therapy in the following three situations: (1) the baseline HIV RNA level is greater than 500,000 copies/mL, (2) the persons undergoing treatment has chronic hepatitis B virus (HBV) or the HBV status is unknown, or (3) results from the HIV genotypic resistance testing are not available at the time antiretroviral therapy is planned to start.[61] Except for the HIV RNA level restriction for dolutegravir-lamivudine, all of these regimens can be used without regard to pretreatment HIV RNA level or CD4 cell count.

#### For People Who Received Long-Acting Cabotegravir for PrEP

The Adult and Adolescent ART Guidelines give specific recommendations for initial antiretroviral therapy for individuals who are diagnosed with HIV and have a history of receiving long-acting cabotegravir for HIV PrEP. Because injectable cabotegravir, an INSTI, has a long half-life and can remain at quantifiable levels in plasma for months to years (up to 4 years for some individuals), an individual who acquires HIV infection after long-acting cabotegravir use has risk of INSTI resistance, which could affect efficacy of the dolutegravir or bictegravir-based combinations.[62] Therefore, in this scenario, the guidelines recommend one of two approaches: (1) obtain genotype drug resistance testing, including for integrase resistance, and then initiate one of the INSTI-based first-line regimens (described above as **Recommended Regimens for Most People with HIV**), or (2) obtain genotype resistance testing, including for integrase resistance, and initiate boosted darunavir (darunavir-cobicistat or darunavir plus ritonavir) with two NRTIs—tenofovir alafenamide (or tenofovir DF) plus emtricitabine (or lamivudine)—while awaiting the results. If a baseline integrase genotype does not show evidence of INSTI resistance, one can then change the boosted darunavir to a recommended INSTI, such as dolutegravir or bictegravir.

### Recommended Initial Regimens in Certain Clinical Situations

Multiple antiretroviral regimens are available that are effective and tolerable, but are considered inferior to the regimens listed above. The Adult and Adolescent ART Guidelines denotes this category as **Recommended Initial Regimens in Certain Clinical Situations** (Table 3).[61] This category also addresses regimens to consider when abacavir, tenofovir alafenamide, and tenofovir DF cannot be used or are not optimal to use, as well as addressing specific circumstances that apply to certain 2-drug regimens.[61,63,64,65]

### Antiretroviral Regimens or Components Not Recommended

The Adult and Adolescent ART Guidelines also includes a category for **Antiretroviral Regimens or Components Not Recommended as Initial Therapy** (Table 4).[61]
Special Considerations for Persons of Childbearing Potential

The Adult and Adolescent ART Guidelines has specific recommendations for Individuals trying to conceive or who cannot use effective contraception.\cite{66,67} Based on updated data, dolutegravir is now considered as a preferred in women of child-bearing age who are trying to conceive.\cite{66,67} For people trying to conceive, the recommended antiretroviral regimens consist of an anchor drug (dolutegravir, raltegravir, atazanavir boosted with ritonavir, or darunavir boosted with ritonavir) plus a dual NRTI backbone (abacavir-lamivudine, tenofovir alafenamide-emtricitabine, tenofovir DF-emtricitabine, or tenofovir DF plus lamivudine).\cite{66,67}
Choosing Specific Antiretroviral Regimen

Factors to Consider for Selecting Initial Regimen

In clinical practice, a number of specific clinical scenarios exist that may warrant consideration to avoid or using certain regimens. The following summarizes the recommendations in the Adult and Adolescent ART Guidelines.[68]

- **Pretreatment HIV RNA Level**: The following regimens should not be used with pretreatment HIV RNA levels greater than 100,000 copies/mL due to higher rates of virologic failure: rilpivirine-based regimens, abacavir-lamivudine (when used with efavirenz or ritonavir-boosted atazanavir), and raltegravir plus ritonavir-boosted darunavir. Dolutegravir-lamivudine should not be used when the pretreatment HIV RNA level is greater than 500,000 copies/mL based on limited data for the use of this regimen in persons with pretreatment HIV RNA levels greater than 500,000 copies/mL.

- **Pretreatment CD4 Cell Count**: Higher rates of virologic failure have occurred with rilpivirine-based regimens and raltegravir plus ritonavir-boosted darunavir when the pretreatment CD4 count is less than 200 cells/mm$^3$. Accordingly, these regimens should not be used in persons who have a pretreatment CD4 count less than 200 cells/mm$^3$.

- **Treatment of HIV Before Drug Resistance Results Available**: It is essential to use an antiretroviral regimen that has a high genetic barrier to resistance in the situation when treatment is initiated prior to availability of the HIV genotypic drug resistance test results. In general, NNRTI-based regimens should be avoided in this setting. The following regimens are recommended in this situation:
  - Bictegravir-tenofovir alafenamide-emtricitabine
  - Dolutegravir plus (tenofovir alafenamide or tenofovir DF) plus (emtricitabine or lamivudine)
  - Darunavir (boosted with ritonavir or cobicistat) plus (tenofovir alafenamide or tenofovir DF) plus (emtricitabine or lamivudine)

- **History of Prior Exposure to Long-Acting Cabotegravir**: If an individual diagnosed with HIV has received long-acting cabotegravir in the past, results of an integrase genotype should be available prior to initiating an INSTI-based regimen. If initiating antiretroviral therapy prior to availability of integrase genotype results, the recommended ART option is boosted darunavir plus tenofovir alafenamide (or tenofovir DF) with emtricitabine (or lamivudine).

- **Food Requirements**: The NRTI backbone combinations of abacavir-lamivudine, tenofovir DF-emtricitabine, and tenofovir alafenamide-emtricitabine can be taken with or without food. The INSTIs raltegravir and dolutegravir can be taken with or without food; the single-tablet regimens bictegravir-tenofovir alafenamide-emtricitabine, dolutegravir-abacavir-lamivudine, dolutegravir-lamivudine, and doravirine-tenofovir DF-lamivudine can also be taken with or without food. Efavirenz should be taken on an empty stomach. The following medications should be taken with food: rilpivirine, atazanavir boosted with either ritonavir or cobicistat, darunavir boosted with either ritonavir or cobicistat, elvitegravir-cobicistat-tenofovir DF-emtricitabine, and elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine.

- **Chronic Kidney Disease**: For persons who have a pretreatment estimated glomerular filtration rate (eGFR) less than 60 mL/min, any regimen containing tenofovir DF should be avoided. If the eGFR is less than 30 mL/min, any regimen containing tenofovir alafenamide-emtricitabine should be avoided.

- **Osteoporosis**: In patients with known osteoporosis, tenofovir DF or any fixed-dose combination that contains tenofovir DF should be avoided.

