

Antiretrovirals

Five drug classes that each block a different step of the HIV replication cycle, always combined at least three drugs deep because HIV's own high mutation rate makes any single agent, or any two-drug regimen outside a few specifically studied exceptions, a fast route to resistance.

Online guide: <https://www.medguideglobal.com/pharmacology/antivirals-antifungals-antiparasitics/antiretrovirals>

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Quick revision

One Liner: HIV is never treated with one drug: current guidelines build a regimen from an integrase strand transfer inhibitor plus two nucleoside/nucleotide reverse transcriptase inhibitors, because combining agents from different classes closes off the escape routes any single drug leaves open to HIV's fast-mutating reverse transcriptase.

1. The DHHS adult and adolescent guidelines recommend an oral second-generation integrase strand transfer inhibitor (INSTI) plus two NRTIs - bictegravir/tenofovir alafenamide/emtricitabine or dolutegravir plus TAF/FTC, TDF/FTC or TDF/lamivudine - as initial therapy for most people with HIV. [8]
2. NRTIs (e.g. tenofovir, emtricitabine, lamivudine, abacavir) are chain terminators: they lack the 3'-hydroxyl group DNA synthesis needs to keep extending, so viral DNA synthesis stops once one is incorporated. [7]
3. NNRTIs (e.g. efavirenz, nevirapine, rilpivirine, doravirine) bind reverse transcriptase directly at a site away from the active centre and block the enzyme's conformational movement rather than terminating the growing DNA chain. [7]
4. Protease inhibitors (e.g. darunavir, atazanavir, lopinavir) block the HIV protease that cleaves precursor polyproteins into mature structural and enzymatic proteins, so virions assembled in their presence are immature and non-infectious. [7]
5. Integrase strand transfer inhibitors (e.g. dolutegravir, bictegravir, raltegravir, cabotegravir) block integrase from inserting the reverse-transcribed viral DNA into the host genome. [7]
6. Abacavir carries an FDA-mandated HLA-B*5701 screening requirement: patients who test positive for that allele are at materially higher risk of a multi-organ hypersensitivity reaction and abacavir is contraindicated for them, and once hypersensitivity is suspected in anyone, abacavir is stopped for good. [3]
7. Tenofovir disoproxil fumarate and tenofovir alafenamide both carry renal and bone-density warnings; acute renal failure, Fanconi syndrome and decreases in bone mineral density are described in their labelling. [2]
8. Darunavir, like most HIV protease inhibitors used today, is not given alone: its own label states it must be co-administered with low-dose ritonavir (or cobicistat) as a pharmacokinetic booster to reach adequate plasma concentrations. [5]

Overview

1. Antiretroviral therapy (ART) is built around a principle that has held since the mid-1990s: HIV is treated with a combination regimen, not a single drug. Standard therapy uses three medications drawn from at least two antiretroviral classes, targeting different steps of the replication cycle at once. This is not a dosing convenience - it is a direct response to how fast HIV's reverse transcriptase makes copying errors, which lets drug-resistant variants emerge under the selective pressure of a single agent far faster than they would against two or three simultaneously. [7]
2. The classes in routine use each interrupt a different stage. Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) both act on reverse transcriptase, but by different mechanisms - one by terminating the growing DNA chain, the other by binding an allosteric site and freezing the enzyme's motion. Protease inhibitors act later, blocking the cleavage step that turns a newly budded, structurally immature virion into an infectious one. Integrase strand transfer inhibitors act in between, stopping the reverse-transcribed viral DNA from being spliced into the host cell's own genome. A smaller group of entry and

attachment inhibitors, plus a fusion inhibitor and a capsid inhibitor, acts earliest of all, before the virus gets inside the cell or before its genetic material is even uncoated. [7]

3. Current DHHS guidance for adults and adolescents starting therapy recommends an INSTI-based regimen - an integrase inhibitor plus two NRTIs - as the preferred starting point for most people with HIV, reflecting durable virologic efficacy and a comparatively favourable tolerability profile relative to older NNRTI- or protease-inhibitor-based regimens. A small number of specifically studied two-drug regimens, such as dolutegravir plus lamivudine, are now also used in selected patients, but this is a defined exception built on its own trial evidence rather than a general retreat from combination therapy. [8]

4. Two toxicities recur across this field of otherwise very different drugs and are worth holding in mind together. Abacavir hypersensitivity is an immunologically mediated, potentially fatal multi-organ reaction strongly associated with the HLA-B*5701 allele, and it is managed by pre-treatment genetic screening plus permanent discontinuation if it is ever suspected - not by dose adjustment. Tenofovir, in either its older disoproxil fumarate form or the newer, lower-dose alafenamide prodrug, carries a renal and bone-density signal that is monitored with baseline and periodic labs rather than screened for genetically. Both are class-defining safety issues that a student is expected to be able to name, not generic antiviral side effects. [3][2]

Classification and drug examples

Intro: Antiretrovirals are grouped by the step of the HIV replication cycle each class interrupts. The five classes below cover the drugs in routine combination regimens; a smaller set of newer entry, attachment, post-attachment and capsid inhibitors is reserved mainly for multidrug-resistant disease and is noted rather than covered drug-by-drug here.

