

Class Review: HIV Antiretroviral Agents

Month/Year of Review: July 2015

Research Questions:

- What are the current antiretroviral recommendations in the United States (U.S.) for management of Human Immunodeficiency Virus type 1 (HIV-1, or HIV)?
- What antiretroviral agents and formulations are currently available?
- What are the current challenges with antiretroviral therapy?

Conclusions:

- Recent high quality evidence demonstrates antiretroviral agents (ARV) should be initiated in all HIV-infected patients regardless of baseline CD4 T-lymphocyte cell count (CD4).^{1,2} Current published U.S. guidelines³⁻⁶ do not reflect this evidence but updated recommendations have already been made.⁷ European⁸ and international⁹ guidelines suggest it may be appropriate to wait for CD4 counts to decrease below 500 cells/ μ L, or even 350 cells/ μ L, depending on resources available.
- The U.S. Department of Health and Human Services (HHS)⁴ and the International Antiviral Society-USA (IAS-USA)³ publish the two primary evidence-based guidelines for management of HIV in the U.S. Both guidelines are largely congruent in their recommendations for initial ARV in treatment-naïve HIV-infected persons. There is high quality evidence the type of ARV regimen should be determined by baseline resistance testing and patient characteristics, with consideration for patient preference.^{3,4} The IAS-USA recommend an ARV regimen consisting of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) with either an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) pharmacokinetically enhanced (ie, boosted) with ritonavir or cobicistat.³ The HHS makes similar recommendations but have preferential recommendations for an INSTI-based regimen (ie, with dolutegravir or raltegravir) or a ritonavir-boosted PI regimen (ie, with darunavir) because of less associated drug-drug interactions, improved tolerability or genetic barrier to develop resistance.⁴
- Specific considerations for special populations in both U.S. guidelines are largely based on observational data and clinical experience:
 - Pregnancy: Pregnancy should not preclude the use of an optimal ARV regimen initiation as the rate of congenital birth defects following exposure to ARV during pregnancy is not higher than that reported in the general population. However, a regimen of zidovudine/lamivudine plus either ritonavir-boosted lopinavir or ritonavir-boosted atazanavir in treatment-naïve patients is commonly used.⁶
 - Pediatrics: ARV for children should generally consist of two NRTIs plus one active drug from the following classes: NNRTI or PI, generally boosted with low-dose ritonavir. Although INSTIs may be considered first-line treatment in adults, there are insufficient data to recommend these agents as preferred agents for initial therapy in children.⁵
 - Patients with significant cardiovascular risk factors: low-quality evidence suggests abacavir, ritonavir-boosted lopinavir, and ritonavir-boosted fosamprenavir may be associated with higher rates of cardiovascular events than other agents.³

- Hepatitis B virus (HBV): emtricitabine, lamivudine and tenofovir have activity against HBV. If HIV treatment is needed, fully suppressive ARV initiated with the NRTI backbone combination of emtricitabine plus tenofovir or lamivudine plus tenofovir is recommended.³
- Hepatitis C virus (HCV): selection of optimal ARV is determined by potential drug interactions if concomitant HCV treatment is being given.³
- Immunosuppression/Cancer: because of their favorable drug interaction profiles, dolutegravir- or raltegravir-based regimens are recommended in patients receiving immunosuppressants or chemotherapy for malignancies.³
- In adherent patients presenting with virological failure, drug-resistance testing should be performed while the patient is taking the failing ARV regimen or within 4 weeks of treatment discontinuation, if possible. A new regimen should include at least two, and preferably three, fully active agents.^{3,4}
- Primary challenges specific to ARV includes improving access to HIV care to vulnerable populations and minority populations; choosing a tolerable and convenient regimen that maximizes adherence in order to reduce morbidity, mortality and drug resistance; reducing fraud, waste and abuse of antiretroviral drugs; and continued research to improve efficacy and safety of ARV, understanding of HIV and development of a cure.

Recommendations:

- Create a *voluntary* Preferred Drug List (PDL) for all HIV antiretroviral drugs and combination products, including NRTIs, NNRTIs, INSTIs, PIs, Fusion Protein Inhibitors, CCR5 Antagonists, and ARV-specific CYP P450 Inhibitors.
- Designate all drugs as *preferred* at this time.

Background:

The advancement of management of HIV since the initial outbreaks of opportunistic infections and Kaposi's sarcoma reported in California and New York are among the greatest accomplishments in modern medicine.¹⁰ Once a universally fatal disease associated with complete CD4 cell loss, ARV today is not only potent and reduces morbidity and mortality, but is also convenient and well tolerated. Treatment initiated before advanced disease develops reduces plasma HIV RNA concentrations to undetectable values in most motivated patients who have access to these drugs.¹¹ The degree of immunological recovery varies, but patients treated before onset of advanced immunodeficiency (ie, CD4 <200 cells/ μ L) have significantly sustained CD4 count gains after ARV is initiated.¹¹

The average CD4 count in adults without HIV is about 900 cells/ μ L.¹² However, in HIV-infected persons, the infection will eventually develop progressive immunosuppression without treatment, as evident by CD4 cell depletion, leading to AIDS-defining illnesses and premature death.⁴ Symptomatic disease often emerges as the peripheral CD4 count falls to lower than 350 cells/ μ L.¹¹ The risks of most AIDS-defining opportunistic infections (eg, *Pneumocystis jirovecii* pneumonia) and cancers (eg, Kaposi's sarcoma) increase as the CD4 count falls below 200 cells/ μ L.¹¹ Thus, a CD4 count of 350 cells/ μ L is generally the threshold at which the benefits of starting ARV clearly outweigh the risk of delaying treatment. However, the U.S. guidelines^{3,4} make stronger recommendations to starting HIV treatment earlier (ie, CD4 count >350 cells/ μ L) than recommendations made by European and international guidelines,^{8,9} which is strengthened by new evidence to suggest that starting ARV earlier leads to significantly increased CD4 normalization rates,¹² as well as the premise that suppressing HIV earlier reduces risk of viral transmission and reduces chronic inflammation thought to contribute to cardiovascular complications and other end-organ damage leading to liver disease, kidney disease, neurologic complications, and malignancies reported in HIV-infected cohorts.^{4,11}

The immediate goal of therapy is to reduce HIV viral load to a threshold less than 200 copies of RNA/mL, but preferably less than 50 copies of RNA/mL, an "undetectable" range for most commercial assays and below which the virus does not evolve and drug resistance does not emerge.¹¹ Ultimately, however, the goal is to restore immune function early in order to reduce HIV-associated morbidity and mortality and prevent HIV transmission.⁴

Quantitative viral load, which is the concentration of plasma HIV RNA, is measured before ARV begins, but its primary value is in monitoring treatment response or failure.¹¹ Chronic established HIV infection is often associated with a stable HIV RNA set point, which varies between individuals, but which is associated with the rate of CD4 decline and with the risk of AIDS and death.⁴ Current ARV therapy in treatment-naïve persons suppress plasma viral loads below assay detection limits in over 90% of clinical trial participants – rates that are often also seen in real world clinical use.¹¹ Once viremia is controlled for 1-2 years, virological failure is uncommon.¹¹ Predictors of virologic success include:

- High potency ARV regimen,
- Strict adherence to the ARV regimen,
- Low baseline viremia,
- Higher baseline CD4 count (>200 cells/ μ L), and
- Rapid reduction of viremia in response to treatment.⁴

At present, ARV therapy is considered lifelong. Sustained viral suppression is the foundation for immune recovery, optimal health and prevention of resistance and viral transmission.³ Thus, it is paramount to maximize adherence and minimize toxicity by treating HIV-infected patients with an effective therapy that is well tolerated and convenient, and has limited drug interactions and little effect on comorbid conditions.³ In resource-rich countries like the U.S., individualization of therapy is common and best managed by healthcare providers with HIV expertise where individualized care can be provided.^{3,11}