- **Psychiatric Illness**: Efavirenz, and possibly rilpivirine, have been associated with worsening of psychiatric symptoms, and consideration should be given to avoiding these medications in persons with psychiatric illness.

- **Hyperlipidemia**: The INSTIs bictegravir, dolutegravir, and raltegravir are considered lipid neutral. Tenofovir DF has a favorable impact on lipids. The following medications often cause dyslipidemia: ritonavir-boosted PIs, cobicistat-containing regimens, and efavirenz.

- **Concern for Excess Weight Gain**: Use of INSTIs, particularly dolutegravir plus tenofovir alafenamide-emtricitabine and bictegravir-tenofovir alafenamide-emtricitabine have been associated with
significant weight gain in some individuals after starting antiretroviral therapy. Weight gain on these regimens has disproportionately impacted women and Black and Hispanic people.

- **Dementia**: Efavirenz should be avoided in persons with dementia.
- **Cardiac QTc Interval Prolongation**: Since efavirenz, rilpivirine, and fostemsavir may prolong QTc, they should be avoided in persons taking other medications that may prolong QTc.

### Choosing the Anchor Drug in Regimen

The choice of the third drug, commonly referred to as the anchor drug, to combine with an NRTI backbone for an initial antiretroviral regimen depends on clinical, pharmacologic, and patient-level factors. In the Adult and Adolescent ART Guidelines, the Recommended Initial Regimens for Most People with HIV utilize the INSTI bictegravir or dolutegravir as the anchor drug; the recommendation to use these two INSTIs as the anchor drug is based on high efficacy, high genetic barrier to resistance, low adverse effect profile, and minimal drug interactions.[61] In previous years, the Adult and Adolescent ART Guidelines included the INSTI elvitegravir, raltegravir, protease inhibitors, and NNRTIs as the anchor drug in the recommended regimen category, but certain limitations, such as poor tolerability, restrictions for use based on CD4 cell count and/or HIV RNA level, and lower genetic barrier to resistance have relegated these anchor drugs to the alternative regimen category.

### Choice of INSTI

In the Adult and Adolescent ART Guidelines, two of the INSTIs (bictegravir and dolutegravir) are included as the anchor drug components of the Recommended Initial Regimens for Most People with HIV.[61] Note that bictegravir is available only as a fixed-dose combination. In the SPRING-2 study, once-daily dolutegravir was non-inferior to twice-daily raltegravir in treatment-naive patients with HIV infection.[69] In study 1490, initial therapy with bictegravir-tenofovir alafenamide-emtricitabine showed similar virologic responses as dolutegravir plus tenofovir alafenamide-emtricitabine.[70] Bictegravir and dolutegravir have emerged as the most attractive INSTI-based options based on strong potency, high genetic barrier to resistance, and good tolerability. Typically, for a person starting their first antiretroviral regimen, the regimen will include bictegravir or dolutegravir as the anchor drug.[61] An exception may be if the person has previously received long-acting cabotegravir as PrEP. Usage of long-acting cabotegravir prior to HIV diagnosis raises concern for INSTI resistance, which could include cross-resistance to bictegravir and dolutegravir. Therefore, if a person has received long-acting cabotegravir prior to diagnosis of HIV, an integrase genotype should be performed to confirm the efficacy of the INSTI medications prior to initiation of INSTI-based therapy.[61]

### Choice of PI

The Adult and Adolescent ART Guidelines recommend two NRTIs plus either boosted darunavir or boosted atazanavir as the only protease inhibitor-based options in the category Recommended Initial Regimens in Certain Clinical Situations.[61] In the ARTEMIS trial, initial therapy with a ritonavir-boosted darunavir regimen was superior to a lopinavir-ritonavir regimen, both in terms of virologic suppression and tolerability.[71] In the ACTG A5257 study, initial therapy with a ritonavir-boosted darunavir regimen had similar virologic efficacy to a ritonavir-boosted atazanavir regimen, but more patients discontinued the ritonavir-boosted atazanavir regimen due to adverse events (primarily hyperbilirubinemia).[72] Boosted darunavir and atazanavir can be dosed once daily (with food) and boosting can be achieved with either ritonavir or cobicistat. Coformulated boosted preparations are available as atazanavir-cobicistat and darunavir-cobicistat. Darunavir may cause rash in patients with a sulfa allergy, but atazanavir often causes hyperbilirubinemia.

### Choice of NNRTI

Multiple regimens that utilize an NNRTI as the anchor drug are available in the category of Recommended Initial Regimens in Certain Clinical Situations; in this category, the NNRTI anchor drugs include doravirine, efavirenz, and rilpivirine.[61] The ECHO and THRIVE studies, which compared efavirenz- and rilpivirine-based regimens, reported similar levels of undetectable HIV RNA levels at 48 weeks in the two
Rilpivirine should not be used in persons who have baseline HIV RNA level greater than or equal to 100,000 copies/mL or a CD4 count less than or equal to 200 cells/mm$^3$. In addition, rilpivirine is contraindicated for individuals who are taking a proton pump inhibitor and must be taken with a meal of at least 500 calories.[61] For a person with uncontrolled or untreated depression, most experts would avoid the use of efavirenz, which has a high rate of central nervous system toxicities and an association with increased suicidality. Rilpivirine also causes central nervous system adverse effects in some patients, but to a lesser degree than efavirenz. Doravirine is better tolerated than efavirenz, it can be used in combination with proton pump inhibitors, and it can be taken with or without food. The NNRTI etravirine is approved only for use in antiretroviral treatment-experienced persons.

Choosing NRTI Backbone in Regimen

The Adult and Adolescent ART Guidelines include four different NRTI backbone combinations: abacavir-lamivudine, tenofovir alafenamide-emtricitabine, tenofovir DF-emtricitabine, and tenofovir DF-lamivudine.[61] Abacavir has been associated with increased cardiovascular risk, and although data is conflicting about this association, many experts would avoid abacavir in the setting of known cardiovascular disease risk factors. Tenofovir DF is linked to increased risk of renal dysfunction and loss of bone mineral density; accordingly, tenofovir DF is not recommended for patients with renal disease or osteoporosis. Tenofovir alafenamide has a less favorable lipid profile than tenofovir DF.
What Not to Use

The Adult and Adolescent ART Guidelines provides a category for antiretroviral medications which, either alone or in combination, should not be offered for use at any time.[76] Regimens (or components of regimens) that are considered in the What Not to Use category include:

**Antiretroviral Drugs Not Recommended**

- Delavirdine
- Didanosine
- Indinavir
- Nelfinavir
- Stavudine

**Antiretroviral Regimens Not Recommended**

- Monotherapy with any antiretroviral medication
- Dual therapy with two NRTIs
- Triple therapy with three NRTIs

