Antiretroviral Medications and Initial Therapy

This is a PDF version of the following document:
Section 1: Antiretroviral Therapy
Topic 1: Antiretroviral Medications and Initial Therapy

You can always find the most up to date version of this document at https://www.hiv.uw.edu/go/antiretroviral-therapy/general-information/core-concept/all.

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, non-nucleoside reverse transcriptase inhibitors, integrase strand transfer inhibitors, and protease inhibitors. In addition, as of June 2017, the U.S. Food and Drug Administration had approved 6 single-tablet regimens for HIV treatment. 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 envelop 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 co-receptor 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 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 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. 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 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 two subclasses: (1) CCR5 co-receptor antagonists and (2) fusion inhibitors, with one FDA-approved drug from each subclass.[17,18]

- **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 (Figure 4).[19,20] 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 5).[19,21] 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 tropism assay should be performed to determine whether the patient has pure R5 HIV; the tropism assay reports on the presence of R5, X4, and dual/mixed (the reports do not differentiate dual and mixed isolates).[19,21].

- **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 6); 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.[20,22,23] 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 7).[24] 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.[24]

#### Reverse Transcription

The HIV reverse transcription 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 in 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 8). 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.[24]

**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 9).

- **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 10).[25,26] 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.[25,27] The NNRTI hydrophobic binding pocket region is predominantly lined by amino acid codons 98 to 108 and 179 to 190.[28]

**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 Mg\(^{2+}\) or Mn\(^{2+}\)) and this region forms the active catalytic site (Figure 11).[29,30,31] 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.[31]

**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.[30,31,32] Initially, the HIV integrase (most likely in the dimer form) binds to each end of the newly formed HIV DNA as part of a intracellular nucleoprotein particle known as the preintegration complex (Figure 12).[30] 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.[32] 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 (LEDFG)/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.[30,33] 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.[32]

**Integrase 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) [34, 35]. The INSTIs only bind to the integrase enzyme when the integrase enzyme is attached to the viral DNA.[36] 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 13).[30] 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.[36] 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.[32]

**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 14). This enzyme has a key role in post-transcriptional processing of the Gag (Pr55) and Gag-Pol (Pr160) polyproteins.[37] The HIV protease has three major conformational forms: open, semi-open, and closed (Figure 15). The protease enzyme has 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). 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.[38] 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.[39] The HIV protease initially catalyzes its own release from the 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 16).[38, 40, 41] 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.[40] 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 17).[37, 38] 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 Health and Human Services (HHS) Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV recommends initiation of antiretroviral therapy for all persons with HIV infection, regardless of CD4 cell count 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 [42] This recommendation is based on the established benefits associated with the use antiretroviral therapy in persons living with HIV infection to (1) reduced AIDS-related disease progression and mortality, (2) lower rates of non-AIDS related morbidity and mortality associated with ongoing viral replication, and (3) decreased HIV transmission.[42]

Data for Clinical Benefit of Antiretroviral Therapy

The antiretroviral therapy 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 infection who started three-drug antiretroviral therapy and identified baseline CD4 cell count when starting antiretroviral therapy as the most important prognostic factor for new AIDS-defining illness or death (Figure 18).[43] 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 to 350 cells/mm$^3$ compared with those who initiated therapy with a CD4 count between 351 and 500 cells/mm$^3$. [44]

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 to 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. [45] In an interim analysis of the study, participants who began antiretroviral therapy with CD4 counts of 200 to 350 cells/mm$^3$ had a lower mortality rate and lower incidence of tuberculosis than participants who deferred therapy (Figure 19).[45]

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 20).[46]

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 patients with a CD4 count of 351 to 500 cells/mm$^3$ who deferred therapy until the CD4 count declined to 350 cells/mm$^3$ or less had a 69% increased risk of death when compared with those who did not defer antiretroviral
therapy. In this same study, a parallel analysis involving patients 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 less was associated with a 94% increased risk of death when compared with initiation of antiretroviral therapy earlier.

