Antiretroviral Medications and Initial Therapy

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Section 1: Antiretroviral Therapy
Topic 1: Antiretroviral Medications and Initial Therapy

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Background

The availability of highly effective antiretroviral therapy in the mid-1990s transformed HIV from a fatal infection to a manageable, chronic disease. Persons living with HIV infection who take modern combination antiretroviral therapy significantly reduce morbidity and mortality associated with HIV infection,[1,2,3] as well as lower their risk of transmitting HIV to others.[4,5,6] Several decades of research have resulted in the development of an array of antiretroviral medications that target multiple specific points in the HIV life cycle (Figure 1).[7,8] The United States Food and Drug Administration has approved medications in five different classes to treat HIV infection: entry inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNTRIs), 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 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; this interaction is a prerequisite for the major functional components of HIV to gain entrance into the host cell. The HIV envelope is synthesized from the env gene as a glycoprotein (gp) 160 polyprotein precursor, which is subsequently processed by a host cellular protease to form the two structural envelope 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] The gp120 protein has approximately 480 amino acids and is structurally arranged with an outer domain, inner domain, and a bridging sheet. 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 and on the outermost surface of gp120 and the more internal variable 3 (V3) region. The gp120 V3 region plays a major role in determining the coreceptor tropism of HIV. The surface of the gp120 is coated with 80-90 glycans that make up an immunoprotective glycan shield. The gp41 subunit has approximately 345 amino acids divided into three domain: 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 hydrophic 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 folds 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 four key steps: (1) attachment of HIV with the host cell, (2) HIV gp120-host CD4 binding, (3) HIV gp120-host chemokine coreceptor binding, and (4) fusion of HIV with the host surface membrane.[9,15] After initial attachment to the host cell via non-specific interactions, HIV gp120 interacts with the host CD4 surface receptor, with binding occurring at the CD4 binding pocket on the HIV gp120 and the extracellular domain 1 (D1) of CD4.[16] Following the CD4 binding, the 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. The HIV gp120-coreceptor interaction is believed to activate the gp41 fusion machinery, which initially triggers the initial insertion of the gp41 fusion peptide into the host cell membrane.[9,16] Next, each of the the three gp41 in the trimer 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]

- **CD4 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 5); the net effect of ibalizumab is prevention of viral entry.[19,20] 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 patient's HIV subtype. The HIV subtype that binds to the CCR5 coreceptor is known as R5 HIV (or CCR5-tropic HIV) whereas the X4 HIV (or subtype CXCR4-tropic HIV) binds to the CXCR4 coreceptor; subtypes of HIV that are capable of binding to either the CCR5 or CXCR4 coreceptor are known as dual-tropic HIV.[21,22] Patients with a detectable mixture of R5 and X4 HIV are considered to have mixed-tropic HIV. The CCR5 antagonists exert their mechanism of action by binding to the CCR5 coreceptor, causing a conformational change in the coreceptor that prevents the HIV gp120 from binding with the CCR5 coreceptor (Figure 6).[21,23] In contrast, the CCR5 antagonists do not block the viral 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 patients only if they have documented pure R5 HIV (CCR5-tropic HIV); patients with X4, dual tropic, or mixed tropic HIV should not receive maraviroc. Accordingly, prior to starting a patient on maraviroc, an HIV coreceptor tropism assay should be performed to determine whether the patient has pure R5 HIV; the co-receptor tropism assay reports on the presence of R5, X4, and dual/mixed (the reports do not differentiate dual and mixed isolates).[21,23,24].

- **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 7); 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.[22,25,26] 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 8).[27] The p66 subunit, which primarily has a catalytic role, is comprised 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 has 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.[27]

**Reverse Transcription**
The HIV reverse transcriptase process is a multi-step complicated 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 to the elongating primer strand, which is forming opposite to the HIV template strand (Figure 9). During the reverse transcriptase process, the finger and thumb regions of the polymerase have dynamic movement that helps to align the host nucleotide into the active site and facilitate incorporation into the elongating DNA strand.[27]

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 can not be added to the NRTI drug, hence the name chain terminator (Figure 10).