**Antiretroviral Components Not Recommended**

- Atazanavir plus indinavir
- Cobicistat plus ritonavir as pharmacokinetic enhancers
- Didanosine plus stavudine
- Didanosine plus tenofovir DF
- Two NNRTIs in combination
- Emtricitabine plus lamivudine
- Efavirenz plus an unboosted protease inhibitor
- Efavirenz plus ritonavir-boosted fosamprenavir
- Efavirenz plus ritonavir-boosted tipranavir
- Nevirapine in women with CD4 count above 250 cells/mm$^3$ or in men with CD4 count above 400 cells/mm$^3$
- Unboosted darunavir, saquinavir, or tipranavir
- Stavudine plus zidovudine
- Tenofovir alafenamide plus tenofovir DF
Monitoring Response to Antiretroviral Therapy

After initiating antiretroviral therapy, it is essential to monitor the virologic and immunologic response to therapy. The following outlines recommendations in the Adult and Adolescent ART Guidelines for monitoring HIV RNA levels and CD4 cell counts in persons on antiretroviral therapy.[77,78]

**HIV RNA Monitoring**

During the first 8 to 12 weeks after starting antiretroviral therapy, most individuals will achieve a reduction in HIV RNA levels to less than 50 copies/mL. For some individuals, particularly those with extremely high baseline HIV RNA levels, the time for virologic suppression may extend past 12 weeks. The important parameter is whether the HIV RNA levels continue to decline. In general, INSTI-based regimens cause a more rapid reduction in HIV RNA levels than with NNRTI- or PI-based regimens.[79,80]

- **Baseline:** All individuals initiating antiretroviral therapy should have a baseline HIV RNA level.
- **After Initiating Therapy:** After starting antiretroviral therapy, an HIV RNA level should be obtained preferably within 4 to 8 weeks. Subsequently, HIV RNA levels should be repeated thereafter every 4 to 8 weeks until the HIV RNA is suppressed to less than 50 copies/mL.
- **After Virologic Suppression:** Once HIV RNA levels are suppressed, the frequency of HIV RNA monitoring should extend to every 3 to 4 months.
- **With Long-Term Virologic Suppression:** For adherent individuals who have consistently suppressed HIV RNA for at least 2 years (and stable immunologic status), HIV RNA monitoring can be extended to 6-month intervals.
- **After Antiretroviral Regimen Change:** Following any change in the antiretroviral regimen, the HIV RNA level should be checked within 4 to 8 weeks, whether the medication change was for drug toxicity, regimen simplification, or another reason. This recommendation holds even when the person has virologic suppression at the time of change in the antiretroviral regimen.
- **Virologic Breakthrough:** In persons on antiretroviral therapy who have virologic breakthrough, monitoring of HIV RNA levels should be adjusted as needed.
- **Change in Clinical Status:** If an individual has a change in clinical status or has to initiate therapy with chronic corticosteroids or chemotherapy, the HIV RNA levels should be checked every 3 months.

**CD4 Cell Count**

Individuals who suppress HIV RNA levels on antiretroviral therapy typically have an increase in CD4 count of approximately 50 to 150 cells/mm$^3$ after the first year, with subsequent average yearly increases of approximately 50 to 100 cells/mm$^3$ until a steady state is attained.[81,82]

- **Baseline:** All persons starting on antiretroviral therapy should have a baseline CD4 cell count.
- **After Initiating Therapy:** A repeat CD4 cell count should be obtained 3 months after starting therapy.
- **During First 2 Years:** After Initiating Therapy: During the first 2 years after starting antiretroviral therapy, the CD4 count monitoring should be every 3 months if the CD4 cell count is less than 300 cells/mm$^3$ and every 6 months if the CD4 count is greater than 300 cells/mm$^3$.
- **With Long-Term Stable Virologic Suppression:** After 2 years on antiretroviral therapy, the frequency of CD4 cell count monitoring for adherent patients with consistently suppressed HIV RNA levels should be determined by immune status:
  - If the CD4 count is less than 300 cells/mm$^3$, CD4 monitoring can be extended to every 6 month intervals.
  - If the CD4 count is consistently in the 300 to 500 cells/mm$^3$ range, monitoring can be extended to 12-month intervals.
If the CD4 count is consistently greater than 500 cells/mm$^3$, monitoring should be considered optional.

- **Change in Clinical Status:** If an individual on antiretroviral therapy has a change in clinical status or has to initiate therapy with chronic corticosteroids or chemotherapy, the CD4 cell counts should be checked as clinically indicated.
Poor CD4 Response to Antiretroviral Therapy

After starting antiretroviral therapy, the virologic response is the most important factor in predicting an overall successful treatment outcome. Typically, adults with HIV have a brisk increase in CD4 cells in the first 3 to 6 months after starting antiretroviral therapy, predominantly due to a release of memory CD4 cells trapped within lymphoid tissues.[83] In the second phase of CD4 recovery, there is a gradual increase in CD4 counts that continues for 3 to 6 years; this phase involves both naïve CD4 cells (from the thymus) and memory CD4 cells. In general, persons with lower nadir CD4 cell counts have lower likelihood of having a high or near normal CD4 count upon recovery following years of antiretroviral therapy (Figure 25).[84,85,86] Approximately 15% of persons with HIV and advanced immunosuppression fail to recover their CD4 count at a level greater than 200 cells/mm$^3$ despite virologic suppression.[87] These “discordant” virologic-immunologic responses can generate concern, especially since persistent low CD4 is associated with increased AIDS-related and non-AIDS-related morbidity and mortality.[88,89]

Factors Associated with Poor CD4 Recovery

Investigators have identified multiple factors associated with a poor CD4 count response to antiretroviral therapy: older age, pretreatment CD4 count less than 200 cells/mm$^3$, hepatitis C coinfection, HIV-2 coinfection, coexistence of other chronic medical conditions, and the use of antiretroviral regimens that contain certain medications, such as zidovudine or the combination of tenofovir DF and didanosine.[88,90] A meta-analysis of different antiretroviral regimens found that ritonavir-boosted protease inhibitor-based regimens produced better CD4 cell responses than either unboosted protease inhibitor regimens or non-nucleoside reverse transcriptase inhibitor-based regimens.[91] In addition, studies have shown greater CD4 count increases in raltegravir- and dolutegravir-based regimens than with efavirenz-based regimens.[80,92] Some medications, such as interferon-alfa, peginterferon-alfa, or chemotherapeutic agents, can significantly reduce the CD4 count, with a gradual return to normal after the medication is discontinued; these types of medications generally do not impact the CD4 percentage nearly as much as the absolute CD4 cell count.