Antiretroviral therapy consists of a combination of drugs targeting the HIV life cycle with the aim of stopping HIV replication. Because of the high replication and mutation rates of HIV-1, usually three antiretroviral agents from two or more drug classes must be taken simultaneously to suppress replication and prevent the development of resistance.¹³ Individual drugs are generally classified by the viral life cycle step they inhibit, which currently includes six classes that target five unique steps: binding, fusion, reverse transcription, integration and proteolytic cleavage (see **Figure in Appendix 1**). Extracellular virions enter the cell through a complex three-step process, which is (1) attachment to the CD4 receptor, (2) binding to the CCR5 or CXCR4 co-receptors, or both, and (3) membrane fusion.¹¹ CCR5 antagonists block CCR5 binding and fusion inhibitors block fusion of the virion. The HIV reverse transcriptase enzyme catalyzes transcription of HIV RNA to double-stranded DNA, a step inhibited by nucleoside (or nucleotide) and nonnucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs, respectively). The HIV integrase enzyme facilitates incorporation of HIV DNA into host chromosomes, a step inhibited by integrase strand transfer inhibitors (INSTI). After transcription and translation of the HIV genome, immature virions are produced and bud from the cell surface. The HIV protease enzyme cleaves polypeptide chains, allowing the virus to mature, a step inhibited by HIV protease inhibitors (PIs).¹¹ HIV enters its preferred target cells by binding to one or both of the chemokine receptors CCR5 and CXCR4. Nearly all patients with primary HIV infection harbor a virus that binds to CCR5, but as the disease progresses over time, many untreated individuals develop a virus that also binds to CXCR4. Since one therapeutic drug class specifically targets CCR5, testing is needed if this class is utilized to define which tropism of the virus (CCR5 vs. CXCR4) is present.¹¹

Antiretroviral agents listed by drug class are described in **Table 1**. The exception is the addition of two pharmacokinetic enhancers, or boosters, used solely to improve the pharmacokinetic profiles of the PIs and the INSTI elvitegravir.⁴ Several well tolerated and highly effective regimens are available for treatment-naïve patients. The differences in terms of virological outcomes for the available regimens are subtle.¹¹ Therefore, baseline resistance testing and patient characteristics should guide design of the specific regimen, with convenience, pill burden, tolerability and long-term toxic effects important factors to consider when decisions are made between the various therapeutic options.^{4,11} In general, ARV therapy is initiated as a regimen consisting of two NRTIs (the “backbone”) combined with a third agent (the “anchor”), which consists of an NNRTI, a boosted PI, or an INSTI.

Table 1. Antiretroviral Agents by Class.^{3,11}

Antiretroviral Class	Drug	Comments	
Nucleoside Reverse Transcriptase Inhibitors (NRTI)	Abacavir* Emtricitabine* Lamivudine*^ Tenofovir*^	Didanosine Stavudine Zidovudine	A combination of 2 NRTIs (often tenofovir and emtricitabine) is the foundation of recommended ARV therapy. Abacavir and lamivudine had lower rates of viral suppression than tenofovir and emtricitabine when combined with ritonavir-boosted atazanavir or efavirenz when baseline HIV-1 RNA levels were >100,000 copies/mL. However, there is no difference if these drugs are combined with INSTIs dolutegravir or raltegravir. Abacavir should only be used in HLA-B*5701-negative persons to reduce risk of hypersensitivity reactions. Evidence whether abacavir increases risk for myocardial infarction is conflicting. Long-term use of tenofovir is associated with increased risk of kidney injury, which is accentuated by concomitant use of boosted PIs. Tenofovir is more strongly associated with early and non-progressive decrease in bone mineral density.
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)	Efavirenz* Rilpivirine*	Delavirdine Etravirine Nevirapine	Efavirenz has long-term efficacy and safety data but has inferior tolerability to some INSTI-based regimens. There is conflicting evidence whether efavirenz may be associated with increased risk of suicidality or not. Rilpivirine is only an option for persons with HIV-1 RNA levels <100,000 copies/mL.
Integrase Strand Transfer Inhibitors (INSTI)	Dolutegravir* Elvitegravir* Raltegravir*		Compared with NNRTI-based or boosted PI-based regimens, INSTI-based regimens have consistently shown higher rates of viral suppression. Elvitegravir requires boosting with cobicistat. Elvitegravir boosted with cobicistat has similar rates of resistance as raltegravir; variants of HIV resistant to one drug should be considered cross-resistant with the other drug, though dolutegravir may be active against HIV strains resistant to raltegravir or elvitegravir. Raltegravir was the first INSTI approved and has demonstrated durable efficacy since coming to market in 2007; this durability is likely a class effect.
Protease Inhibitors (PI)	Atazanavir* Darunavir* (ritonavir)**	Fosamprenavir Indinavir Lopinavir Nelfinavir Saquinavir Tipranavir	PIs are commonly used in combination with 2 NRTIs for initial ARV therapy. Most PIs are extensively metabolized by cytochrome P450 CYP3A system; ritonavir is generally given at low doses (100-200 mg/day) to inhibit CYP3A4 enzymes and boost the co-administered PIs. Cobicistat may also be used as a booster. Most PIs are associated with hyperlipidemia and other metabolic abnormalities such as insulin resistance. Long-term PI exposure has been associated with increased risk of cardiovascular disease. Newer PIs are less frequently associated with these adverse effects. Atazanavir blocks bilirubin conjugation, which can cause jaundice in some people but does not represent hepatotoxicity. Atazanavir may also be associated with cholelithiasis, nephrolithiasis and renal impairment. Atazanavir may be inferior to darunavir and raltegravir due to increased discontinuation rates observed with increased bilirubin levels. Darunavir contains a sulfa moiety and results in rash in about 10% of patients; incidence/severity of rash are similar in patients with or without a documented sulfa allergy.
CCR5 Inhibitors	Maraviroc		Maraviroc is only active in patients who do not have virions that use CXCR4 for cell entry. A specialized assay is therefore needed to screen for co-receptor tropism. Drug interactions may affect dosing.
Fusion Inhibitors	Enfuvirtide		Enfuvirtide must be given subcutaneously twice daily.

*These drugs are recommended as part of an initial ARV regimen in treatment-naïve HIV-infected patients by the IAS-USA and/or HHS guidelines.^{3,4}

**Ritonavir is generally given at low doses to inhibit the P450 CYP3A system to boost co-administered PIs, which would otherwise be extensively metabolized by these enzymes.

^NRTI used as part of an ARV regimen for HIV or for Hepatitis B.

There are still several challenges with management of HIV infection:

- First, ARV therapy cannot eliminate HIV and only suppresses the virus, which still persists in reservoirs found in specialized immune cells and tissues.¹³ Continued research is needed to better understand HIV and evaluate ARV therapy. Historically, many of the sentinel studies used to make policy decisions on when and how to treat HIV infection used endpoints such as suppression of virus replication in the peripheral blood, increases in peripheral blood CD4 count, or progression to AIDS.¹⁴ Despite success using these outcomes, significant immunologic abnormalities were documented in these studies: CD4 cells continued to be dysfunctional, lymphoid tissues remained depleted of CD4 cells, markers of immune activation remained elevated, the CD8 T-cell responses remained abnormal, and responses to vaccines continued to be suboptimal.¹⁴
- Second, rapid development of drug resistance is the major cause of therapeutic failure.⁴ High adherence to ARV is not achieved in many patients though it is necessary to maintain adequate viral control and reduce resistance and viral transmission.¹¹ Incomplete adherence leads to ongoing HIV replication, which, in the presence of suboptimal drug exposure, can select for viral strains with mutations conferring resistance to those agents.¹³ A number of factors are associated with lower levels of adherence, including the stigma associated with HIV infection, depression, alcohol or drug use, young age, adverse effects of ARV, and pill burden.^{13,15} A recent meta-analysis of 19 randomized controlled trials (n=6321) found that once-daily ARV regimens were associated with a modestly higher rate of adherence than twice-daily regimens, though the difference in adherence between the two groups were not associated with a difference in viral suppression.¹⁵ Each antiretroviral drug, and to some degree each drug class, varies in its ability to generate drug resistance.¹¹ For example, the NRTIs and NNRTIs are more susceptible to development of resistance, while the PIs have a higher threshold for development of resistance and may be more forgiving in terms of non-adherence.¹¹ Transmission of drug-resistant variants can also occur, so a baseline genotypic resistance test is recommended once HIV infection is diagnosed.¹¹ The genotypic characterization of these mutations is now a routine part of clinical management and has improved outcomes.¹¹ Once resistance mutations are selected, they can persist indefinitely in infected cells, increasing the risk of treatment failure if the affected drug is used at later point of time.¹¹
- Third, access to HIV care remains limited in marginalized communities in the U.S.¹¹ The U.S. Centers for Disease Control and Prevention estimates that only 50% of the people living with HIV in the U.S. receive regular HIV care and that among individuals receiving ARV, only 76% have suppressed viral loads.¹⁶ Moreover, rates of adherence to ARV tend to decline over time, even when ARV therapy is provided at no cost.¹³ Among the estimated 1.1 million persons living in the U.S. with HIV in 2009, 18.1% were undiagnosed, 45.2% were aware of their infection but not retained in care, 4.1% were retained in care but not prescribed ARV, 7.2% were prescribed ARV but not virally suppressed, and 25.3% were virally suppressed.¹⁷ Forty-four percent were black; 19% were Hispanic; and 33% were white.¹⁸ Most patients living with HIV (61%) were 35 to 54 years of age; 15% were 25 to 34 years of age; and 7% were 13 to 24 years of age.¹⁸ Male individuals constituted 76% of the HIV population.¹⁸ The percentages of black and Hispanics who were aware of their infection were lower than whites; the percentages linked to care, retained in care, prescribed ARV, and with a suppressed viral load were also lower among blacks and Hispanics compared with whites.¹⁸ Persons who had undiagnosed HIV or diagnosed HIV but not retained in care accounted for 63.3% of the population infected with HIV in 2009 but were responsible for 91.5% of the estimated HIV transmissions during that time.¹⁷ In contrast, persons who were virally suppressed were 94.0% (0.4 transmissions per 100 person-years) less likely to transmit HIV.¹⁷ Fortunately, there are positive trends in some populations. The annual rate of HIV diagnoses during the last decade decreased by more than 33.2%, from 24.1 per 100,000 persons in 2002 to 16.1 in 2011.¹⁹ The annual number of HIV diagnoses decreased the most in persons with infection attributed to injection drug use or heterosexual contact. Diagnoses attributed to male-to-male sexual contact, however, increased among males aged 13-24 years and 45 years and older.¹⁹