1. Name: Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)

1. Note: Chain-terminating analogues of the natural nucleotides reverse transcriptase uses to build viral DNA; the backbone of almost every standard regimen.

1. Name: Tenofovir disoproxil fumarate

1. TDF

2. Viread

1. Route: Oral

1. Note: Component of TRUVADA and several other fixed-dose combinations; carries renal and bone-density warnings. [2]

2. Name: Tenofovir alafenamide

TAF

2. Route: Oral

2. Note: Lower-dose prodrug of tenofovir with lower plasma tenofovir exposure than TDF; component of BIKTARVY. [1]

3. Name: Emtricitabine

FTC

3. Route: Oral

3. Note: Cytosine analogue NRTI; near-universal backbone partner paired with a tenofovir salt. [2]

4. Name: Lamivudine

3TC

4. Route: Oral

4. Note: Used in HIV regimens (e.g. dolutegravir/lamivudine) and, separately, in chronic hepatitis B. [8]

5. Name: Abacavir

1. ABC

2. Ziagen

5. Route: Oral

5. Note: Requires HLA-B*5701 screening before first use because of a serious multi-organ hypersensitivity reaction. [3] [7]

2. Name: Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

2. Note: Bind reverse transcriptase at an allosteric pocket rather than the active site, blocking the conformational change the enzyme needs to catalyse DNA synthesis.

1. Name: Efavirenz

Sustiva

1. Route: Oral

1. Note: Notable for neuropsychiatric adverse effects - dizziness, abnormal dreams, insomnia - most pronounced in the first one to two weeks; dosed at bedtime on an empty stomach to reduce them. [6]

2. Name: Nevirapine

Viramune

2. Route: Oral

2. Note: First-generation NNRTI; largely superseded by newer agents in first-line regimens. [7]

3. Name: Rilpivirine

Edurant

3. Route: Oral

3. Note: Second-generation NNRTI, requires adequate viral load and CD4 count for first-line use; also the oral lead-in for a long-acting injectable regimen. [7] [7]

3. Name: Protease inhibitors (PIs)

3. Note: Block the HIV protease enzyme that cleaves Gag and Gag-Pol polyprotein precursors into mature structural and enzymatic proteins during virion maturation; almost always given with a pharmacokinetic booster.

1. Name: Darunavir

Prezista

1. Route: Oral, with ritonavir or cobicistat boosting

1. Note: Its own label states it must be co-administered with ritonavir, with food, to achieve the intended antiviral effect. [5]

2. Name: Ritonavir

Norvir

2. Route: Oral

2. Note: Used almost exclusively today at low dose as a CYP3A4-inhibiting pharmacokinetic booster for other protease inhibitors rather than at its original antiviral dose. [5]

3. Name: Lopinavir/ritonavir

Kaletra

3. Route: Oral

3. Note: Co-formulated protease inhibitor and booster in one tablet. [7]

4. Name: Fosamprenavir

Lexiva

4. Route: Oral, with ritonavir boosting

4. Note: Prodrug of amprenavir. [7] [7]

4. Name: Integrase strand transfer inhibitors (INSTIs)

4. Note: Block the strand-transfer step of viral DNA integration into the host genome; the class DHHS guidelines now recommend as the anchor of most initial regimens.

1. Name: Bictegravir

component of Biktarvy

1. Route: Oral

1. Note: Second-generation INSTI with a high genetic barrier to resistance; only available as part of BIKTARVY. [1]

2. Name: Dolutegravir

Tivicay

2. Route: Oral

2. Note: Interacts with polyvalent cations (antacids, iron, calcium) - dosing must be separated from these by several hours. [4]

3. Name: Raltegravir

Isentress

3. Route: Oral

3. Note: First-in-class INSTI, approved 2007; lower genetic barrier to resistance than bictegravir or dolutegravir. [7]

4. Name: Cabotegravir

1. Vocabria

2. Apretude

4. Route: Oral lead-in and long-acting intramuscular injection

4. Note: Available as a long-acting injectable, given with injectable rilpivirine for treatment or alone for PrEP. [7] [8]

5. Name: Entry, fusion, attachment, post-attachment and capsid inhibitors

5. Note: A smaller, mechanistically varied group acting before or during viral entry, or on the capsid; mainly reserved for heavily treatment-experienced or multidrug-resistant patients rather than first-line use.