Recommendations for Patients with Persistently Low CD4 Counts

For persons with HIV who have a poor CD4 count recovery (CD4 count remains below 200 cells/mm$^3$ despite having suppressed HIV RNA levels for at least 2 years), the Adult and Adolescent ART Guidelines do not recommend intensifying or switching the antiretroviral regimen.[88] It is important to evaluate whether the individual is taking any medications (not used to treat HIV) that suppress the bone marrow or whether they have clinical manifestations (pancytopenia, systemic symptoms) that may suggest a bone marrow infiltrative process. In addition, individuals who have persistently low CD4 counts should receive appropriate prophylaxis for opportunistic infections, if indicated. Two large randomized trials (ESPRIT and SILCATT) showed interleukin-2 given to patients with suboptimal CD4 cell count responses causes a significant increase in CD4 cell counts, but the increase was not associated with any clinical benefit (Figure 26) and (Figure 27).[93] Thus, use of interleukin-2 to boost CD4 cell counts is not recommended.
Discontinuation or Treatment Interruption

Discontinuation of antiretroviral therapy may be necessary at certain times due to acute side effects, illness, surgery that prohibits oral intake, or unavailability of the medications; aside from these factors, persons with HIV should not interrupt antiretroviral therapy. Planned treatment interruptions, often referred to as strategic treatment interruptions, at one time were thought to be potentially beneficial to limit long-term antiretroviral therapy toxicity. Subsequently, discontinuation of therapy was shown to be detrimental to overall outcomes, as it allows for viremia, which can cause acute symptoms and illness, and immune decline.

Data Related to Strategic Treatment Interruptions

In the Strategies for Management of Antiretroviral Therapy (SMART) trial, investigators randomly assigned patients with CD4 counts greater than 350 cells/mm$^3$ to continuous versus episodic use of antiretroviral therapy (the episodic group waited until the CD4 count decreased to 250 cells/mm$^3$ to start, then stopped when the count reached 350 cells/mm$^3$, and reinitiated therapy if the CD4 count declined to less than 250 cells/mm$^3$).[52] The investigators found that the episodic therapy group had a significantly increased risk of opportunistic infection or death (from any cause), when compared with the continuous therapy group. Several other studies have shown that antiretroviral treatment interruption usually results in viral rebound, decreases in CD4 cell count, and eventually clinical progression.[94,95] Strategic treatment interruptions are not recommended.[96]

Recommendations

For patients who require a short-term, temporary discontinuation due to surgery or acute illness, or who make a planned interruption despite advice against interruption, the Adult and Adolescent ART Guidelines provide specific recommendations for how to safely stop the medications, particularly for patients who are taking medications with significantly different half-lives.[96]
Summary Points

- Five classes of antiretroviral medications, which target specific points of intervention in the multi-step HIV life cycle, have been developed for clinical use: (1) entry inhibitors, (2) NRTIs, (3) NNRTIs, (4) INSTIs, and (5) PIs.

- The Adult and Adolescent ART Guidelines recommend initiation of antiretroviral therapy for all persons with HIV to reduce disease progression and prevent transmission; this recommendation reflects evidence from clinical trials and cohort studies that have shown the benefits of starting antiretroviral therapy earlier in the course of HIV infection.

- In the Adult and Adolescent ART Guidelines, the Recommended Initial Regimens for Most People with HIV, in the absence of a history of long-acting cabotegravir for PrEP, consists of an INSTI anchor drug plus a 2-drug NRTI backbone. Other effective regimen options are available for use in certain clinical situations.

- If a person is diagnosed with HIV while or after receiving long-acting cabotegravir for PrEP, an integrase genotype is indicated and should be performed prior to initiating INSTI-based antiretroviral therapy. If antiretroviral therapy is initiated prior to integrase genotype results, a boosted darunavir-based regimen should be prescribed.

- The choice of the initial antiretroviral regimen depends on multiple patient factors, including medical and psychiatric comorbidities, patient preferences, drug interactions, and prior PrEP usage.

- After the initiation of antiretroviral therapy, laboratory monitoring is important to measure the HIV RNA response to therapy, to follow the CD4 count, and to monitor for antiretroviral toxicity.

- Virologic response to antiretroviral therapy is the most important factor in predicting an overall successful treatment outcome, and most patients will achieve virologic suppression (HIV RNA below the lower level of detection of the assay, usually less than 20 to 75 copies/mL, depending on the assay used) within 24 weeks.

- Typically, individuals with HIV have a brisk increase in CD4 cells in the first 3 to 6 months after starting antiretroviral therapy, although a small proportion of patients fail to recover their CD4 count at a level greater than 200 cells/mm³ despite sustained virologic suppression.

- Scheduled antiretroviral treatment interruption is not recommended since this practice has been linked to an increased risk of opportunistic infection and death.


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Figures

Figure 1 Reproductive Cycle of HIV-1 and Sites of Action of Major Classes of Antiretroviral Medications

Step 1 represents HIV-1 entry into the host cell, which involves the binding of the viral envelope protein, glycoprotein 120 (gp120), to the CD4 molecule, followed by a conformational change in gp120 that allows binding to the chemokine host-cell receptor (e.g. CCR5 or CXCR4). Glycoprotein 41 (gp41), also part of the virus envelope, then mediates HIV-cell fusion to permit viral entry. The fusion inhibitor, enfuvirtide, blocks fusion between the virus (through gp41) and the CD4 molecule, and the CCR5 coreceptor antagonist, maraviroc, blocks viral binding (through gp120) to CCR5. Step 2 is reverse transcription, in which the single-stranded HIV-1 RNA is transcribed into double-stranded DNA by the HIV enzyme (polymerase) called reverse transcriptase. This step is the site of action of nucleoside and nucleotide reverse-transcriptase inhibitors (NRTIs) and non-nucleoside reverse-transcriptase inhibitors (NNRTIs). Step 3 is the migration of HIV DNA into the nucleus and its integration into the DNA of the host cell, a process catalyzed by the viral enzyme integrase. Integrase strand-transfer inhibitors (INSTIs) target this step. Step 4 is the transcription of the HIV-1 DNA into HIV messenger RNA (mRNA) and HIV genomic RNA. Step 5 is the transport of the HIV-1 RNA out of the nucleus and the translation of HIV-1 mRNA into viral polyproteins. To be functional, the transcribed proteins must be cleaved into smaller component proteins, a process that occurs in step 6 through the action of the HIV-1 enzyme protease. This is the site of action of protease inhibitors. Step 7 is the assembly of viral genomic RNA and viral enzymes (reverse transcriptase, integrase, and protease) into viral particles. Step 8 is the budding and maturation of new viral particles, which then go on to infect other host cells.