- Other, non-clinical challenges also exist. Recently the Community Access National Network (CANN), a group that supports access to HIV care, and the Partnership for Safe Medicines, a non-profit organization targeting counterfeit medication, published a document alerting clinicians and patients to evidence that HIV medications are being resold illegally.²⁰ In some cases, counterfeit medications were sold to patients or pharmacies; in other cases, fraudulently acquired medications were repackaged and sold to pharmacies.²⁰ An August 2014 report by the HHS Office of Inspector General (OIG) also highlighted potential fraud involving prescription medications paid for by Medicare's Part D program.²¹ According to the OIG, the high cost of ARV and the potential for the drugs to be abused may make them a target for fraud.²¹ Data from the Centers for Medicare & Medicaid Services (CMS) between 2011 and 2012 included records of 135,554 patients who allegedly received ARV during a 1-year span costing the Part D program \$2.8 billion.²¹ Of these patients, 1,600 patients had no evidence of an HIV diagnosis in their Medicare records, used an unusually high number of pharmacies or prescribers, received excessive amounts of the drugs, or received simultaneous prescriptions for drugs that should not be used together.²¹ The OIG also found evidence of "doctor shopping" in which 179 beneficiaries received prescriptions from at least 6 different prescribers.²¹ Although the numbers of potentially fraudulent cases are relatively small and the data has some limitations, the OIG has recommended that CMS take further steps to monitor prescription fraud with these drugs.²² From a clinical perspective, fraud involving ARV poses special risks to patients because it can contribute to the development of resistant strains of the virus.²²

Purpose for Class Review:

The purpose of this guideline-centered review is to establish preferred drug lists of classes of HIV antiretroviral agents for the Oregon Health Plan (OHP) population, establish a basis to monitor for appropriate utilization and, if necessary, provide future evidence-based recommendations for the management of these agents as treatments evolve and more options become available.

Methods:

The two primary sources of practice guidelines utilized in the U.S. to guide management of HIV were reviewed: the IAS-USA guidelines and the HHS guidelines.³⁻⁶ The World Health Organization (WHO) HIV/AIDS guidelines for key populations⁹ were also consulted.

Guidelines:

International Antiviral Society-USA

Recommendations of the IAS-USA Panel on antiretroviral treatment of adult HIV infection were recently updated in 2014.³ The recommendations were developed by a volunteer, international panel of experts in HIV research and patient care selected by the IAS-USA and vetted for suitability, expertise, conformance to the group's conflict of interest criteria, and ability to work toward consensus.³ Strength of recommendations were graded as **A** (strong support), **B** (moderate support) or **C** (limited support).³ Quality of evidence was graded as **Ia** (≥ 1 RCT published in peer-reviewed literature), **Ib** (≥ 1 RCT published as an abstract), **IIa** (case-controls or cohorts published in peer-reviewed literature), **IIb** (case-controls or cohorts published in abstract) or **III** (panel analysis and opinion).³

Initiating ARV Therapy:

In patients with HIV infection willing and ready to start therapy, ARV is recommended regardless of CD4 cell count.³ Baseline genotypic testing for resistance should be performed in all treatment-naïve patients (**A IIa**).³ The strength of recommendations and the quality of the evidence increase as the CD4 cell counts decrease and in the presence of certain concurrent conditions:

- For CD4 cell counts $\leq 500/\mu\text{L}$: **A Ia**
- For CD4 cell counts $>500/\mu\text{L}$: **B III**
 - Except pregnancy (**A Ia**); chronic hepatitis B virus co-infection (**A IIa**); or HIV-associated nephropathy (**A IIa**)³

During the acute phase of primary HIV infection, ARV is recommended and should be offered, regardless of symptoms (**B III**) to reduce viral load, lower viral set-point, induce robust immune reconstitution and increase in CD4 cell counts.³ It should be started as soon as possible, preferably within the first 2 weeks of diagnosis, in patients with opportunistic infections (**A Ia**) and AIDS-defining illnesses (**A Ia**).³ An exception is in the setting of cryptococcal meningitis, where data on when best to initiate ARV are still unknown but should be considered when expert management of both cryptococcal and HIV infection is available (**B III**).³ ARV is recommended in all HIV-infected persons with tuberculosis (TB) and should be started within 2 weeks of TB treatment when the CD4 cell counts is $<50/\mu\text{L}$, and by 8 to 12 weeks for those with higher CD4 cell counts (**A Ia**).³

Monitoring ARV Therapy:

HIV RNA levels should be monitored at about 4 weeks after treatment is initiated or changed, and then every 3 months thereafter to confirm viral suppression is below the detectable limit of sensitive commercial assays (**A Ia**).³ Once HIV RNA level is suppressed at 1 year and CD4 cell count is stable at $\geq 350/\mu\text{L}$, viral load and CD4 cell count can be monitored at intervals of ≤ 6 months in patients with good adherence (**C III**).³ Once viral load is suppressed consistently for more than 2 years and CD4 cell counts are consistently $>500/\mu\text{L}$, monitoring CD4 cell counts is optional unless virological failure occurs or there are concurrent immunosuppressive treatments or conditions (**C III**).³ HIV-1 RNA level >200 copies/mL should prompt evaluation of factors leading to failure and consideration of switching ARV (**A IIa**).³ Genotypic testing for resistance should also be performed in cases of virologic failure (**A Ia**).³ Laboratory monitoring for ARV toxicity is also recommended.³ After 16 weeks of successful treatment, the frequency of monitoring is generally decreased to between every 3 to 6 months (**C III**).³

Recommended ARV Regimens:

Initial ARV therapy is based on baseline resistance testing and patient characteristics but also involves consideration for patient preference.³ Recommended first-line ARV is based on the combination of two NRTIs with either an INSTI, a NNRTI or a PI boosted with ritonavir or cobicistat.³ Recommended and alternative regimens are listed in **Table 2** and **Table 3**.