- **Non-nucleoside Reverse Transcriptase Inhibitors**: The NNRTIs bind to a hydrophobic pocket in the p66 subunit, which is in close proximity to the active polymerase site (Figure 11).[28,29] Binding of the NNRTI causes hyperextension of the reverse transcriptase thumb region, which cause a conformational change in this polymerase domain, thereby blocking the process of DNA polymerization, a critical step in HIV reverse transcription.[28,30] The NNRTI hydrophobic binding pocket region is predominantly lined by amino acid codons 98 to 108 and 179 to 190.[31]

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 (either Mg2+ or Mn2+) and this region forms the active catalytic site (Figure 12).[32,33,34]. The HIV integrase enzyme can exist in the form of a monomer, dimer, tetramer, and possibly higher order forms, such as octomers. Each HIV-1 virion has an estimated 40-100 integrase enzymes.[34]

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.[33,34,35] 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 13).[33] The DNA-bound integrase removes two nucleotides on the 3’-ends of the DNA, forming sticky ends that are capable of insertion into a the host DNA.[35] 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.[33,36] 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.[35]

Integrate Strand Transfer Inhibitors

Multiple potential sites of inhibition exist with the HIV integration process. Currently available HIV integrase inhibitors utilize multiple mechanism to block the integrase strand transfer step and are thus referred to as integrase strand transfer inhibitors (INSTIs) [37,38]. The INSTIs only bind to the integrase enzyme when the integrase enzyme is attached to the viral DNA.[39] 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 14).[33] 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.[39] Further, the binding of the INSTI prevents binding of the host DNA with the HIV complex. When the HIV integration process is blocked, the HIV DNA becomes a substrate for host repair enzymes that convert the HIV DNA complex into a byproduct 2-LTR circles.[35]

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 15). This enzyme has a key role in post-transcriptional processing of the Gag (Pr55) and Gag-Pol (Pr160) polyproteins.[40] The HIV protease has three major conformational forms: open, semi-open, and closed (Figure 16). 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 scissors.

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 are part of Gag, with spacer peptide 1 (p2) interspersed between the capsid and nucleocapsid; the spacer peptide 2 (p1) is positioned between the nucleocapsid and p6 (Figure 17). During approximately 5-10% of the Gag translation events, a ribosomal frameshift occurs that results in and extended translation to create the Gag-Pol polyprotein.[41] 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.[42] The HIV protease initially catalyzes its own release from the the Gal-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 17).[41,43,44] 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 end result is the processing of the Gag and Gag-Pol polyproteins is the release of matrix, capsid, nucleocapsid, p6, protease, reverse transcriptase, and integrase proteins. Although HIV polyprotein processing is not necessary for HIV assembly it is mandatory for morphologic
changes that occur in the late maturation stage and HIV protease is essential for subsequent viral infectivity.[43] The HIV protease enzyme is not involved in the processing of the gp160 envelope precursor protein.

**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 18).[40,41] The HIV protease inhibitors disrupt the normal Gag and Gag-Pol polyprotein processing, cause arrest of normal maturation process, and prevent infectivity 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 ARV 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.[45] In addition, antiretroviral therapy should be started immediately, or as possible, after the HIV diagnosis.[45]

Data for Clinical Benefit of Antiretroviral Therapy

The Adult and Adolescent ARV 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 three-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 19).[46] 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 collaboration 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$^3$.[47]

- **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.[48] 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 20).[48]

- **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 21).[49]

- **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 initiation of antiretroviral therapy earlier.[2]

- **SMART**: The multi-national 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$^3$. 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$^3$.[50]

- **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$^3$.\footnote{1} In this study, the INSIGHT investigators randomized 4685 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 22). \footnote{1}

- **Swiss Cohort Study:** In the Swiss Cohort, investigators compared early initiation of antiretroviral therapy (patients with CD4 counts greater than 350 cells/mm$^3$) versus deferred therapy (patients 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 23).\footnote{51}

**Data for Antiretroviral Therapy Reducing HIV Transmission**

The Adult and Adolescent ARV 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%.\footnote{52} 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 96% when compared with persons who deferred antiretroviral therapy.

- **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.\footnote{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.\footnote{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).\footnote{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 only for serodifferent gay men.\footnote{53} The enrollment period analyzed for PARTNER-2 was September 2010 to July 31, 2017 and included a total of 972 serodifferent gay male couples.\footnote{53} 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.\footnote{53} There were, however, 15 new HIV infections during the study period, but none of these were phylogenetically linked.\footnote{53}
• **Opposites Attract**: The Opposites Attract trial was conducted from 2012-2016 and enrolled 358 HIV-serodifferent gay male couples in Thailand, Brazil, and Australia.[54] 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.[54] 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 was taking antiretroviral therapy and had an HIV RNA less than 200 copies/mL, and (3) the HIV-uninfected partner was not taking preexposure prophylaxis.[54] There were three new HIV infections during the study period, but none were phylogenetically linked.[54]

**Recommendations for Elite Controllers**

In 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/mm³.[55] 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.[55] The viremic controllers also usually have high CD4 cell counts, but are typically have less stable and lower CD4 cell counts than elite controllers.[56] The optimal antiretroviral management of elite controllers and viremic controllers has generated controversy since, without antiretroviral therapy, these individuals naturally control of 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.[55,57,58] The Adult and Adolescent ARV Guidelines make the following key recommendations for "elite controllers":[45]

- 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 ARV Guidelines stratify antiretroviral regimens for initial therapy as (1) Recommended for Most People with HIV, (2) Recommended in Certain Clinical Situations, (3) Other Antiretroviral Regimens for Initial Therapy When Abacavir, Tenofovir alafenamide, and Tenofovir DF Cannot Be Used, and (4) Not Recommended as Initial Therapy.