**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$^3$.

**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 infection who have a CD4 count greater than 350 cells/mm$^3$. In this study, the INSIGHT investigators randomized 4685 adults with HIV infection to one of two arms: (1) start antiretroviral therapy immediately (immediate-initiation group) or (2) to defer antiretroviral therapy until the CD4 count decreased to 350 cells/mm$^3$, or the development of 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 21).

**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 22).

**Data for Antiretroviral Therapy Reducing HIV Transmission**

The recommendations regarding use of antiretroviral therapy to prevent HIV transmission are based primarily on the tremendous success of antiretroviral therapy in preventing perinatal transmission of HIV and multiple studies that indicate antiretroviral therapy dramatically lowers the risk of 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%. 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 serodiscordant (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 uninfected partner by 96% when compared with persons who deferred antiretroviral therapy.[4,51]

PARTNER

No published randomized studies have specifically focused on treatment as prevention in men who have sex with men or in injection drug users. The ongoing large European PARTNER study at least partially addresses this knowledge gap, as 40% of the first 1,100 couples enrolled have been homosexual couples.[6] Complete results are not anticipated until 2017 but in the first 2 years of the study, there have been no transmissions within any couples from a partner with an undetectable HIV RNA levels.

Recommendations for Elite Controllers

In a small percentage of persons naturally control their HIV infection 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$^3$.[52] 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.[52] The viremic controllers also usually have high CD4 cell counts, but are typically have less stable and lower CD4 cell counts than elite controllers.[53] 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.[52,54,55] The Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV makes the following key antiretroviral therapy recommendations for "elite controllers":[42]

- The clinical benefit of antiretroviral therapy in elite controllers remains uncertain.
- 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 Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV stratifies 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.

Dolutegravir Safety Alert

On May 18, 2018, an FDA Safety Alert was posted that warned of potential serious neural tube birth defects in infants born to mothers who received dolutegravir at the time of becoming pregnant or early in the first trimester. On May 30, 2018, the HHS Antiretroviral Guideline Panels issued Recommendations Regarding Dolutegravir that address the use of dolutegravir in adults and adolescents with HIV who are pregnant or of child-bearing potential. Note that dolutegravir is also a component of two fixed-dose combinations: dolutegravir-abacavir-lamivudine and dolutegravir-rilpivirine.

Recommended Initial Regimens for Most People with HIV

The Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV classifies seven regimens as Recommended Initial Regimens for Most People with HIV (Table 2).[56] Prior to starting antiretroviral therapy, HIV drug resistance genotypic testing should be performed to guide the selection of the regimen. Each of the regimens in the category Recommended Initial Regimens for Most People with HIV consists of an INSTI anchor drug in combination with a two-drug NRTI backbone. All eight of these regimens are INSTI-based regimens. 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 the medications in the Recommended Initial Regimens for Most People with HIV can be dosed once daily. In addition with 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 category listed above. The antiretroviral therapy guidelines denotes this category as Recommended Initial Regimens in Certain Clinical Situations (Table 3).[56]

Other Antiretroviral Regimens for Initial Therapy

The Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV includes the category—Other Regimen Options for Initial Therapy when Abacavir, Tenofovir alafenamide, and Tenofovir DF cannot be used; this category includes potential use of four dual antiretroviral therapy regimens: ritonavir-boosted darunavir plus raltegravir,[57] lopinavir-ritonavir plus lamivudine,[58, 59] dolutegravir plus lamivudine,[60] and ritonavir-boosted darunavir plus lamivudine.[61] The regimens listed are grouped based on the supporting evidence for their use.

- **Strategies with Good Supporting Evidence**
  - Ritonavir-boosted darunavir plus raltegravir
  - Lopinavir-ritonavir plus lamivudine

- **Strategies Under Evaluation and Not Yet Recommended**
  - Dolutegravir plus lamivudine
  - Ritonavir-boosted darunavir plus lamivudine
Choosing Specific Antiretroviral Regimen

Factors to Consider for Selecting Initial Antiretroviral Regimen

In clinical practice, a number of scenarios arise that warrant consideration for avoiding or using certain regimens. The following summarizes recommendations in the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV.[56]

- **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.