Figure 2 HIV Envelope Glycoprotein

Each HIV envelope spike is a trimeric structure, with each trimer comprised of gp120 subunits paired with gp41 subunits. The trimer of heterodimers is arranged in a tripod-like conformation. The gp120 is coated with an immunoprotective glycan shield that helps HIV evade the host immune system.

Illustration by David Ehlert, Cognition Studio and David H. Spach, MD
Figure 3 HIV Envelope Surface Proteins

Each HIV has approximately 14 irregularly spaced envelope glycoprotein spikes on the surface of HIV.

Illustration by David Ehlert, Cognition Studio and David Spach, MD
Figure 4 (Image Series) - HIV Tropism and Binding to Host Coreceptors (Image Series) - Figure 4 (Image Series) - HIV Tropism and Binding to Host Coreceptors

Image 4A: R5-Tropic HIV

In this illustration, the R5-tropic HIV is represented by the blue envelope spikes; the R5 HIV binds to the host CCR5 coreceptor during the viral cell entry process.

Illustration by David Spach, MD
Figure 4 (Image Series) - HIV Tropism and Binding to Host Coreceptors
Image 4B: X4-Tropic HIV

In this illustration, the X4-tropic HIV is represented by the purple envelope spikes; the X4 HIV binds to the host CCR5 coreceptor during the viral cell entry process.

Illustration by David Spach, MD
Figure 4 (Image Series) - HIV Tropism and Binding to Host Coreceptors

Image 4C: Dual-Tropic HIV

In this illustration, the dual-tropic HIV is represented by both blue and purple envelope spikes; the dual-HIV can bind to the host CCR5 or CXCR4 coreceptors during the viral cell entry process.

Illustration by David Spach, MD
Figure 4 (Image Series) - HIV Tropism and Binding to Host Coreceptors
Image 4D: Mixed-Tropic HIV

In this illustration, the mixed-tropic HIV is represented by a mixture of R5-tropic HIV (blue envelope spikes) and X4-tropic HIV (purple envelope spikes); the R5 HIV binds to the CCR5 coreceptor and the X4 HIV binds to the CXCR4 coreceptor.

Illustration by David Spach, MD
Figure 5 Mechanism of Action of Attachment Inhibitors

The attachment inhibitor fostemsavir is hydrolyzed to its active form temsavir, which binds to HIV gp120 and prevents normal attachment of the host CD4 receptor with HIV gp120.

Illustration by David H. Spach, MD
Figure 6 Mechanism of Action of CD4 Postattachment Inhibitors

The CD4 postattachment inhibitor ibalizumab is a humanized monoclonal antibody that binds to the domain 2 region of the human CD4 cell receptor. This binding does not prevent attachment of HIV gp120 with the host CD4 receptor, but, through steric hindrance it prevents normal postbinding conformational changes in gp120 that are required for gp120-coreceptor binding.

Illustration by David H. Spach, MD
**Figure 7 Mechanism of Action of CCR5 Antagonists**

The CCR5 antagonist maraviroc binds to the host CCR5 coreceptor, rendering a conformational change in the coreceptor, which causes unfavorable binding of the V3 region of gp120 in the R5 strains of HIV.

Illustration by David H. Spach, MD
The fusion inhibitor enfuvirtide is a 36-amino-acid peptide that represents a segment of the HIV gp41 HR2 domain. In the native gp41 configuration, a segment of gp41 folds back on itself and this involves tight coiling of the HR1 and HR2 segments. The drug enfuvirtide mimics the HR2 segment and binds to HR1, thus interfering with the normal HR1 and HR2 interaction.
Reverse transcriptase is a DNA polymerase heterodimer comprised of p66 and p51 subunits. The p66 and p51 subunits are 560 and 440 amino acids in length, respectively. These two subunits share the same first 440 amino acids.

Illustration by David Ehlert, Cognition Studio
Figure 9 (Image Series) - Structure of HIV Reverse Transcriptase
Image 9B: HIV Reverse Transcriptase: p66 Subunit

The p66 subunit is 560 amino acids in length comprised of the polymerase domain (N-terminal 440 amino acids) and the RNase H domain (C-terminal 120 amino acids).

Illustration by David Ehlert, Cognition Studio and David H. Spach, MD
The p66 subunit contains the active site for polymerase and RNase H. The polymerase active site is located in the palm subdomain of the polymerase domain and RNase H active site is in the RNase H domain.

Illustration by David Ehlert, Cognition Studio and David H. Spach, MD
Figure 9 (Image Series) - Structure of HIV Reverse Transcriptase
Image 9D: HIV Reverse Transcriptase: Polymerase Domain

The structure of the polymerase domain resembles a right hand and consists of four domains: fingers, palm, thumb, and connection.

Illustration by David Ehlert, Cognition Studio and David H. Spach, MD
The key function of HIV reverse transcriptase is to convert HIV RNA to HIV DNA. The actual reverse transcriptase process is a multiple-step, highly complicated process that involves polymerase, RNase H, and an RNA-DNA intermediate hybrid.

Illustration by David Ehlert, Cognition Studio and David H. Spach, MD
The HIV reverse transcription process occurs by incorporating human nucleotides into the elongating strand of DNA. Thus, conceptually it is important to understand the nucleotide building blocks of the HIV RNA and DNA are human in origin.

Illustration by David H. Spach, MD
The reverse transcriptase, similar to other DNA polymerase enzymes, utilizes both a primer and a template. This simplified depiction shows the HIV RNA genome serving as the template and strand functioning as the primer where new nucleotides are added.

Illustration by David H. Spach, MD
The nucleoside reverse transcriptase inhibitors, in their triphosphate form, mimic the host nucleotides that are incorporated into the elongating strand of DNA. The host cellular kinases convert the nucleoside reverse transcriptase inhibitors to their active triphosphate form. In the active form, the nucleoside reverse transcriptase inhibitors compete with human nucleotides for a spot in the elongating DNA chain.

Illustration by David Spach, MD
Figure 11 (Image Series) - Nucleoside Reverse Transcriptase Inhibitors: Mechanism of Action
Image 11B: Incorporation of Nucleoside Reverse Transcriptase Inhibitors

After the nucleoside reverse transcriptase inhibitors become activated to a triphosphate form, they can compete with human nucleotides to be incorporated into the elongating DNA chain.

Illustration by David H. Spach, MD
The incorporation of the nucleoside reverse transcriptase inhibitor into the elongating strand of DNA is referred to as primer blocking.

Illustration by David H. Spach, MD
All of the nucleoside reverse transcriptase inhibitors approved to treat HIV lack a 3'-hydroxyl component and thus additional nucleotides cannot be linked to the nucleoside reverse transcriptase inhibitor. The nucleoside reverse transcriptase inhibitors thus act as chain terminators when incorporated into the viral DNA by the HIV reverse transcriptase.