Special Considerations for Persons of Childbearing Potential

The Adult and Adolescent ARV Guidelines has updated recommendation on the use of dolutegravir and other INSTIs in persons of child-bearing potential (Table 2).[59] These recommendations were updated due to additional data from the Botswana study that showed prevalence of neural tube defects in infants who were exposed to dolutegravir at the time of conception that was lower (0.3%) than the prevalence reported in the preliminary data; the 0.3 prevalence of neural tube defects was still higher than the 0.1% observed in infants who were exposed to antiretroviral medications that did not include dolutegravir.[60,61]

Recommended Initial Regimens for Most People with HIV

The Adult and Adolescent ARV Guidelines regimens as Recommended Initial Regimens for Most People with HIV include an INSTI anchor drug in combination with at least one NRTI (Table 3).[59] All recommended combinations consist of 3-drug regimens, except for the 2-drug dolutegravir-lamivudine regimen.[59] 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 requirements to take with or without food). All of these recommended regimens can be dosed once daily. Note that dolutegravir-lamivudine should not be used as initial therapy in the following four situations: the baseline HIV RNA level is greater than 500,000 copies/mL, the persons undergoing treatment has chronic hepatitis B virus (HBV), the HBV status is unknown, or results from the HIV genotypic resistance testing for reverse transcriptase or HBV testing are not available at the time antiretroviral therapy is planned to start.[59] Except for the HIV RNA level restriction for dolutegravir-lamivudine, all of the Recommended Initial Regimens for Most People with HIV can be used without regard to pretreatment HIV RNA level or CD4 cell count.

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 ARV Guidelines denotes this category as Recommended Initial Regimens in Certain Clinical Situations (Table 4).[59] 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.[59,62,63,64]

Antiretroviral Regimens or Components Not Recommended

The Adult and Adolescent ARV Guidelines also includes a category for antiretroviral regimens or components that are not recommended as initial therapy (Table 5).[59]
Choosing Specific Antiretroviral Regimen

Factors to Consider for Selecting Initial Regimen

In clinical practice, a number of scenarios arise that warrant consideration for avoiding or using certain regimens. The following summarizes recommendations in the Adult and Adolescent ARV Guidelines.[59]

- **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, raltegravir, or ritonavir-boosted atazanavir), and raltegravir plus ritonavir-boosted darunavir.[59] Dolutegravir-lamivudine should not be used when the pretreatment HIV RNA level is greater than 500,000 copies/mL.[59]

- **Pretreatment CD4 Cell Count**: Higher rates of virologic failure have occurred when the pretreatment CD4 count is less than 200 cells/mm$^3$ in rilpivirine-based regimens and raltegravir plus ritonavir-boosted darunavir. Accordingly, these regimens should not be used in person who have a pretreatment CD4 count less than 200 cells/mm$^3$.[59]

- **Treatment of Early HIV Infection Before Drug Resistance Results Available**: In the setting where treatment is warranted in persons with early HIV prior to receiving the HIV genotypic drug resistance test results, it is essential to use a regimen that has a high genetic barrier to resistance. The following regimens are recommended in this situation:[65]
  - Bictegravir-tenofovir alafenamide-emtricitabine
  - Dolutegravir with (tenofovir alafenamide or tenofovir DF) plus (emtricitabine or lamivudine)
  - Boosted darunavir with (tenofovir alafenamide or tenofovir DF) plus (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 regimen bictegravir-tenofovir alafenamide-emtricitabine 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.

- **Pretreatment Chronic Kidney Disease**: For patients 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 should be avoided.

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

- **Preexisting Psychiatric Illness**: Efavirenz, and probably 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 INSTI 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.

- **Cardiac QTc Interval Prolongation**: Efavirenz and rilpivirine may prolong QTc interval; therefore these medications should be avoided in persons taking other medications that may prolong the QTc.