- **Pretreatment CD4 Cell Count**: Higher rates of virologic failure have occurred when the pretreatment CD4 count is less than 200 cells/mm³ in rilpivirine-based regimens and raltegravir plus ritonavir-boosted darunavir. Accordingly, these regimens should not be used in patients who have a pretreatment CD4 count less than 200 cells/mm³.

- **Need to Initiate Therapy Prior to Availability Drug Resistance Results**: In the setting where treatment is warranted prior to receiving the HIV drug resistance test results, it is essential to use a regimen with a high genetic barrier to resistance. The following regimens are recommended in this situation: (1) darunavir boosted with either ritonavir or cobicistat plus either tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine, or (2) dolutegravir plus either tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine.

- **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. 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 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 and thus these medications should be avoided in the patient is 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. All of the recommended initial regimens for most people with HIV in the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV utilize an INSTI anchor drug; the priority for use of integrase inhibitors is based on the high efficacy, low adverse effect profile, and minimal drug-drug interactions.[56] In previous years, the HHS guidelines included additional protease inhibitors as well as non-nucleoside reverse transcriptase inhibitors 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, rilpivirine), these drugs are now considered alternative regimens.

**INSTIs: Dolutegravir versus Elvitegravir versus Raltegravir**

In the antiretroviral therapy guidelines, all three FDA-approved integrase strand transfer inhibitors (dolutegravir, elvitegravir, and raltegravir) are included as components of the recommended regimens for treatment-naive patients with HIV.[56] To date, only one clinical trial has evaluated the relative efficacy and tolerability of different INSTIs. In SPRING-2, once daily dolutegravir was non-inferior to twice daily raltegravir in treatment-naive patients with HIV infection.[62] Dolutegravir has emerged as a very attractive INSTI option given its potency and relatively higher genetic barrier to resistance than raltegravir or elvitegravir. Elvitegravir is available alone, but it is primarily used in clinical practice in as a coformulated single-tablet regimen (elvitegravir-cobicistat-tenofovir DF-emtricitabine or elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine). All three INSTIs are available as once daily dosing.

**PIs: Darunavir versus Atazanavir versus Lopinavir-Ritonavir**

The antiretroviral guidelines recommendations include boosted-darunavir and boosted-atazanavir as the only protease inhibitor plus 2RNTI options in the category recommended initial regimens in certain clinical situations.[56] In the ARTEMIS trial, darunavir was shown to be superior to lopinavir-ritonavir both in terms of efficacy and tolerability, and in ACTG A5257, ritonavir-boosted darunavir had similar virologic efficacy to, ritonavir-boosted atazanavir, but more patients discontinued ritonavir-boosted atazanavir due to adverse events (primarily hyperbilirubinemia).[63,64] Both darunavir and atazanavir can be dosed once daily with food and require pharmacologic boosting with either ritonavir or cobicistat, and both are available as coformulated boosted preparations: atazanavir-cobicistat and darunavir-cobicistat. Darunavir may cause rash in patients with a sulfa allergy. Lopinavir-ritonavir requires a higher dose of ritonavir, and has an increased the rate of adverse effects (such as lipid abnormalities and gastrointestinal complaints) and drug interactions.

**NNRTIs: Efavirenz versus Rilpivirine**

Three single-tablet regimens that have non-nucleoside reverse transcriptase inhibitor (NNRTI) as the anchor drug are available and are both are considered as options in the category of recommended initial regimens in certain situations: efavirenz-tenofovir DF-emtricitabine, rilpivirine-tenofovir alafenamide-emtricitabine, and rilpivirine-tenofovir DF-emtricitabine.[56] 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.[65,66,67] When compared to the efavirenz-based regimen, the rilpivirine-based regimen was better tolerated with fewer adverse events and an 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 is not 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 use 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.