Illustration by David H. Spach, MD
The non-nucleoside reverse transcriptase inhibitors work by directly binding to the non-nucleoside reverse transcriptase inhibitors binding pocket region, a region in the polymerase domain proximal to the polymerase active site. This binding directly impedes the function of the reverse transcriptase enzyme.

Illustration by David Ehlert, Cognition Studio and David H. Spach, MD
The functional impact of non-nucleoside reverse transcriptase inhibitor binding to reverse transcriptase is likely multifactorial, and not entirely understood; one proposed mechanism suggests that non-nucleoside reverse transcriptase inhibitor binding results in a locked hyperextension of the polymerase thumb region (and possibly also the fingers region). This conformational change is believed to alter the polymerase binding site, impacting the functional role of the reverse transcriptase.

Illustration by David Ehlert, Cognition Studio and David H. Spach, MD
The HIV enzyme integrase plays a critical role in the process of integrating the HIV proviral DNA into the human DNA. Humans do not have an integrase enzyme. The HIV integrase enzyme is a 288 amino-acid protein that consists of three distinct structural domains: the carboxy (C)-terminal domain, the amino (N)-terminal domain, and the catalytic core domain. The catalytic core domain contains a trio of amino acids that coordinate binding with a divalent metal (either Mg$^{2+}$ or Mn$^{2+}$) and form an active catalytic site.

Illustration by David Ehlert, Cognition Studio and David H. Spach, MD
The HIV integrase enzyme can exist in the form of a monomer, dimer, tetramer, and possibly higher order forms, such as octamers.

Illustration by David Ehlert, Cognition Studio and David H. Spach, MD
The HIV integrase binds to HIV DNA (most likely in the dimer form); the integrase-HIV DNA complex is part of a particle known as the preintegration complex. This newly formed preintegration complex has to migrate inside the host nucleus for integration to occur.

Illustration by David Ehlert, Cognition Studio and David H. Spach, MD
Figure 14 (Image Series) - Integration of HIV DNA into Host DNA
Image 14B: HIV Integrase Strand Transfer

This strand transfer reaction is initiated as the HIV integrase catalyzes the HIV DNA 3-hydroxyl group attack on the host DNA. The attack by the viral DNA occurs on opposite strands of the host DNA in a staggered fashion, typically 4-6 base pairs apart.

Illustration by David Ehlert, Cognition Studio and David H. Spach, MD
Figure 14 (Image Series) - Integration of HIV DNA into Host DNA
Image 14C: Unfolding of Integrated HIV DNA

At this point, the newly joined viral-host DNA region unfolds. The insertion of the new HIV DNA induces a host cellular DNA damage response. This host response is critical in the final step of integration, known as gap repair.

Illustration by David Ehlert, Cognition Studio and David H. Spach, MD
Figure 14 (Image Series) - Integration of HIV DNA into Host DNA
Image 14D: Proviral HIV DNA

The HIV DNA that is incorporated into the host DNA is referred to as proviral DNA.

Illustration by David Ehler, Cognition Studio and David H. Spach, MD
Figure 15 Integrase Strand Transfer Inhibitor

With binding to the HIV integrase, the INSTIs have a multifaceted mechanism of action that includes sequestering the Mg$^{2+}$ ions and blocking the binding site, displacing the 3'-hydroxyl ends of viral DNA that play a critical role in strand transfer, and prevention of host DNA substrate with the HIV complex.

Illustration by David Ehlert, Cognition Studio and David H. Spach, MD
Figure 16 HIV Protease

HIV protease is a 99-amino-acid dimer made up of two identical subunits.

Illustration by David Ehlert, Cognition Studio and David H. Spach, MD
**Figure 17 HIV Protease and Configurations**

This figure shows the HIV protease enzyme in three configurations: open, semi-closed, and closed.

Illustration by David Ehlert, Cognition Studio and David H. Spach, MD
Figure 18 Sequential Steps in HIV Gag Protein Processing by HIV Protease

The HIV Gag protein processing occurs with sequential cleavages (steps 1 to 5) by HIV protease. The end result of this process is the separation of four proteins: matrix (MA), capsid (CA), nucleocapsid (NC), and p6. This cleavage process also separates out spacer peptide 1 (SP1) and spacer peptide 2 (SP2). Myristic acid moiety (myr) plays a key role in matrix binding to the phospholipid membrane.

Illustration: David H. Spach, MD
**Figure 19 HIV Protease Inhibitor**

The HIV protease inhibitor (red pentagon) bind to the active site of HIV protease and prevent protease processing of the Gag and Gag-Pol polyproteins.

Illustration by David Ehlert, Cognition Studio and David H. Spach, MD
Figure 20 ART Cohort Collaboration: Risk of Developing New AIDS-Defining Disease or Death After 3 Years Based on CD4 Cell Count and HIV RNA Level at the Time of

The analysis is based on 12,574 antiretroviral-naïve adult patients who started on antiretroviral therapy that consisted of a combination of at least 3 medications. An AIDS-defining illness was based on the 1993 CDC classification (except those persons who developed a CD4 count less than 200 cells/mm$^3$ were not classified as having a new AIDS-defining illness).

In this open label trial conducted in Haiti, 816 adults with HIV and CD4 counts between 200 and 350 cells/mm$^3$ were randomized to either early-treatment (immediate initiation of antiretroviral therapy) or standard-treatment (initiation of antiretroviral therapy when the CD4 count dropped to 200 cells/mm$^3$ or less or when clinical AIDS developed). There were 23 deaths in the standard-treatment group, as compared with 6 in the early-treatment group (hazard ratio with standard treatment, 4.0; 95% confidence interval [CI], 1.6 to 9.8; $P = 0.001$).


**CIPRA-HT-001: Kaplan–Meier Estimates of Survival in Treatment Groups**

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months</th>
<th>Early treatment</th>
<th>Standard treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>408</td>
<td>0</td>
<td>0.999</td>
<td>0.995</td>
</tr>
<tr>
<td>327</td>
<td>2</td>
<td>0.990</td>
<td>0.960</td>
</tr>
<tr>
<td>153</td>
<td>4</td>
<td>0.930</td>
<td>0.880</td>
</tr>
<tr>
<td>22</td>
<td>6</td>
<td>0.870</td>
<td>0.830</td>
</tr>
</tbody>
</table>

$P=0.001$ by log-rank test
Figure 22 Disease Progression Related to Baseline CD4 Cell Count and Status of Virologic Suppression

In this study, 1,173 patients were followed on highly active antiretroviral therapy and data was analyzed according to the baseline CD4 cell count, durable virologic suppression, and evidence of disease progression. A durable virologic response was defined as having a greater number of undetectable (less than 400 copies/mL) viral loads than detectable viral loads after initiating therapy; disease progression was defined as a new AIDS-defining illness or death.