Choosing Anchor Drug in Regimen

The choice of the third drug, commonly referred to as the anchor drug, to combine with a two-drug
NRTI backbone for an initial antiretroviral regimen depends on clinical, pharmacologic, and patient-level factors. In the Adult and Adolescent ARV Guidelines, all of the Recommended Initial Regimens for Most People with HIV utilize an INSTI anchor drug; the use of INSTIs as the preferred anchor drug is based on high efficacy, low adverse effect profile, and minimal drug interactions.[59] In previous years, the Adult and Adolescent ARV Guidelines included the INSTI elvitegravir, protease inhibitors, and NNRTIs as the anchor drug in the recommended regimens category; however, due to considerations such as tolerability (atazanavir, efavirenz), limitations to use based on CD4 count and/or viral load (rilpivirine), and lower genetic barrier to resistance (efavirenz, elvitegravir, and rilpivirine), these drugs are now considered alternative regimens.

**INSTIs: Bictegravir versus Dolutegravir versus Elvitegravir versus Raltegravir**

In the Adult and Adolescent ARV Guidelines, three of the INSTIs (bictegravir, dolutegravir, and raltegravir) are included as components of the Recommended Initial Regimens for Most People with HIV.[59] 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-naïve patients with HIV infection.[66] In study 1490, initial therapy with bictegravir-tenofovir alafenamide-emtricitabine showed similar virologic responses as dolutegravir plus tenofovir alafenamide-emtricitabine.[67] Bictegravir and dolutegravir have emerged the most attractive INSTI-based options based on strong potency, high genetic barrier to resistance, and good tolerability. Raltegravir has excellent potency, but has a lower genetic barrier to resistance than bictegravir or dolutegravir. Elvitegravir was previously available as single INSTI agent, but it is now manufactured only as coformulated single-tablets (elvitegravir-cobicistat-tenofovir DF-emtricitabine or elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine); these fixed-dose regimens are considered less than optimal due to drug interactions with cobicistat and a genetic barrier to resistance with elvitegravir that is lower than with bictegravir or dolutegravir. All four INSTIs are available as once daily dosing.

**PIs: Boosted Darunavir versus Boosted Atazanavir**

The Adult and Adolescent ARV 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.[59] 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.[68] In ACTG A5257, 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).[69] Boosted darunavir and atazanavir can be dosed once daily (with food) and boosting can be achieved with either 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.

**NNRTIs: Doravirine versus Efavirenz versus Rilpivirine**

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.[59] The comparison of efavirenz and rilpivirine was done in the ECHO and THRIVE studies regimens with either efavirenz or rilpivirine had similar percentage of participants with undetectable HIV RNA levels at 48 weeks.[70, 71, 72] When compared to the efavirenz-based regimen, the rilpivirine-based regimen was better tolerated with fewer adverse events and fewer lipid abnormalities, but had higher rates of virologic failure in the subset of patients who had baseline HIV RNA levels greater than 100,000 copies/mL. Accordingly, 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/mm³. In addition, rilpivirine is contraindicated for patients who are taking a proton pump inhibitor. For a patient with uncontrolled or untreated depression, most experts would avoid the use efavirenz, which has a high rate of...
Central nervous system toxicities and an association with increased suicidality. Rilpivirine also causes adverse central nervous system adverse effects in some patients, but to a lesser degree than efavirenz. Doravirine is better tolerated than efavirenz. Unlike rilpivirine, there are no CD4 count or HIV RNA level restriction for the use of doravirine and doravirine can be used in combination with proton pump inhibitors. The NNRTI etravirine is approved only for use in antiretroviral treatment-experienced persons.

**Choosing NRTI Backbone in Regimen**

The Adult and Adolescent ARV Guidelines include four different NRTI backbone combinations: abacavir-lamivudine, tenofovir alafenamide-emtricitabine, tenofovir DF-emtricitabine, and tenofovir DF-lamivudine.\[59\] 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. The following three study summaries compare tenofovir DF and abacavir.

- **ACTG 5202**: The AIDS Clinical Trials Group (ACTG) 5202 study examined the relative effectiveness and safety of tenofovir DF-emtricitabine and abacavir-lamivudine NRTI backbones when given with either ritonavir-boosted atazanavir or efavirenz in treatment-naïve patients.\[73,74\] Patients were randomized to one of four regimens: (1) efavirenz plus abacavir-lamivudine, (2) atazanavir boosted with ritonavir plus abacavir-lamivudine, (3) efavirenz plus tenofovir DF-emtricitabine, or (4) atazanavir boosted with ritonavir plus tenofovir DF-emtricitabine. The primary endpoints were time to virologic failure, regimen modification, or safety events. Patients with baseline HIV RNA levels greater than 100,000 copies/mL had a significantly higher rate of virologic failure if they received abacavir-lamivudine when compared with those who received tenofovir DF-emtricitabine, regardless of the third drug they received in the regimen. For those with a baseline HIV RNA level less than 100,000 copies/mL, the time to virologic failure with abacavir-lamivudine and tenofovir DF-emtricitabine was similar. In addition, abacavir-lamivudine was more likely to cause hyperlipidemia.