**CHOOSING NRTI Backbone in REGIMEN**

The Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV include three different NRTI combinations: tenofovir alafenamide-emtricitabine, tenofovir DF-emtricitabine,
and abacavir-lamivudine.[56] 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.[68,69] 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.[70] 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.[71] 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.[71] Discontinuation due to adverse effects was similar in both groups.
Antiretroviral Regimens or Components Not Recommended for Use

The Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV provides a category for antiretroviral medications which, either alone or in combination, should not be offered for use at any time.[72] Regimens (or components of regimens) that are considered in the What Not to Use category include:

**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 and ritonavir
- Didanosine plus stavudine
- Didanosine plus tenofovir DF
- Two NNRTIs
- 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. 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.[73,74] Individuals who suppress HIV RNA levels on antiretroviral therapy typically have an increase in CD4 count of approximately 50-150 cells/mm$^3$ after the first year, with subsequent average yearly increases of approximately 50-100 cells/mm$^3$ until a steady state is attained.[75,76] The following outlines recommendations in the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV for monitoring HIV RNA levels and CD4 counts in persons on antiretroviral therapy.[77]

HIV RNA Monitoring

All individuals initiating antiretroviral therapy should have a baseline HIV RNA level and a repeat level obtained 2-8 weeks after initiating therapy. Subsequently, HIV RNA levels should be repeated thereafter every 4-8 weeks until the viral load is suppressed. Once HIV RNA levels are suppressed, monitoring should expand to every 3-4 months. For adherent patients who have consistently suppressed viral load and stable immunologic status for at least 2 years, HIV RNA monitoring can be extended to 6-month intervals. If a patient has a change in clinical status or has to initiate therapy with chronic corticosteroids, chemotherapy, or interferon, the HIV RNA levels should be checked every 3 months.

CD4 Cell Count

All persons starting on antiretroviral therapy should have a baseline CD4 cell count and a repeat value 3 months after starting therapy. During the first 2 years on antiretroviral therapy the CD4 count should be monitored every 3-6 months. After 2 years on antiretroviral therapy, adherent patients with consistently suppressed viral load should have the frequency of CD4 cell count monitoring determine by immune status: (1) if the CD4 count is less than 300 cells/mm$^3$, monitoring should continue every 3-6 months, (2) if the CD4 count is consistently in the 300-500 cells/mm$^3$ range, monitoring can be extended to 12-month intervals, and (3) if CD4 count consistently greater than 500 cells/mm$^3$, monitoring should then be considered optional. If a patient has a change in clinical status or has to initiate therapy with chronic corticosteroids, chemotherapy, or interferon, the CD4 cell counts levels 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 patients who have a poor CD4 count recovery 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 patient is taking a regimen that includes zidovudine or the combination of tenofovir DF and didanosine. Augmentation of the antiretroviral regimen with an additional agent also is neither effective nor recommended by the guidelines. For a patient with a persistently low CD4 count, it is important to make certain the patient is receiving appropriate prophylaxis for opportunistic infections, is not taking any other medications that can suppress bone marrow, and does not have clinical manifestations (pancytopenia, systemic symptoms) of a bone marrow infiltrative process. 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. Accordingly, use of interleukin-2 is not recommended for the management of patients with suboptimal CD4 count responses to antiretroviral therapy.
Discontinuation or Treatment Interruption

Discontinuation of antiretroviral therapy may be necessary at certain times due to acute side effects, illness, surgery, or unavailability of the medications; aside from these factors, patients 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. More recently, discontinuation of therapy has clearly been shown to be detrimental 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$^3$).[47] 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.[90, 91]

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 Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV Infection provides specific recommendations for how to safely stop the medications, particularly for patients who are taking medications with significantly different half-lives.[92]
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 and NtRTIs, (3) NNRTIs, (4) PIs, and (5) INSTIs.
- Initiation of antiretroviral therapy is recommended for all persons living 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.
- All recommended initial regimens for most people with HIV use 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-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 copies/mL) within 24 weeks.
- Typically, individuals with HIV infection 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/mm$^3$ 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.
- There has been considerable interest in the feasibility of simplifying antiretroviral therapy regimens in patients who have achieved virologic suppression on a stable, three-drug regimen; for now, combination antiretroviral therapy with at least three drugs is recommended in most clinical scenarios.
Citations


42. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of
antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services. Initiation of antiretroviral therapy. October 17, 2017. [AIDSinfo]


[PubMed Abstract]

[PubMed Abstract]

[AIDSinfo]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]


[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

77. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services. Laboratory testing: plasma HIV-1 RNA (viral load) and CD4 count monitoring. May 1, 2014.
[AIDSinfo]