Table 2. Recommended Initial ARV Regimens Equally Recommended by the International Antiviral Society-USA.³

Type of Regimen	Antiretroviral Drug Combination	Rating
Integrase Strand Transfer Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors	Dolutegravir plus tenofovir/emtricitabine	A la
	Dolutegravir plus abacavir/lamivudine**	A la
	Elvitegravir/cobicistat*/tenofovir/emtricitabine	A la
	Raltegravir plus tenofovir/emtricitabine	A la
Non-nucleoside Reverse Transcriptase Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors	Efavirenz/tenofovir/emtricitabine	A la
	Efavirenz plus abacavir/lamivudine**	A la
	Rilpivirine^/tenofovir/emtricitabine	A la
Protease Inhibitor (boosted) + 2 Nucleoside Reverse Transcriptase Inhibitors	Atazanavir (boosted with ritonavir) plus tenofovir/emtricitabine	A la
	Atazanavir (boosted with ritonavir) plus abacavir/lamivudine**	A la
	Darunavir (boosted with ritonavir) plus tenofovir/emtricitabine	A la

*Cytochrome P450 3A4 inhibitor without antiretroviral activity used to increase exposure of certain antiretroviral agents. Cobicistat has less drug interactions as ritonavir and is not interchangeable with ritonavir. Concomitant use of cobicistat and tenofovir is recommended only in patients with an estimated creatinine clearance ≥ 70 mL/min.

**Abacavir/lamivudine may perform less well with baseline HIV-1 RNA $>100,000$ copies/mL, unless combined with dolutegravir.

^Rilpivirine-based regimens recommended only in patients with pre-treatment HIV RNA $<100,000$ copies/mL and CD4 cell count >200 cells/ μ L.

Table 3. Alternative Initial Regimens Recommended by the International Antiviral Society-USA.³

Type of Regimen	Antiretroviral Drug Combination	Rating
Integrase Strand Transfer Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors	Raltegravir plus abacavir/lamivudine**	B la
Non-nucleoside Reverse Transcriptase Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors	Nevirapine plus 2 NRTIs	B la
	Rilpivirine^ plus abacavir/lamivudine**	A la
Protease Inhibitor (boosted) + 2 Nucleoside Reverse Transcriptase Inhibitors	Atazanavir/cobicistat plus 2 NRTIs [#]	B la
	Lopinavir (boosted with ritonavir) fixed-dose combination with 2 NRTIs	B la
	Darunavir (boosted with ritonavir) plus abacavir/lamivudine**	B lb
	Darunavir/cobicistat plus 2 NRTIs [#]	B III
Nucleoside Reverse Transcriptase Inhibitors-limiting* or Nucleoside Reverse Transcriptase Inhibitors-sparing*	Lopinavir (boosted with ritonavir) plus lamivudine	B la
	Lopinavir (boosted with ritonavir) plus raltegravir	B la
	Darunavir (boosted with ritonavir) plus raltegravir	B lb

* Appropriate in clinical situations in which minimizing or eliminating NRTI exposure is desired (eg, high risk of cardiovascular disease; positive HLA-B*5701 assay who also has chronic kidney disease or osteoporosis).³

^ Rilpivirine-based regimens recommended only in patients with pre-treatment HIV RNA $<100,000$ copies/mL and CD4 cell count >200 cells/ μ L.

** Abacavir/lamivudine may perform less well with baseline HIV-1 RNA $>100,000$ copies/mL.

[#] Concomitant use of cobicistat and tenofovir is recommended only in patients with an estimated creatinine clearance ≥ 70 mL/min.

Specific Populations:

Pregnancy: The rate of congenital birth defects following exposure to ARV during pregnancy is not higher than that reported in the general population and is not greater with exposure during the first trimester than later during pregnancy.³ Clinical experience supports initiation with zidovudine/lamivudine plus either ritonavir-boosted lopinavir or ritonavir-boosted atazanavir.³ Efavirenz is no longer contraindicated in pregnancy but is still generally avoided in clinical practice, especially during the first trimester.³ Pharmacokinetic changes during pregnancy may necessitate dose modification of ritonavir-boosted atazanavir when given with either tenofovir or acid suppressant drugs.³

Cardiovascular, Renal and Bone Diseases: Consideration should be given to avoiding use of abacavir, ritonavir-boosted lopinavir, and ritonavir-boosted fosamprenavir in persons at high risk for cardiovascular disease because these regimens have been associated with increased risk of cardiovascular events in some studies.³ Patients with reduced renal function should generally avoid tenofovir, especially in combination with a boosted PI.³ Initiation of ARV therapy generally results in a 2% to 6% loss of bone mineral density (BMD) over the following 1 to 2 years.³ Loss of BMD is greater with tenofovir than with abacavir, and less with raltegravir than with ritonavir-boosted atazanavir or ritonavir-boosted darunavir when combined with tenofovir/emtricitabine.³

HBV Infection: Recommended ARV therapy includes tenofovir and emtricitabine (or lamivudine) as the backbone NRTI regimen.³

HCV Infection: Drug interactions between ARV and direct-acting antivirals for HCV are common because many of these drugs are substrates for CYP P450 or P-glycoprotein.³ Therefore, selection of an optimal ARV regimen is determined by potential drug interactions.³

Malignancy and Immunosuppressive Therapy: Because of their favorable drug interaction profiles, dolutegravir- or raltegravir-based regimens are recommended in patients receiving anticancer or immunosuppressive agents.³

Treatment-Experienced Patients:

Consideration of a new ARV regimen in the setting of virologic failure should always include consideration for the potential reasons for failure, such as adverse effects, exacerbation of comorbidities, drug interactions, pill burden, dosing frequency, and food requirements, all of which can affect adherence.³ Interpretation of mutations and cross-resistance can be complex and consideration for a new ARV regimen is done with expert advice.³ Rates of virologic failure are comparable at 1 year for NNRTI and boosted PI regimens; however, NNRTI-based regimens are associated with more NNRTI and NRTI mutations than PI-based regimens.³ Higher rates of treatment failure are also reported in patients receiving alternative recommended ARV, which may suggest patients receiving alternative recommended ARV are more non-adherent to the regimen.³ The second regimen used after initial virologic failure should generally include a boosted PI because of the high barrier to resistance, especially if there is evidence of a compromised NRTI backbone.³ If there is initial failure with an NNRTI-based regimen, there is evidence for a boosted PI with at least one other active agent (NRTI, NNRTI or INSTI).³ In the setting of multidrug resistance, inclusion of a potent boosted PI (eg, darunavir) in the new regimen is recommended because of its higher barrier to resistance.³ ARV typically used with a boosted PI in regimens for multidrug-resistant HIV include ertravirine, dolutegravir, maraviroc, and in exceptional circumstances, the fusion inhibitor enfuvirtide.³

U.S. Department of Health and Human Services

The HHS guideline on use of antiretroviral agents in HIV-1-infected adults and adolescents was last updated April 2015.⁴ Pre-treatment genotypic resistance testing should guide selection of the most optimal initial ARV regimen since 6-16% of HIV drug resistance is found in ARV-naïve patients and the presence of transmitted drug-resistant viruses may lead to suboptimal virologic response.⁴ Suboptimal adherence may result in reduced treatment response.⁴ Patient factors such as active substance abuse or depression, the complexity of the ARV regimen, access to medication, and inadequate treatment education and support should all be considered and addressed in order to improve adherence to the ARV.⁴ Initial patient characteristics that should be considered when choosing an ARV regimen are:

- Pre-treatment HIV RNA level (viral load);
- Pre-treatment CD4 cell count;
- HIV genotypic drug resistance testing results;
- HLA-B*5701 status;
- Patient preferences; and
- Patient's anticipated adherence/motivation.⁴

The Panel on Antiretroviral Guidelines for Adults and Adolescents graded strength of recommendations as **A** (strong support), **B** (moderate support) or **C** (optional). Quality of evidence was graded as **I** (data from RCTs), **II** (data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes) or **III** (expert opinion).⁴

Deferring ARV therapy until the CD4 count declines places a person at risk for AIDS-defining conditions and has been associated with higher risk of morbidity and mortality. In addition, the magnitude of CD4 recovery is directly correlated with CD4 count at ARV initiation, and many individuals who start treatment with CD4 counts <350 cells/μL never achieve counts >500 cells/μL until up to 6 years after initiating ARV therapy. Two recent randomized clinical trials (START¹ and TEMPRANO²) both demonstrated that the clinical benefits of ARV are greater if started early, with pre-treatment CD4 counts >500 cells/μL, than when initiated at a lower CD4 count threshold.^{1,2} Therefore, initiation of ARV in treatment-naïve patients is recommended for all HIV-infected persons regardless of pre-treatment CD4 count (**A I**).⁷