- **ASSERT**: The ASSERT study compared the NRTI backbone regimen of abacavir-lamivudine versus tenofovir DF-emtricitabine in treatment-naïve patients negative for HLA-B*5701.\[75\] In this open-label study, all 385 patients also received efavirenz. The percentage of participants who achieved an HIV RNA less than 50 copies/mL at week 48 was lower among those treated with abacavir-lamivudine than with tenofovir DF-emtricitabine.

- **HEAT**: In the HEAT study, investigators enrolled 686 antiretroviral treatment-naïve individuals and compared abacavir-lamivudine versus tenofovir DF-emtricitabine when given with lopinavir-ritonavir.\[76\] Baseline screening for HLA-B*5701 was not performed. At week 48, no significant differences were observed in virologic responses, even among patients with baseline HIV RNA levels of 100,000 copies/mL or greater.\[76\] Discontinuation due to adverse effects was similar in both groups.
What Not to Use

The Adult and Adolescent ARV Guidelines provides a category for antiretroviral medications which, either alone or in combination, should not be offered for use at any time.[77] 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
- Etravirine plus an unboosted protease inhibitor
- Etravirine plus ritonavir-boosted fosamprenavir
- Etravirine 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 ARV Guidelines for monitoring HIV RNA levels and CD4 cell counts in persons on antiretroviral therapy.[78, 79]

HIV RNA Monitoring

During the first 6 months after starting antiretroviral therapy most individuals will achieve a reduction in HIV RNA levels to less than 50 copies/mL. In some individuals, particularly those with extremely high baseline HIV RNA levels, the time to virologic suppression may extend past 6 months. The important parameter is whether the HIV RNA levels are continuing to decline. In general, INSTI-based regimens cause a more rapid reduction in HIV RNA levels than with NNRTI- or PI-based regimens.[80, 81]

- **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 2 to 4 weeks and no later than 8 weeks. Subsequently, HIV RNA levels should be repeated thereafter every 4 to 8 weeks until the HIV RNA is suppressed.
- **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.
- **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.[82, 83]

- **Baseline**: All persons starting on antiretroviral therapy should have a baseline CD4 cell count.
- **After Initiating Therapy**: A repeat CD4 cell count value should be obtained at 3 months after starting therapy.
- **During First 2 Years After Initiating Therapy**: During the first 2 years on antiretroviral therapy the CD4 count should be monitored every 3 to 6 months.
- **With Long-Term Stable Virologic Suppression**: After 2 years on antiretroviral therapy, adherent patients with consistently suppressed HIV RNA levels should have the frequency of CD4 cell count monitoring determine by immune status:
  - If the CD4 count is less than 300 cells/mm$^3$, monitoring should continue every 3 to 6 months,
  - 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 consistently greater than 500 cells/mm$^3$, monitoring should then 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 indicated clinically.
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, patients 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. 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 naive CD4 cells (from the thymus) and memory CD4 cells. In general, patients 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. Approximately one-third of patients who maintain continuous suppression of HIV do not recover their CD4 cell count to a level above 500 cells/mm$^3$ after 5 years. A smaller proportion of patients (approximately 15%) fail to recover their CD4 count at a level greater than 200 cells/mm$^3$ despite virologic suppression. These “discordant” virologic-immunologic responses can generate concern both for patients and clinicians, and low CD4 counts despite HIV RNA suppression on antiretroviral therapy are associated with increased AIDS-related and non-AIDS-related morbidity and mortality; absolute risk goes is greatly reduced, however, after 6 months of viral suppression regardless of CD4 response. Unfortunately, no widely accepted definition of immunologic failure exists.

Factors Associated with Poor CD4 Recovery

Investigators have identified multiple factors associated with a poor CD4 count response to antiretroviral therapy: older age, pre-treatment 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. 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. In addition, studies have shown greater CD4 count increases in raltegravir- and dolutegravir-based regimens than with efavirenz-based regimens. 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), there is generally no indication to switch the antiretroviral regimen, unless the person is taking a regimen that includes zidovudine or the combination of tenofovir DF and didanosine. 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. Attempt to increase CD4 count by augmentation of the antiretroviral regimen with an additional agent is neither effective nor is it recommended in the Adult and Adolescent ARV Guidelines. Antiretroviral therapy should be continued since multiple studies have shown that achieving a durable virologic response translates into clinical benefit independent of CD4 count. 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.
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, individuals living 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$^3$).[50] The investigators found that the episodic therapy group had a significant 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.[96,97]