[PubMed Abstract]

79. 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.
[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[AIDSinfo]

References

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]


Jegede O, Babu J, Di Santo R, McColl DJ, Weber J, Quiñones-Mateu M. HIV type 1 integrase
[PubMed Abstract] -

[PubMed Abstract] -

- Lee PK, Kieffer TL, Siliciano RF, Nettles RE. HIV-1 viral load blips are of limited clinical significance. 2006;57:803-5.  
[PubMed Abstract] -

[PubMed Abstract] -

- Lok JJ, Bosch RJ, Benson CA, et al. Long-term increase in CD4+ T-cell counts during combination antiretroviral therapy for HIV-1 infection. AIDS. 2010;24:1867-76.  
[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[AIDSinfo] -

- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Considerations for antiretroviral use in patients with coinfections: hepatitis
B (HBV)/HIV coinfection. Last Updated: October 17, 2017.


**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
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

Mixed-Tropic HIV

R5 HIV

X4 HIV

CD4

CCR5

CXCR4

Intracellular Space

Host Cell
Figure 5 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
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
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 Ehler, Cognition Studio and David Spach, MD
Figure 8 (Image Series) - HIV Reverse Transcription (Image Series) - Figure 8 (Image Series) - HIV Reverse Transcription  
Image 8A: HIV Reverse Transcription: Conversion of RNA to DNA

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
Figure 8 (Image Series) - HIV Reverse Transcription
Image 8C: Reverse Transcription: Primer and Template Strands

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
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
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 impedes 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
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 12 (Image Series) - Integration of HIV DNA into Host DNA
Image 12B: 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 12 (Image Series) - Integration of HIV DNA into Host DNA
Image 12C: 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
The HIV DNA that is incorporated into the host DNA is referred to as proviral DNA.

Illustration by David Ehler, Cognition Studio and David Spach, MD
Figure 13 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 integrase.

Illustration by David Ehlerst, Cognition Studio and David Spach, MD
Figure 14 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 15 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 16 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 17 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 18 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).

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 22 Swiss Cohort


Swiss HIV Cohort Study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Antiretroviral Therapy</th>
<th>Deferred Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC Stage B/C</td>
<td>6.4</td>
<td>21.2</td>
</tr>
<tr>
<td>AIDS</td>
<td>1.8</td>
<td>5.3</td>
</tr>
<tr>
<td>Death</td>
<td>2.1</td>
<td>6.4</td>
</tr>
</tbody>
</table>
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 24 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 25 Outcome of Patients in SILCATT Trial

This graph shows the outcome of 1695 patients with a CD4 count less than 200 cells/mm³ 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 Living with HIV**

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

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

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

Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, 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 living with HIV. Department of Health and Human Services. Initiation of antiretroviral therapy. October 17, 2017. [AIDSinfo]
Table 2. **Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living 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).

<table>
<thead>
<tr>
<th>Integrase Strand Transfer Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bictegravir-tenofovir alafenamide-emtricitabine (AI)—only in adults ≥18 years of age</td>
</tr>
<tr>
<td>• Dolutegravir-abacavir-lamivudine&lt;sup&gt;a&lt;/sup&gt; (AI)—only if HLA-B*5701 negative</td>
</tr>
<tr>
<td>• Dolutegravir plus tenofovir alafenamide&lt;sup&gt;b&lt;/sup&gt;-emtricitabine (AI)</td>
</tr>
<tr>
<td>• Dolutegravir plus tenofovir DF&lt;sup&gt;b&lt;/sup&gt;-emtricitabine&lt;sup&gt;a&lt;/sup&gt; (AI)</td>
</tr>
<tr>
<td>• Elvitegravir-cobicistat-tenofovir alafenamide&lt;sup&gt;b&lt;/sup&gt;-emtricitabine (AI)</td>
</tr>
<tr>
<td>• Elvitegravir-cobicistat-tenofovir DF&lt;sup&gt;b&lt;/sup&gt;-emtricitabine (AI)</td>
</tr>
<tr>
<td>• Raltegravir&lt;sup&gt;c&lt;/sup&gt; plus tenofovir DF&lt;sup&gt;b&lt;/sup&gt;-emtricitabine&lt;sup&gt;a&lt;/sup&gt; (AI)</td>
</tr>
<tr>
<td>• Raltegravir&lt;sup&gt;c&lt;/sup&gt; plus tenofovir alafenamide&lt;sup&gt;b&lt;/sup&gt;-emtricitabine (AI)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Lamivudine may substitute for emtricitabine or vice versa, if a non-fixed dose NRTI combination is desired.