Figure 23 The START Trial: Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

In the START trial, investigators randomized symptomatic individuals with HIV who had a CD4 count greater than 350 cells/mm$^3$ to immediately start antiretroviral therapy or defer therapy. The number of serious AIDS- or non-AIDS-defining events occurred in fewer patients in the immediate therapy group versus those in the deferred therapy group (1.8% versus 4.1%).

Figure 24 Swiss Cohort

In the Swiss HIV Cohort Study, investigators compared early initiation of antiretroviral therapy (patients with CD4 counts greater than 350 cells/mm$^3$) versus deferred therapy (patients monitored without therapy).

In this study, 5,299 antiretroviral therapy-naïve patients were followed to observe CD4 cell count responses after 7 years of antiretroviral therapy. Groups were stratified by baseline CD4 count and although all groups had significant increases in CD4 counts, the recovery to near normal CD4 count levels was much more likely to occur in those with higher baseline CD4 counts.

Source: Gras L, Kesselring AM, Griffin JT, et al. CD4 cell counts of 800 cells/mm³ or greater after 7 years of highly active antiretroviral therapy are feasible in most patients starting with 350 cells/mm³ or greater. J Acquir Immune Defic Syndr. 2007;45:183-92.
**Figure 26 Outcome of Patients in ESPRIT Trial**

This graph shows the outcome of 4,111 patients with a CD4 count greater than 350 cells/mm$^3$ who were randomized to receive interleukin-2 plus antiretroviral therapy or antiretroviral therapy alone. Abbreviations: OI = opportunistic infection.

Figure 27 Outcome of Patients in SILCATT Trial

This graph shows the outcome of 1,695 patients with a CD4 count less than 200 cells/mm$^3$ who were randomized to receive interleukin-2 plus antiretroviral therapy or antiretroviral therapy alone. Abbreviations: OI = opportunistic infection.

### Panel's Recommendations for Initiating Antiretroviral Therapy in Treatment-Naive Patients

- Antiretroviral therapy (ART) is recommended for all individuals with HIV to reduce morbidity and mortality (AI) and to prevent the transmission of HIV to others (AI).
- Initiate 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

**Source:**

- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. Initiation of antiretroviral therapy. December 18, 2019. [HIV.gov]
Table 2. **Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV**

### Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use. Choice of antiretroviral therapy during pregnancy should be guided by recommendations from the Perinatal Guidelines.

**For people who do not have a history of long-acting cabotegravir use as PrEP, the following regimens are recommended:**

**INTI + 2 NRTIs:**

- Bictegravir-tenofovir alafenamide-emtricitabine (AI)<sup>a</sup>
- Dolutegravir-abacavir-lamivudine<sup>a</sup> (AI)—only for individuals who are **HLA-B*5701 negative and without chronic HBV coinfection**
- Dolutegravir plus (tenofovir alafenamide or tenofovir DF)<sup>b</sup> plus (emtricitabine or lamivudine) (AI)

**INSTI + 1 NRTI**

- Dolutegravir-lamivudine (AI)—except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom antiretroviral therapy is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available

**For people with HIV and a history of using long-acting cabotegravir as PrEP, integrase genotypic drug resistance testing should be done before the start of antiretroviral therapy. If treatment is begun prior to the results of genotypic testing, the following regimen is recommended:**

- Darunavir (boosted with cobicistat or ritonavir) plus (tenofovir alafenamide or tenofovir DF) plus (emtricitabine or lamivudine)—pending the results of the genotype test (AIII).

**Abbreviations:** INSTI = integrase strand transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor

<sup>a</sup>Because of insufficient data, bictegravir should not be prescribed to people who are pregnant.

<sup>b</sup>Tenofovir alafenamide and tenofovir DF are two forms of tenofovir approved by the FDA. Tenofovir alafenamide has fewer bone and kidney toxicities than tenofovir DF, whereas tenofovir DF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

**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, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion

**Source:**

- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. What to start: initial combination regimens for people with HIV. September 21, 2022. [HIV.gov]
### Table 3. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

#### Recommended Initial Regimens in Certain Clinical Situations

These regimens are effective and tolerable, but have some disadvantages when compared with the regimens listed in the Recommended Regimens for Most People with HIV, or they have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred.

<table>
<thead>
<tr>
<th>INSTIs + 2 NRTIs:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elvitegravir-cobicistat-tenofovir alafenamide(^b)-emtricitabine (BI)(^a)</td>
</tr>
<tr>
<td>Elvitegravir-cobicistat-tenofovir DF(^b)-emtricitabine (BI)(^a)</td>
</tr>
<tr>
<td>Raltegravir plus tenofovir DF(^b)-emtricitabine (BI)</td>
</tr>
<tr>
<td>Raltegravir plus tenofovir alafenamide(^b)-emtricitabine (BII)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Boosted PI plus 2 NRTIs:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(in general, boosted Darunavir is preferred over boosted Atazanavir):</td>
</tr>
<tr>
<td>Darunavir plus ritonavir plus (tenofovir alafenamide or tenofovir DF)(^b) plus (emtricitabine or lamivudine) (AI)</td>
</tr>
<tr>
<td>Darunavir-cobicistat(^a) plus (tenofovir alafenamide or tenofovir DF)(^b) plus (emtricitabine or lamivudine) (AI)</td>
</tr>
<tr>
<td>Atazanavir plus ritonavir plus (tenofovir alafenamide or tenofovir DF)(^b) plus (emtricitabine or lamivudine) (AI)</td>
</tr>
<tr>
<td>Atazanavir-cobicistat(^a) plus (tenofovir alafenamide or tenofovir DF)(^b) plus (emtricitabine or lamivudine) (BII)</td>
</tr>
<tr>
<td>Darunavir plus ritonavir plus abacavir-lamivudine—(\text{if HLA-B}^*5701\text{ negative}) (BII)</td>
</tr>
<tr>
<td>Darunavir-cobicistat(^a) plus abacavir-lamivudine—(\text{if HLA-B}^*5701\text{ negative}) (BII)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NNRTI + 2 RTIs:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doravirine-tenofovir DF(^b)-lamivudine (BI)</td>
</tr>
<tr>
<td>Doravirine plus tenofovir alafenamide(^b)-emtricitabine (BII)</td>
</tr>
<tr>
<td>Efavirenz (600 mg)-tenofovir DF(^b)-emtricitabine (BI)</td>
</tr>
<tr>
<td>Efavirenz (400 mg)-tenofovir DF(^b)-emtricitabine (BI)</td>
</tr>
<tr>
<td>Efavirenz (600 mg) plus tenofovir alafenamide(^b)-emtricitabine (BII)</td>
</tr>
<tr>
<td>Rilpivirine-tenofovir DF(^b)-emtricitabine (BI)—(\text{if HIV RNA} &lt;100,000\text{ copies/mL and CD4 count} &gt;200\text{ cells/mm}^3)</td>
</tr>
<tr>
<td>Rilpivirine-tenofovir alafenamide(^b)-emtricitabine (BII)—(\text{if HIV RNA} &lt;100,000\text{ copies/mL and CD4 count} &gt;200\text{ cells/mm}^3)</td>
</tr>
</tbody>
</table>