An ARV regimen for treatment-naïve patients generally consists of two NRTIs (one of which is emtricitabine/tenofovir or abacavir/lamivudine) in combination with a third active antiretroviral drug from one of three drug classes: an INSTI, an NNRTI, or a PI boosted with cobicistat or ritonavir.⁴ The choice of the NRTI combination is typically guided by differences between tenofovir and abacavir because emtricitabine and lamivudine have similar safety and efficacy profiles.⁴ The choice between an INSTI, NNRTI or PI as the third drug in an initial ARV regimen should be guided by the regimen's efficacy, genetic barrier to resistance, adverse effects profile, patient convenience, the patient's comorbidities, and drug-drug interactions.⁴ The panel classifies the regimens in **Table 4** as *recommended* regimens for antiretroviral-naïve patients.⁴

Table 4. Recommended Initial ARV Regimens in Treatment-naïve Patients.⁴

Type of Regimen	Antiretroviral Drug Combination	Rating
Integrase Strand Transfer Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors	Dolutegravir/abacavir/lamivudine*	A I
	Dolutegravir plus tenofovir/emtricitabine	A I
	Elvitegravir/cobicistat/tenofovir/emtricitabine [^]	A I
	Raltegravir plus tenofovir/emtricitabine	A I
Protease Inhibitor (boosted) + 2 Nucleoside Reverse Transcriptase Inhibitors	Darunavir/ritonavir plus tenofovir/emtricitabine	A I

*Recommended only in patients who are HLA-B*5701 negative.

[^]Concomitant use of cobicistat and tenofovir is recommended only in patients with an estimated creatinine clearance ≥ 70 mL/min.

The INSTI-based regimens are recommended because of their high virologic efficacy, excellent safety and tolerability profiles and, with dolutegravir and raltegravir, low number of drug-drug interactions.⁴ For patients who are at high risk for intermittent therapy because of poor adherence or have transmitted NRTI drug resistance, a ritonavir-boosted PI-based regimen is preferred given the PIs high genetic barrier to resistance.⁴

Alternative regimens are also recommended on the basis of individual patient characteristics and needs.⁴ These regimens are effective and tolerable, but have potential disadvantages when compared with the recommended regimens, have limitations for use in certain patient populations, or have less supporting data from randomized clinical trials.⁴ The panel classifies the regimens in **Table 5** as *alternative* regimens for antiretroviral-naïve patients.⁴

Table 5. Alternative Initial ARV Regimens in Treatment-naïve Patients.⁴

Type of Regimen	Antiretroviral Drug Combination	Rating
Non-nucleoside Reverse Transcriptase Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors	Efavirenz/tenofovir/emtricitabine	B I
	Rilpivirine/tenofovir/emtricitabine*	B I
Protease Inhibitor (boosted) + 2 Nucleoside Reverse Transcriptase Inhibitors	Atazanavir/cobicistat plus tenofovir/emtricitabine**	B I
	Atazanavir with ritonavir plus tenofovir/emtricitabine	B I
	Darunavir with ritonavir plus abacavir/lamivudine [^]	B II
	Darunavir/cobicistat plus tenofovir/emtricitabine**	B II
	Darunavir/cobicistat plus abacavir/lamivudine [^]	B III

* Rilpivirine-based regimens recommended only in patients with pre-treatment HIV RNA $< 100,000$ copies/mL and CD4 cell count > 200 cells/ μ L.

** Concomitant use of cobicistat and tenofovir is recommended only in patients with an estimated creatinine clearance ≥ 70 mL/min.

[^] Abacavir/lamivudine may perform less well with baseline HIV-1 RNA $> 100,000$ copies/mL. Recommended only in patients who are HLA-B*5701 negative.

Other regimen options are regimens that, in comparison to *recommended* and *alternative* regimens, may have reduced virologic activity, limited supporting data from large comparative clinical trials, or other factors such as more toxicities, higher pill burden, poor drug interaction profile, or limitations for use in certain patients populations.⁴ The panel classifies the regimens in **Table 6** as *other optional* regimens for antiretroviral-naïve patients.⁴

Table 6. Other Optional Initial ARV Regimens in Treatment-naïve Patients.⁴

Type of Regimen	Antiretroviral Drug Combination	Rating
Integrase Strand Transfer Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors	Raltegravir plus abacavir/lamivudine*	C II
Non-nucleoside Reverse Transcriptase Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors	Efavirenz plus abacavir/lamivudine*	C I
Protease Inhibitor (boosted) + 2 Nucleoside Reverse Transcriptase Inhibitors	Atazanavir with ritonavir plus abacavir/lamivudine*	C I
	Lopinavir/ritonavir plus abacavir/lamivudine*	C I
	Lopinavir/ritonavir plus tenofovir/emtricitabine	C I
Other Regimens When Tenofovir or Abacavir Cannot be Used	Atazanavir with cobicistat plus abacavir/lamivudine*	C III
	Darunavir with ritonavir plus raltegravir	C I
	Lopinavir/ritonavir plus lamivudine	C I

* Abacavir/lamivudine may perform less well with baseline HIV-1 RNA >100,000 copies/mL. Recommended only in patients who are HLA-B*5701 negative.

HIV/HCV Co-infection:

All HIV-infected patients should be screened for HCV.⁴ ARV may slow the progression of liver disease by preserving and restoring immune function and reducing HIV-related immune activation and inflammation.⁴ For most HIV/HCV-coinfected patients, including those with cirrhosis, the benefits of ARV therapy outweigh concerns regarding drug-induced hepatotoxicity.⁴ Therefore, ARV should be initiated in most HIV/HCV-coinfected patients, regardless of the CD4 count (**B II**).⁴ However, combined treatment of HIV and HCV can be complicated by drug-drug interactions, increased pill burden and toxicities; therefore, in patients with CD4 counts >500 cells/μL, ARV therapy may be deferred until HCV treatment is completed (**C III**).⁴ In patients with lower CD4 counts (eg, <200 cells/μL), ARV therapy should be initiated promptly (**A I**) and HCV therapy may be delayed until the patient is stable on HIV treatment (**C III**).⁴ Initial ARV regimens recommended for most HIV/HCV-coinfected patients are the same as those recommended for patients without HCV infection.⁴ However, the ARV regimen should be selected with consideration for potential drug-drug interactions and overlapping toxicities if given concurrently with the HCV treatment regimen.⁴

HIV/HBV Co-infection:

Prior to initiation of ARV therapy, all patients who test positive for hepatitis B surface antigen should be tested for HBV DNA using a quantitative assay to determine the level of activity of HBV replication (**A III**).⁴ Emtricitabine, lamivudine and tenofovir have activity against HBV.⁴ If HIV treatment is needed, fully suppressive ARV initiated with the NRTI backbone combination of emtricitabine plus tenofovir or lamivudine plus tenofovir is recommended (**A I**).⁴ If HBV treatment is needed and tenofovir cannot be safely used, the alternative recommended HBV therapy is entecavir in addition to a fully suppressive ARV regimen (**B I**).⁴ Other HBV treatment regimens include peginterferon alfa monotherapy or adefovir in combination with lamivudine or emtricitabine or telbivudine in addition to a fully suppressive ARV regimen (**B II**).⁴ Discontinuation of agents with anti-HBV activity may cause serious hepatocellular damage resulting from reactivation of HBV.⁴

Pregnancy:

The use of ARV therapy and the resultant reduction of HIV RNA levels decrease perinatal transmission of HIV.⁶ Thus, ARV therapy is recommended for all HIV-infected pregnant women, regardless of virologic, immunologic or clinical parameters **(A I)**.⁶ Genotypic resistance testing is recommended for all pregnant women before ARV initiation **(A III)** and for pregnant women with detectable HIV RNA levels while on ARV **(A I)**.⁶ Pregnancy should not preclude the use of an optimal ARV regimen.⁶

Pediatrics:

Few randomized, Phase 3 clinical trials of ARV in pediatric patients exist that provides direct comparison of different treatment regimens.⁵ Most pediatric drug data come from Phase I/II safety and pharmacokinetic trials and non-randomized, open-label studies.⁵ ARV for children should generally consist of two NRTIs plus one active drug from one of the following classes: a NNRTI or a PI boosted with low-dose ritonavir.⁵ Limited evidence indicates INSTIs may have also be effective in pediatric patients, but there are still insufficient data to prefer an INSTI-based regimen over the other commonly used pediatric regimens at this time.⁵ Selection of an initial regimen should be individualized based on a number of factors including characteristics of the proposed regimen, patient characteristics, and results of viral resistance testing **(A III)**.⁵ The panel recommends initiating combination ARV in treatment-naïve children using one of the following preferred agents in combination with **2 NRTIs**:

- For neonates/infants aged ≥ 42 weeks postmenstrual and ≥ 14 days postnatal and children < 3 years: lopinavir/ritonavir **(A I)**;
- For children aged 3 years to < 6 years: efavirenz or lopinavir/ritonavir **(A I)**;
- For children aged ≥ 6 years: atazanavir/ritonavir or efavirenz or lopinavir/ritonavir **(A I)**.⁵

The panel recommends the following preferred 2-NRTI combinations:

- For infants < 3 months: zidovudine plus (lamivudine or emtricitabine) **(A I)**;
- For children aged ≥ 3 months: abacavir plus (lamivudine or emtricitabine) **(A I)** or zidovudine plus ((lamivudine or emtricitabine) **(A I)**);
 - HLA-B*5701 genetic testing should be performed before initiating abacavir-based therapy, and abacavir should not be given to a child who tests positive for HLA-B*5701 **(A II)**;
- For children aged ≥ 12 years: abacavir plus lamivudine or plus emtricitabine **(A I)**;
- For adolescents at Tanner Stage 4 or 5: abacavir plus lamivudine or plus emtricitabine **(A I)** or tenofovir plus lamivudine or plus emtricitabine **(A I)**.⁵

HIV-2 Infection:

HIV-2 infection is endemic in West Africa.⁴ It has had only limited spread outside this area and should be considered in persons of West Africa origin or in those who have had sexual contact or shared needles with persons of West Africa origin.⁴ Like HIV-1, HIV-2 infection can progress to AIDS but is generally characterized by a longer asymptomatic stage, lower plasma HIV-2 viral loads, and lower mortality rate relative to HIV-1 infection.⁴ There have been no randomized trials addressing the question of when to start ARV or the choice of initial or second-line therapy.⁴ Although the optimal CD4 count threshold for initiating ARV in HIV-2 is unknown, ARV therapy should be started before there is clinical progression.⁴ However, NNRTIs and enfuvirtide should be avoided as HIV-2 is intrinsically resistant to these drugs.⁴ Pending more data, an initial ARV regimen for HIV-2 infected patients, or HIV-1/HIV-2 co-infected patients, should include two NRTIs plus a boosted PI or an INSTI.⁴

Virologic Failure:

ARV regimens currently recommended for initial therapy of HIV-infected patients have a high likelihood of achieving and maintaining plasma HIV RNA levels below the limits of detection of currently used assays.⁴ Patients on ARV who do not achieve this treatment goal or who experience virologic rebound often develop resistance mutations to one or more components of their regimen.⁴ Many patients with detectable viral loads are non-adherent to treatment.⁴ Once virologic failure is confirmed, every effort should be made to assess whether suboptimal adherence or drug-drug interactions may be contributing to inadequate virologic response to ARV.⁴ If virologic failure persists after these issues have been addressed, resistance testing should be performed, and the regimen should be changed as soon as possible to avoid progressive accumulation of resistance mutations.⁴ In all cases, expert advice is critical.⁴ Drug-resistance testing should be performed while the patient is taking the failing ARV regimen (**A I**) or within 4 weeks of treatment discontinuation (**A II**).⁴ A new regimen should include at least two, and preferably three, fully active agents (**A I**).⁴ A fully active agent is one that is expected to have uncompromised activity on the basis of the patient's treatment history and drug-resistance testing results.⁴ In general, adding a single ARV agent to a virologically failing regimen is not recommended because this may increase the risk of development of resistance to all drugs in the regimen (**B II**).⁴ For some highly ARV-experienced patients, maximal virologic suppression is not possible.⁴ In these cases, ARV therapy should be continued (**A I**) with regimens designed to minimize toxicity, preserve CD4 counts, and delay clinical progression.⁴

World Health Organization

The WHO recently published guidelines on HIV prevention, diagnosis, treatment and care for key populations in 2014.⁹ The guidelines aim to increase awareness of the needs and issues important to five key populations, and provide a comprehensive package of evidence-based HIV-related recommendations for these groups: men who have sex with men, people who inject drugs, people in prisons and other closed settings, sex workers, and transgender people.⁹ Recommendations largely encompass all facets of HIV prevention and care in these populations.⁹ However, there are no clinical ARV recommendations specific to these populations except to note that because of stigma, discrimination and marginalization, these populations frequently present late for treatment and will require immediate initiation of ARV therapy.⁹ The WHO guidelines primarily differ from the U.S. guidelines in that they make no specific recommendation to start ARV therapy when CD4 counts are higher than 500 cell/ μ L.⁹

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Appendix 1: HIV Life Cycle

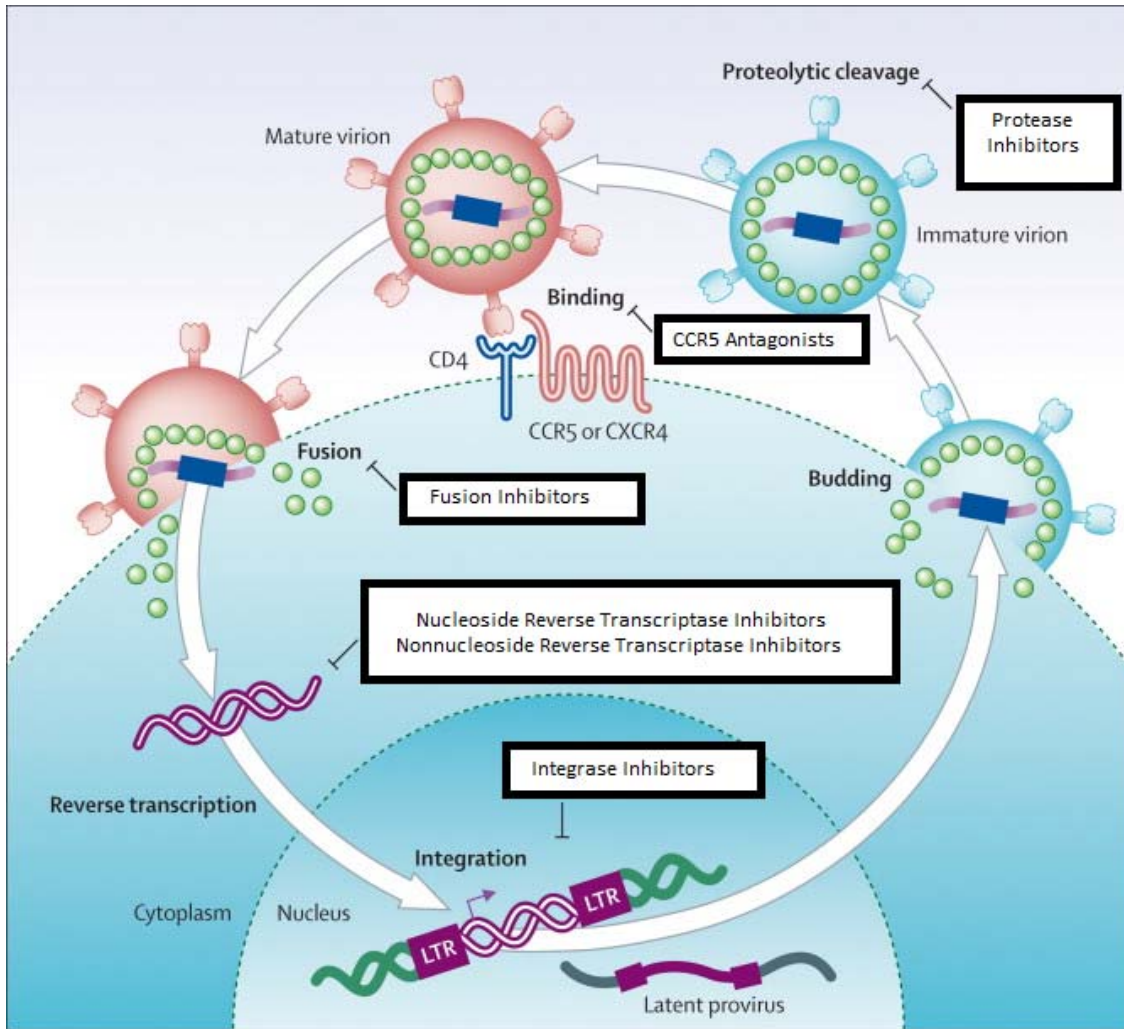


Figure. HIV life cycle and antiretroviral targets. Adapted from Volberding and Deeks. *Lancet* 2010;376.¹¹