<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, while tenofovir DF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

<sup>c</sup>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:

Table 3. **Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living 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.

**Boosted Protease Inhibitor plus 2 Nucleoside Reverse Transcriptase Inhibitors:**

- Darunavir plus ritonavir plus tenofovir alafenamide<sup>a</sup>-emtricitabine<sup>a</sup> (AI)
- Darunavir-cobicistat plus tenofovir alafenamide<sup>b</sup>-emtricitabine<sup>a</sup>(AI)
- Atazanavir plus ritonavir plus tenofovir alafenamide<sup>b</sup>-emtricitabine<sup>a</sup> (BI)
- Atazanavir plus ritonavir plus tenofovir DF<sup>b</sup>-emtricitabine<sup>a</sup> (BII)
- Atazanavir-cobicistat plus tenofovir alafenamide<sup>b</sup>-emtricitabine<sup>a</sup> (BII)
- Atazanavir-cobicistat plus tenofovir DF<sup>b</sup>-emtricitabine<sup>a</sup> (BII)
- Darunavir plus ritonavir plus abacavir-lamivudine<sup>a</sup> (BII)—if HLA-B*5701 negative
- Darunavir-cobicistat plus abacavir-lamivudine<sup>a</sup> (BII)—if HLA-B*5701 negative
- Atazanavir plus ritonavir plus abacavir-lamivudine<sup>a</sup> (BI)—if HLA-B*5701 negative and HIV RNA <100,000 copies/mL
- Atazanavir-cobicistat plus abacavir-lamivudine<sup>a</sup> (BI)—if HLA-B*5701 negative and HIV RNA <100,000 copies/mL

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

- Efavirenz-tenofovir DF<sup>b</sup>-emtricitabine<sup>a</sup> (BII)
- Efavirenz plus tenofovir alafenamide<sup>b</sup>-emtricitabine<sup>a</sup> (BII)
- Rilpivirine-tenofovir DF<sup>b</sup>-emtricitabine<sup>a</sup> (BII)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm<sup>3</sup>
- Rilpivirine-tenofovir alafenamide<sup>b</sup>-emtricitabine<sup>a</sup> (BII)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm<sup>3</sup>

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

- Raltegravir<sup>c</sup> plus abacavir-lamivudine<sup>a</sup> (CII)—if HLA-B*5701 negative and HIV RNA <100,000 copies/mL

**Regimens to Consider when Abacavir, Tenofovir alafenamide, and Tenofovir DF Cannot be Used:**

- Darunavir plus ritonavir plus raltegravir (BID) (CI)—if HIV RNA less than 100,000 copies/mL and CD4 >200 cells/mm<sup>3</sup>
- Lopinavir-ritonavir + lamivudine<sup>a</sup> (BID) (CI)

<sup>a</sup>Lamivudine may substitute for emtricitabine or vice versa, if a non-fixed dose NRTI combination is desired.

<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, while tenofovir DF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs

<sup>c</sup>Raltegravir can be given as 400 mg BID or 1200 mg (two 600-mg tablets) once daily.

<sup>d</sup>Several other NRTI-limiting treatment strategies are under investigation.

<sup>e</sup>Lopinavir-ritonavir plus lamivudine is the only boosted PI plus lamivudine regimen with published 48-week
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.

Data in a randomized controlled trial in ART-naive patients. Limitations of lopinavir-ritonavir plus lamivudine include twice-daily dosing, high pill burden, and greater rates of gastrointestinal side effects than other PIs.

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 Living with HIV. Department of Health and Human Services. What to start: initial combination regimens for the antiretroviral-naive patient. March 27, 2018. [AIDSinfo]