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 ARV Guidelines provides specific recommendations for how to safely stop the medications, particularly for patients who are taking medications with significantly different half-lives.[98]
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) PIs, and (5) INSTIs.
- The Adult and Adolescent ARV 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 ARV Guidelines, the Recommended Initial Regimens for Most People with HIV consists on an INSTI anchor drug plus a two-drug NRTI backbone. Other effective regimen options are available for use in certain clinical situations.
- The choice of the initial antiretroviral regimen depends on multiple patient factors, including medical and psychiatric comorbidities, patient preferences, and drug interactions.
- 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 20-75 copies/mL, depending on the assay used) within 24 weeks.
- Typically, individuals with HIV have a brisk increase in CD4 cells in the first 3-6 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 nonnucleoside 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 pg41 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
Figure 3 HIV Envelope Surface Proteins

Each HIV has approximately 14 irregularly spaced envelope glycoprotein spikes on the surface of the virus. The envelope spikes consists of trimeric structure, with each trimer made by a dimer of the gp120 subunit atop the gp41 subunit.

Illustration by David Ehlert, Cognition Studio and David Spach, MD
Figure 4 (Image Series) - HIV Tropism and Binding to Host Coreceptors (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 binds 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 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 Spach, MD
Figure 6 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 Spach, MD
**Figure 7 Mechanism of Action of Fusion Inhibitor**

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 8 (Image Series) - Structure of HIV Reverse Transcriptase
Image 8B: 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 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 Spach, MD
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 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 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 building blocks of the HIV RNA and DNA are human in origin.

Illustration by David 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 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. Once in their 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 10 (Image Series) - Nucleoside Reverse Transcriptase Inhibitors: Mechanism of Action
Image 10B: 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 Spach, MD
Figure 10 (Image Series) - Nucleoside Reverse Transcriptase Inhibitors: Mechanism of Action
Image 10C: Primer Blocking

The incorporation of the nucleoside reverse transcriptase inhibitor into the elongating strand of DNA is referred to as primer blocking.

Illustration by David 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 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 has a directly impeded the function of the reverse transcriptase enzyme.

Illustration by David Ehlert, Cognition Studio and David Spach, MD
The functional impact of non-nucleoside reverse transcriptase inhibitor binding to reverse transcriptase is likely multi-factorial, and not entirely understood; one proposed mechanism suggests that is 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, impact the functional role of the reverse transcriptase.

Illustration by David Ehlert, Cognition Studio and David 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 Mg2+ or Mn2+) and form an active catalytic site.

Illustration by David Ehlert, Cognition Studio
Figure 12 (Image Series) - HIV Integrase
Image 12B: HIV Integrase: Monomer, Dimer, and Tetrad Forms

The HIV integrase enzyme can exist in the form of a monomer, dimer, tetramer, and possibly higher order forms, such as octomers.

Illustration by David Ehlert, Cognition Studio
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 Spach, MD
**Figure 13 (Image Series) - Integration of HIV DNA into Host DNA**

**Image 13B: 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 Spach, MD
Figure 13 (Image Series) - Integration of HIV DNA into Host DNA
Image 13C: Unfolding of Integrated HIV DNA

At this point, the newly joined viral-host DNA region unfolds. The insertion of the new HIV DNA induce 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 Spach, MD
Figure 13 (Image Series) - Integration of HIV DNA into Host DNA
Image 13D: Proviral HIV DNA

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

Illustration by David Ehlert, Cognition Studio and David Spach, MD
Figure 14 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 Ehler, Cognition Studio and David Spach, MD
**Figure 15 HIV Protease**

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

Illustration by David Ehlert, Cognition Studio and David Spach, MD
**Figure 16 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 Spach, MD
Figure 17 HIV Gag Protein Processing by HIV Protease

The HIV Gag protein processing occurs with sequential cleavages by HIV protease. The end result 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). myr = myristic acid moiety and myr plays a key role in matrix binding to the phospholipid membrane.

Illustration: David H. Spach, MD
**Figure 18 HIV Protease Inhibitor**

The HIV protease inhibitors 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 Spach, MD
Figure 19 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/mm3 were not classified as having a new AIDS-defining illness).

In this open label trial conducted in Haiti, 816 HIV-infected individuals with absolute CD4 counts between 200 and 350 cells/mm³ 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/mm³ 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).

Figure 21 Disease Progression Related to Baseline CD4 Cell Count and Status of Virologic Suppression

In this study, 1173 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.

In the START Trial, investigators randomized symptomatic individuals with HIV infection who have 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 (1.8% versus 4.1%).

Figure 23 Swiss Cohort


Swiss HIV Cohort Study

![Swiss HIV Cohort Study Graph](image_url)
Figure 24 Median CD4 Cell Count Over Time After Starting Antiretroviral Therapy

In this study, 5299 antiretroviral-therapy naive 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 25 Outcome of Patients in ESPRIT Trial**

This graph shows the outcome of 4111 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.