Appendix 2. Drug Information of FDA-Approved Antiretroviral Therapy and Pharmacokinetic Enhancers

Table 1. Antiretroviral Therapy Formulations

Drug Name	Mechanism/Class	Oral Formulation(s)	Dosing Frequency
ZIAGEN (abacavir)	NRTI	Solution; Tablet*	Daily – BID
EPZICOM (abacavir/lamivudine)	NRTI	Tablet	Daily
TRIUMEQ (abacavir/dolutegravir/lamivudine)	NRTI/INSTI	Tablet	Daily
TRIZIVIR (abacavir/lamivudine/zidovudine)	NRTI	Tablet*	BID
EMTRIVA (emtricitabine)	NRTI	Capsule; Solution	Daily
TRUVADA (emtricitabine/tenofovir)	NRTI	Tablet	Daily
ATRIPLA (efavirenz/emtricitabine/tenofovir)	NRTI/NNRTI	Tablet	Daily
COMPLERA (emtricitabine/rilpivirine/tenofovir)	NRTI/NNRTI	Tablet	Daily
STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir)	NRTI/INSTI/CYP P450 Inhibitor	Tablet	Daily
EPIVIR (lamivudine)	NRTI	Solution*; Tablet*	Daily – BID
COMBIVIR (lamivudine/zidovudine)	NRTI	Tablet*	BID
VIDEX EC; VIDEX (didanosine)	NRTI	Capsule*; Solution	Daily – BID
ZERIT (stavudine)	NRTI	Capsule*; Solution*	BID
RETROVIR (zidovudine)	NRTI	Capsule*; Syrup*; Tablet*	BID – TID
SUSTIVA (efavirenz)	NNRTI	Capsule; Tablet	Daily
EDURANT (rilpivirine)	NNRTI	Tablet	Daily
RESCRIPTOR (delavirdine)	NNRTI	Tablet	TID
INTELENCE (etravirine)	NNRTI	Tablet	BID
VIRAMUNE; VIRAMUNE XR (nevirapine)	NNRTI	Suspension*; Tablet*; Tablet ER*	Daily – BID
TIVICAY (dolutegravir)	INSTI	Tablet	Daily – BID
VITEKTA (elvitegravir)	INSTI	Tablet	Daily
ISENTRESS (raltegravir)	INSTI	Chew Tablet; Packet; Tablet	BID
REYATAZ (atazanavir)	PI	Capsule; Packet	Daily
EVOTAZ (atazanavir/cobicistat)	PI/CYP P450 Inhibitor	Tablet	Daily
PREZISTA (darunavir)	PI	Suspension; Tablet	Daily – BID
PREZCOBIX (darunavir/cobicistat)	PI/CYP P450 Inhibitor	Tablet	Daily
LEXIVA (fosamprenavir)	PI	Suspension; Tablet	Daily – BID
CRIXIVAN (indinavir)	PI	Capsules	BID – TID
KALETRA (lopinavir/ritonavir)	PI/CYP P450 Inhibitor	Solution; Tablet	Daily – BID

VIRACEPT (nelfinavir)	PI	Tablet	BID – TID
INVIRASE (saquinavir)	PI	Capsule; Tablet	BID
APTIVUS (tipranavir)	PI	Capsule; Solution	BID
NORVIR (ritonavir)	CYP P450 Inhibitor	Capsule; Solution; Tablet	w/ PI
TYBOST (cobicistat)	CYP P450 Inhibitor	Tablet	Daily
SELZENTRY (maraviroc)	CCR5 Antagonist	Tablet	BID
FUZEON (enfuvirtide)	Fusion Inhibitor	Solution (subcutaneous inj)	BID

*generic formulation available

Table 2. Drug Characteristics (adapted from the HHS HIV Guideline for Adults and Adolescents⁴)

Drug Name	Metabolism/Elimination/Dose Adjustments	Adverse Events
Nucleoside Reverse Transcriptase Inhibitors		
Abacavir (ABC) Fixed Combinations: ABC/ZDV/3TC ABC/3TC ABC/3TC/DTG	<ul style="list-style-type: none"> Metabolized by alcohol dehydrogenase and glucuronyl transferase Renal excretion of metabolites: 82% Dose adjustment for ABC recommended with mild hepatic insufficiency Only NRTI to not require renal dose adjustment 	<ul style="list-style-type: none"> Hypersensitivity Reactions: patients positive for HLA-B*5701 at highest risk; symptoms may include: fever, rash, nausea, vomiting, diarrhea, abdominal pain, malaise, fatigue, or respiratory symptoms (sore throat, cough or shortness of breath) Initial cohort studies suggest increased risk of MI with recent/current use of ABC, but the risk has not been substantiated in other studies
Didanosine (ddl)	<ul style="list-style-type: none"> Renal excretion: 50% Dose adjustment for ddl recommended with renal insufficiency 	<ul style="list-style-type: none"> Pancreatitis Peripheral neuropathy Retinal changes, optic neuritis Lactic acidosis with hepatic steatosis w/ or w/o pancreatitis (rare but life-threatening) Nausea, vomiting Insulin resistance; diabetes mellitus Potential association w/ non-cirrhotic portal hypertension One cohort suggested increased risk of MI with recent/current use of ddl, but the risk has not been substantiated in other studies
Emtricitabine (FTC) Fixed Combinations: FTC/EFV/TDF FTC/RPV/TDF FTC/EVG _c /TDF FTC/TDF	<ul style="list-style-type: none"> Renal excretion: 86% Dose adjustment for FTC recommended with renal insufficiency 	<ul style="list-style-type: none"> Minimal toxicity Hyperpigmentation/skin discoloration
Lamivudine (3TC) Fixed Combinations: 3TC/ZDV 3TC/ABC 3TC/ZDV/ABC 3TC/ABC/DTG	<ul style="list-style-type: none"> Renal excretion: 71% Dose adjustment for 3TC recommended with renal insufficiency 	<ul style="list-style-type: none"> Minimal toxicity Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue 3TC
Stavudine (d4T)	<ul style="list-style-type: none"> Renal excretion: 50% Dose adjustment for d4T recommended with renal 	<ul style="list-style-type: none"> Peripheral neuropathy Hyperlipidemia; lipoatrophy