#### Regimens to Consider when Abacavir, Tenofovir alafenamide, and Tenofovir DF Cannot be Used or Are Not Optimal:

<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir-lamivudine (AI), except for individuals with HIV RNA &gt;500,000 copies/mL, HBV coinfection, or in whom antiretroviral therapy is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available</td>
</tr>
<tr>
<td>Darunavir plus ritonavir once daily plus raltegravir twice daily (CI)—(\text{if HIV RNA} &lt;100,000\text{ copies/mL and CD4 count} &gt;200\text{ cells/mm}^3)</td>
</tr>
<tr>
<td>Darunavir plus ritonavir once daily plus lamivudine (CI)</td>
</tr>
</tbody>
</table>

Abbreviations: INSTI = integrase strand transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor;

\(^a\)Because lower concentrations of cobicistat and its boosted drugs elvitegravir, darunavir, and atazanavir, have been observed during the second and third trimesters, it should be avoided during pregnancy. For women with viral suppression who become pregnant while on a cobicistat-containing regimen but wish to
These regimens are effective and tolerable, but have some disadvantages when compared with the regimens listed in the Recommended Regimens for Most People with HIV, or they have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred. Remain on this regimen after counseling regarding its lower-drug concentration, frequent viral load monitoring is recommended. For further information, refer to the Perinatal Guidelines.

Tenofovir alafenamide and tenofovir DF are two forms of tenofovir approved by the FDA. Tenofovir alafenamide has fewer bone and kidney toxicities than tenofovir DF, while tenofovir DF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak
Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion

Source:

- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. What to start: initial combination regimens for people with HIV. September 21, 2022. [HIV.gov]
Table 4. **Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV**

**Antiretroviral Components or Regimens Not Recommended as Initial Therapy**

<table>
<thead>
<tr>
<th>Antiretroviral Components or Regimens</th>
<th>Reasons for Not Recommending as Initial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Abacavir-lamivudine-zidovudine (coformulated)  
As triple NRTI combination regimen | Inferior virologic efficacy |
| Abacavir-lamivudine-zidovudine plus tenofovir DF (as quadruple-NRTI combination regimen) | Inferior virologic efficacy |
| Stavudine plus lamivudine | Significant toxicities (including lipoatrophy, peripheral neuropathy and hyperlactatemia (including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis) |
| Didanosine plus lamivudine (or emtricitabine) | Inferior virologic efficacy  
Limited clinical trial experience in antiretroviral-naïve patients  
Didanosine toxicities, such as pancreatitis and peripheral neuropathy |
| Didanosine plus tenofovir DF | High rate of early virologic failure  
Rapid selection of resistance mutations  
Potential for immunologic nonresponse/CD4 cell decline  
Increased didanosine drug exposure and toxicities |
| Zidovudine-lamivudine | Greater toxicities (including bone marrow suppression, GI toxicities, skeletal muscle myopathy, cardiomyopathy, and mitochondrial toxicities such as lipoatrophy, lactic acidosis, and hepatic steatosis) than recommended NRTIs |
| **Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)** | |
| Delavirdine | Inferior virologic efficacy  
Inconvenient (three times daily) dosing |
| Etravirine | Insufficient data in antiretroviral-naïve patients |
| Nevirapine | Associated with serious and potentially fatal toxicity (hepatic events and severe rash, including Stevens Johnson Syndrome and toxic epidermal necrolysis)  
When compared to efavirenz, nevirapine did not meet noninferiority criteria |
<p>| <strong>Protease Inhibitors (PIs)</strong> | |
| Atazanavir (unboosted) | Less potent than boosted atazanavir |
| Darunavir (unboosted) | Use without ritonavir or cobicistat has not been studied |</p>
<table>
<thead>
<tr>
<th>Antiretroviral Components or Regimens</th>
<th>Reasons for Not Recommending as Initial Therapy</th>
</tr>
</thead>
</table>
| Fosamprenavir (unboosted) or Fosamprenavir plus ritonavir | • Virologic failure with unboosted fosamprenavir-based regimen may result in selection of mutations that confer resistance to fosamprenavir and darunavir  
• Less clinical trial data for fosamprenavir plus ritonavir than for other ritonavir-boosted PIs |
| Indinavir (unboosted) | • Inconvenient dosing (3 times daily with meal restrictions)  
• Fluid requirement  
• Indinavir toxicities, such as nephrolithiasis and crystalluria |
| Indinavir plus ritonavir | • Fluid requirement  
• Indinavir toxicities, such as nephrolithiasis and crystalluria |
| Lopinavir-ritonavir | • Higher pill burden than other PI-based regimens  
• Higher ritonavir dose than other PI-based regimens  
• Gastrointestinal intolerance |
| Nelfinavir | • Inferior virologic efficacy  
• Diarrhea |
| Ritonavir as sole PI | • High pill burden  
• GI intolerance  
• Metabolic toxicity |
| Saquinavir (unboosted) | • Inadequate bioavailability  
• Inferior virologic efficacy |
| Saquinavir plus ritonavir | • High pill burden  
• Can cause QT and PR prolongation; requires pretreatment and follow-up ECG |
| Tipranavir plus ritonavir | • Inferior virologic efficacy  
• Higher rate of adverse events than other ritonavir-boosted PIs  
• Higher dose of ritonavir required for boosting than other ritonavir-boosted PIs |

**Entry Inhibitors**

| Enfuvirtide (T-20)  
*Fusion Inhibitor* | • Only studied in patients with virologic failure  
• Twice-daily subcutaneous injections  
• High rate of injection site reactions |
| Ibalizumab  
*Postattachment inhibitor* | • Only studied in a very small number of patients with virologic failure  
• Requires intravenous therapy  
• High cost |
| Maraviroc  
*CCR5 Antagonist* | • Requires testing for CCR5 tropism before initiation of therapy  
• No virologic benefit when compared with other recommended regimens  
• Requires twice-daily dosing |

Source:
Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. What to start: initial combination regimens for people with HIV. September 21, 2022. [HIV.gov]