Figure 26 Outcome of Patients in SILCATT Trial

This graph shows the outcome of 1695 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

Table 1. **Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV**

**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).

<table>
<thead>
<tr>
<th>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
</tr>
</tbody>
</table>

Source:

Considerations Before Initiating Dolutegravir and Other Integrase Strand Transfer Inhibitors (INSTIs) as Initial Therapy for Persons of Child-Bearing Potential

Before Initiating an INSTI-Containing Regimen in a Person of Childbearing Potential:

- A pregnancy test should be performed (AIII).  
- To enable individuals of childbearing potential to make informed decisions, providers should discuss the benefits and risks of using dolutegravir around the time of conception, including the low risk of neural tube defects and the relative lack of information on the safety of using other commonly prescribed antiretroviral drugs, including other INSTIs, around the time of conception (AIII).
- **For individuals who are trying to conceive**, the Panel recommends initiating one of the following regimens, which are designated as Preferred regimens during pregnancy in the Perinatal Guidelines: use of an anchor drug (raltegravir, or atazanavir boosted with ritonavir, or darunavir boosted with ritonavir) plus a 2-drug backbone (tenofovir DF-emtricitabine, or tenofovir DF plus lamivudine, or abacavir-lamivudine). Dolutegravir would be an Alternative, rather than a Preferred, option (BII).
- **For individuals who are not planning to conceive but who are sexually active and not using contraception**, consider a regimen’s effectiveness and tolerability, the available data on potential teratogenicity, and the person’s preferences (e.g., low pill burden) when choosing among regimens recommended for initial therapy. In this situation, dolutegravir would be an Alternative, rather than Preferred, option (BII). If the person becomes pregnant, changes to the antiretroviral regimen may be warranted. In this situation, clinicians should refer to the Perinatal Guidelines or recommendations.
- **For individuals who are using effective contraception**, a dolutegravir-based regimen is one of the recommended options; however, clinicians should discuss the risks and benefits of using dolutegravir with patients to allow them to make an informed decision (AIII).
- An approach similar to that outlined for dolutegravir should be considered for bictegravir-containing antiretroviral therapy (AIII).
- Regimens that contain elvitegravir-cobicistat should not be used during pregnancy because of inadequate drug concentrations of elvitegravir in the second and third trimesters (AII).
- Clinicians should refer to the Perinatal Guidelines when prescribing antiretroviral therapy for a pregnant persons with HIV.

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:

Table 3. 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 (listed in alphabetical order).

**Integrase Strand Transfer Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors:**

*Note:* For individuals of childbearing potential, see the table Considerations Before Initiating one of these regimens.

- Bictegravir-tenofovir alafenamide-emtricitabine (AI)
- Dolutegravir-abacavir-lamivudine (AI)—only if HLA-B*5701 negative
- Dolutegravir plus tenofovir alafenamide\(^b\)-emtricitabine (AI)
- Dolutegravir plus tenofovir DF\(^b\)-emtricitabine (AI)
- Dolutegravir-lamivudine (AI)—except for individuals with HIV RNA >500,000 copies/mL, HBV co-infection, 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.
- Raltegravir\(^c\) plus tenofovir DF\(^b\)-emtricitabine (BII)
- Raltegravir\(^c\) plus tenofovir alafenamide\(^b\)-emtricitabine (BII)

\(^a\) Lamivudine may substitute for emtricitabine or vice versa, if a non-fixed dose NRTI combination is desired.

\(^b\) 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.

\(^c\) Raltegravir can be given as 400 mg twice daily or 1200 mg (two 600-mg tablets) once daily.

**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 the antiretroviral-naive patient. December 18, 2019. [AIDSwinfo](#)
Table 4. 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 above, or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred.

Integrase Strand Transfer Inhibitors + 2 Nucleoside Reverse Transcriptase Inhibitors:  
Note: for individuals of childbearing potential, see the table Considerations Before Initiating Dolutegravir and Other Integrase Strand Transfer Inhibitors as Initial Therapy before prescribing one of these regimens.