	insufficiency	<ul style="list-style-type: none"> • Pancreatitis • Lactic acidosis/severe hepatomegaly w/ hepatic steatosis (rare but life-threatening) • Insulin resistance; diabetes mellitus • Rapidly progressive ascending neuromuscular weakness (rare)
Tenofovir (TDF) Fixed Combinations: TDF/EFV/FTC TDF/RPV/FTC TDF/EVG _c /FTC TDF/FTC	<ul style="list-style-type: none"> • Renal excretion is primary route of elimination • Dose adjustment for TDF recommended with renal insufficiency 	<ul style="list-style-type: none"> • Renal insufficiency, Fanconi syndrome, proximal renal tubulopathy • Osteomalacia, decrease in bone mineral density • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue TDF • Asthenia, headache, diarrhea, vomiting and flatulence
Zidovudine (ZDV) Fixed Combinations: ZDV/3TC ZDV/3TC/ABC	<ul style="list-style-type: none"> • Metabolized to azidothymidine glucuronide • Renal excretion of azidothymidine glucuronide • Dose adjustment for ZDV recommended with renal insufficiency 	<ul style="list-style-type: none"> • Bone marrow suppression; macrocytic anemia or neutropenia • Nausea, vomiting, headache, insomnia, asthenia • Nail pigmentation • Lactic acidosis/severe hepatomegaly w/ hepatic steatosis (rare but life-threatening) • Hyperlipidemia; lipoatrophy • Insulin resistance; diabetes mellitus • Myopathy
Non-Nucleoside Reverse Transcriptase Inhibitors		
Efavirenz (EFV) Fixed Combinations: EFV/TDF/FTC	<ul style="list-style-type: none"> • Metabolized by CYP 2B6 (primary), 3A4 and 2A6 • CYP 3A4 mixed inducer/inhibitor (primarily inducer) • CYP 2C9 and 2C19 inhibitor, 2B6 inducer 	<ul style="list-style-type: none"> • Rash • Neuropsychiatric symptoms • Increased transaminase levels • Hyperlipidemia • False-positive results w/ some cannabinoid and benzodiazepine screening assays reported • Teratogenic in primates; potentially teratogenic during first trimester in pregnant women
Etravirine (ETR)	<ul style="list-style-type: none"> • Metabolized by CYP 3A4, 2C9 and 2C19 • Induces CYP 3A4 • Inhibits 2C9 and 2C19 	<ul style="list-style-type: none"> • Rash, including Stevens-Johnson syndrome (rare) • Hypersensitivity reactions, characterized by rash, sometimes organ dysfunction (hepatic failure) • Nausea
Nevirapine (NVP)	<ul style="list-style-type: none"> • Metabolized by CYP P450s • Induces CYP 3A4 and 2B6 • 80% excreted in urine (glucuronidated metabolites; <5% unchanged); 10% in feces 	<ul style="list-style-type: none"> • Rash, including Stevens-Johnson syndrome (rare) • Symptomatic hepatitis, including fatal hepatic necrosis, has been reported <ul style="list-style-type: none"> ○ Rash reported in about 50% of cases ○ ARV-naïve females w/ CD4 counts >250 cells/μL and ARV-naïve males w/ CD4 counts >400 cells/μL are at significantly higher risk. Do not initiate NVP in these patients.
Rilpivirine (RPV) Fixed Combinations: TDF/RPV/FTC	<ul style="list-style-type: none"> • Metabolized by CYP 3A4 	<ul style="list-style-type: none"> • Rash • Depression, insomnia, headache • Hepatotoxicity
Protease Inhibitors		
Atazanavir (ATV) Fixed Combinations: ATV _c	<ul style="list-style-type: none"> • Metabolized by CYP 3A4 • Inhibits CYP 3A4 • Dose adjustment for ATV recommended with hepatic insufficiency • With cobicistat: metabolized and inhibits CYP 3A4 	<ul style="list-style-type: none"> • Indirect hyperbilirubinemia • Prolongs PR interval; reports of first degree symptomatic AV block • Hyperglycemia • Cholelithiasis • Nephrolithiasis • Renal insufficiency • Serum transaminase elevations

		<ul style="list-style-type: none"> Hyperlipidemia, especially w/ RTV boosting; fat maldistribution Skin rash Increase in serum creatinine w/ cobicistat
Darunavir (DRV) Fixed Combinations: DRV,c	<ul style="list-style-type: none"> Metabolized by CYP 3A4 Inhibits CYP 3A4 Induces CYP 2C9 With cobicistat: metabolized and inhibits CYP 3A4 	<ul style="list-style-type: none"> Skin rash (10%); contains a sulfonamide moiety; Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme have been reported Hepatotoxicity Diarrhea, nausea Headache Hyperlipidemia; fat maldistribution Serum transaminase elevation Hyperglycemia Increase in serum creatinine w/ cobicistat
Fosamprenavir (FPV)	<ul style="list-style-type: none"> Metabolized by CYP 3A4 Inhibits and induces CYP 3A4 Dose adjustment for FPV recommended with hepatic insufficiency 	<ul style="list-style-type: none"> Skin rash (12%); contains a sulfonamide moiety Diarrhea, nausea, vomiting Headache Hyperlipidemia; fat maldistribution Serum transaminase elevation Hyperglycemia Nephrolithiasis
Indinavir (IDV)	<ul style="list-style-type: none"> Metabolized by CYP 3A4 Inhibits CYP 3A4 Dose adjustment for IDV recommended with hepatic insufficiency 	<ul style="list-style-type: none"> Nephrolithiasis GI intolerance, nausea Hepatitis; indirect hyperbilirubinemia Hyperlipidemia; fat maldistribution Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia and hemolytic anemia Hyperglycemia
Lopinavir/Ritonavir (LPV,r)	<ul style="list-style-type: none"> Metabolized by CYP 3A4 Inhibits CYP 3A4 	<ul style="list-style-type: none"> GI intolerance, nausea, vomiting, diarrhea Pancreatitis Asthenia Hyperlipidemia (esp. hypertriglyceridemia); fat maldistribution Serum transaminase elevation Hyperglycemia Insulin resistance; diabetes mellitus PR interval and QT interval prolongation
Nelfinavir (NFV)	<ul style="list-style-type: none"> Metabolized by CYP 2C19 and 3A4 to M8 metabolite Inhibits CYP 3A4 Only PI not boosted with RTV 	<ul style="list-style-type: none"> Diarrhea Hyperlipidemia; fat maldistribution Hyperglycemia Serum transaminase elevation
Ritonavir (RTV) Fixed Combinations: LPV,r	<ul style="list-style-type: none"> Metabolized primary by CYP 3A4 and 2D6 Potently inhibits CYP 3A4 and 2D6 Induces CYP 1A2, 2C8, 2C9 and 2C19 and UGT1A1 	<ul style="list-style-type: none"> GI intolerance, nausea, vomiting, diarrhea Paresthesia (circumoral and extremities) Hyperlipidemia (esp. hypertriglyceridemia); fat maldistribution Hepatitis Asthenia Hyperglycemia

Saquinavir (SQV)	<ul style="list-style-type: none"> Metabolized by CYP 3A4 	<ul style="list-style-type: none"> GI intolerance, nausea, and diarrhea Headache Serum transaminase elevation Hyperlipidemia; fat maldistribution Hyperglycemia PR interval and QT interval prolongation
Tipranavir (TPV)	<ul style="list-style-type: none"> Metabolized by CYP 3A4 Induces CYP 3A4, 1A2, 2C19 Inhibits CYP 2D6 Net effect when combined w/ RTV: inhibits CYP 3A4 and 2D6 	<ul style="list-style-type: none"> Hepatotoxicity: clinical hepatitis (including hepatic decompensation and hepatitis-associated fatalities) has been reported Skin rash (3% to 21%); TPV has a sulfonamide moiety Rare cases of fatal and nonfatal intracranial hemorrhages; risks include brain lesion, head trauma, recent neurosurgery, coagulopathy; hypertension; alcoholism; use of anticoagulants/antiplatelets Hyperlipidemia; fat maldistribution Hyperglycemia
Integrase Strand Transfer Inhibitors		
Dolutegravir (DTG) Fixed Combinations: DTG/ABC/3TC	<ul style="list-style-type: none"> UGT1A1-mediated glucuronidation, and to a lesser extent CYP3A 	<ul style="list-style-type: none"> Hypersensitivity reactions including rash, constitutional symptoms, and organ dysfunction (including liver injury) have been reported Insomnia Headache
Elvitegravir (EVG) Fixed Combinations: EVG,c/FTC/TDF	<ul style="list-style-type: none"> Metabolized by CYP 3A, UGT1A1 and 1A3 	<ul style="list-style-type: none"> Nausea diarrhea
Raltegravir (RAL)	<ul style="list-style-type: none"> UGT1A1-mediated glucuronidation 	<ul style="list-style-type: none"> Rash, including Stevens-Johnson syndrome, hypersensitivity reactions, toxic epidermal necrolysis Nausea; diarrhea Headache Pyrexia CPK elevation, muscle weakness and rhabdomyolysis Insomnia
Fusion Inhibitor		
Enfuvirtide (T20)	<ul style="list-style-type: none"> Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool 	<ul style="list-style-type: none"> Local injection site reactions (eg, pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) in almost 100% of patients Increased incidence of bacterial pneumonia Hypersensitivity reactions (<1%); symptoms include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Re-challenge is not recommended.
CCR5 Antagonist		
Maraviroc (MVC)	<ul style="list-style-type: none"> Metabolized by CYP 3A4 	<ul style="list-style-type: none"> Abdominal pain Cough; Upper respiratory tract infections Dizziness Musculoskeletal symptoms Pyrexia Rash Hepatotoxicity, which may be preceded by severe rash or signs of systemic allergic reactions Orthostatic hypotension, especially in patients with severe renal insufficiency

Abbreviations: c = cobicistat; r = ritonavir