- Elviregravir-cobicistat-tenofovir alafenamide\(^b\)-emtricitabine (BI)
- Elviregravir-cobicistat-tenofovir DF\(^b\)-emtricitabine (BI)

Boosted Protease Inhibitor plus 2 Nucleoside Reverse Transcriptase Inhibitors:\(^a\)\(^b\)  
(in general, boosted Darunavir is preferred over boosted Atazanavir):

- Darunavir plus ritonavir plus tenofovir alafenamide\(^b\)-emtricitabine\(^a\) (AI)
- Darunavir plus ritonavir plus tenofovir DF\(^b\)-emtricitabine\(^a\) (AI)
- Darunavir-cobicistat plus tenofovir alafenamide\(^b\)-emtricitabine\(^a\) (AI)
- Atazanavir plus ritonavir plus tenofovir alafenamide\(^b\)-emtricitabine\(^a\) (BI)
- Atazanavir plus ritonavir plus tenofovir DF\(^b\)-emtricitabine\(^a\) (BI)
- Atazanavir-cobicistat plus tenofovir alafenamide\(^b\)-emtricitabine\(^a\) (BI)
- Atazanavir-cobicistat plus tenofovir DF\(^b\)-emtricitabine\(^a\) (BI)
- Darunavir plus ritonavir plus abacavir-lamivudine\(^a\) (BII)—if HLA-B*5701 negative
- Darunavir-cobicistat plus abacavir-lamivudine\(^a\) (BII)—if HLA-B*5701 negative

Non-Nucleoside Reverse Transcriptase Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors:

- Doravirine-tenofovir DF-lamivudine (BI)
- Doravirine plus tenofovir alafenamide-emtricitabine (BIII)
- Efavirenz (600 mg)-tenofovir DF-emtricitabine\(^a\) (BI)
- Efavirenz (400 mg)-tenofovir DF-emtricitabine\(^a\) (BI)
- Efavirenz (600 mg) plus tenofovir alafenamide-emtricitabine\(^a\) (BII)
- Rilpivirine-tenofovir DF\(^b\)-emtricitabine\(^a\) (BI)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm\(^3\)
- Rilpivirine-tenofovir alafenamide\(^b\)-emtricitabine\(^a\) (BI)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm\(^3\)

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

- 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
- Darunavir plus ritonavir plus raltegravir (BID) (CI)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm\(^3\)
- Darunavir plus ritonavir once daily plus lamivudine\(^a\) (CI)

\(^a\) Lamivudine may substitute for emtricitabine or vice versa, if a non-fixed dose NRTI combination is desired.

\(^b\) 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...
These regimens are effective and tolerable, but have some disadvantages when compared with the regimens listed above, or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred.

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:

### Table 5. 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>
<tr>
<td>Abacavir-lamivudine-zidovudine (coformulated) As triple NRTI combination regimen</td>
<td>Inferior virologic efficacy</td>
</tr>
<tr>
<td>Abacavir-lamivudine-zidovudine plus tenofovir DF (as quadruple NRTI combination regimen)</td>
<td>Inferior virologic efficacy</td>
</tr>
<tr>
<td>Stavudine plus lamivudine</td>
<td>Significant toxicities (including lipoatrophy, peripheral neuropathy) and hyperlactatemia (including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis)</td>
</tr>
<tr>
<td>Didanosine plus lamivudine (or emtricitabine)</td>
<td>Inferior virologic efficacy, Limited clinical trial experience in ART-naive patients, Didanosine toxicities, such as pancreatitis and peripheral neuropathy</td>
</tr>
<tr>
<td>Didanosine plus tenofovir DF</td>
<td>High rate of early virologic failure, Rapid selection of resistance mutations, Potential for immunologic nonresponse/CD4 cell decline, Increased didanosine drug exposure and toxicities</td>
</tr>
<tr>
<td>Zidovudine-lamivudine</td>
<td>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</td>
</tr>
<tr>
<td><strong>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</strong></td>
<td></td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Inferior virologic efficacy, Inconvenient (three times daily) dosing</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Insufficient data in antiretroviral-naive patients</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>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</td>
</tr>
<tr>
<td><strong>Protease Inhibitors (PIs)</strong></td>
<td></td>
</tr>
<tr>
<td>Atazanavir (unboosted)</td>
<td>Less potent than boosted atazanavir</td>
</tr>
<tr>
<td>Darunavir (unboosted)</td>
<td>Use without ritonavir or cobicistat has not been studied</td>
</tr>
<tr>
<td>Fosamprenavir (unboosted) or Fosamprenavir</td>
<td>Virologic failure with unboosted</td>
</tr>
<tr>
<td>Antiretroviral Components or Regimens</td>
<td>Reasons for Not Recommending as Initial Therapy</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
</tbody>
</table>
| 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)         | • Only studied in patients with virologic failure  
| Fusion Inhibitor           | • Twice-daily subcutaneous injections  
|                           | • High rate of injection site reactions |
| Ibalizumab                | • Only studied in a very small number of patients with virologic failure  
| Post-attachment inhibitor | • Requires intravenous therapy  
|                           | • High cost |
| Maraviroc                 | • Requires testing for CCR5 tropism before initiation of therapy  
| CCR5 Antagonist           | • 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 the antiretroviral-naïve patient. December 18, 2019. [AIDSinfo]