1. Name: Maraviroc

Selzentry

1. Route: Oral

1. Note: CCR5 antagonist; requires a tropism test confirming CCR5-tropic virus before use. [7]

2. Name: Enfuvirtide

Fuzeon

2. Route: Subcutaneous injection

2. Note: First-in-class fusion inhibitor, blocking gp41-mediated membrane fusion; twice-daily injections limit its use to heavily treatment-experienced patients. [7]

3. Name: Lenacapavir

Sunlenca

3. Route: Oral lead-in then subcutaneous injection twice yearly

3. Note: First-in-class capsid inhibitor, binding HIV capsid protein directly to disrupt multiple steps of the replication cycle. [7] [7]

Mechanism of action

Summary: HIV's replication cycle offers several distinct points a drug can interrupt: reverse transcription of viral RNA into DNA, integration of that DNA into the host genome, and the protease-mediated maturation of newly assembled virions, plus entry and fusion steps before any of that begins. Each antiretroviral class targets one of these steps, and combining classes closes off more escape routes than any single class could alone, which is why standard therapy is built from at least two classes rather than one.

Target: Reverse transcriptase (NRTIs, NNRTIs), integrase (INSTIs), protease (PIs), and viral entry/fusion/capsid machinery (entry, fusion and capsid inhibitors)

Cidal Static: Virustatic - suppresses ongoing replication and new infection of cells rather than eliminating latently infected cells, which is why ART is lifelong rather than curative

Kill Kinetics: Viral load falls over days to weeks of adherent therapy; rebound occurs within weeks of stopping or of resistance developing

1. Step: 1

1. Title: NRTIs terminate the growing viral DNA chain

1. Detail: NRTIs are analogues of the natural deoxynucleotides but lack the 3'-hydroxyl group DNA polymerisation needs to add the next nucleotide, so once reverse transcriptase incorporates one, chain elongation stops. [7]

2. Step: 2

2. Title: NNRTIs jam reverse transcriptase from an allosteric site

2. Detail: NNRTIs bind a pocket near, but distinct from, the enzyme's catalytic site and block the conformational flexibility reverse transcriptase needs to function, without being incorporated into the DNA chain themselves. [7]

3. Step: 3

3. Title: INSTIs block integration of viral DNA into the host genome

3. Detail: After reverse transcription, the pre-integration complex normally uses viral integrase to splice viral DNA into host chromosomal DNA; INSTIs bind integrase and block the strand-transfer step specifically. [7]

4. Step: 4

4. Title: Protease inhibitors block maturation of the budding virion

4. Detail: Newly assembled virions bud from the cell containing long Gag and Gag-Pol polyprotein precursors that must be cleaved by HIV protease into individual structural and enzymatic proteins; protease inhibitors block that cleavage, leaving immature, non-infectious particles. [7]

5. Step: 5

5. Title: Entry, fusion and capsid inhibitors act earliest or latest of all

5. Detail: CCR5 antagonists block the co-receptor step of attachment, fusion inhibitors block gp41-mediated membrane fusion before the viral core enters the cell, and capsid inhibitors like lenacapavir bind the capsid protein to disrupt multiple later steps including uncoating and assembly. [7]

Ritonavir and cobicistat are pharmacokinetic enhancers rather than antivirals in their own right at the doses used today: both inhibit CYP3A4 and are added to raise and sustain plasma levels of a co-administered protease inhibitor or, for cobicistat, certain INSTIs. [7][5]

Spectrum of activity

Intro: Antiretrovirals are active against HIV-1 (and, for some agents, HIV-2) specifically, not against other retroviruses or unrelated viral families; "spectrum" here means which HIV strains and resistance patterns a given class still reaches, rather than a list of unrelated organisms the way an antibacterial spectrum works.

1. Subclass: NRTIs

1. Coverage: HIV-1 and, for several agents, HIV-2; activity depends on absence of key resistance mutations such as M184V (emtricitabine/lamivudine) or the thymidine-analogue mutation pathway. [7]

2. Subclass: NNRTIs

2. Coverage: HIV-1 specifically - most NNRTIs have little or no activity against HIV-2, which has intrinsic resistance to this class because of differences in its reverse transcriptase. [7]

3. Subclass: Protease inhibitors

3. Coverage: HIV-1 and HIV-2; generally retain a higher genetic barrier to resistance than older NRTIs or first-generation NNRTIs when boosted. [7]

4. Subclass: INSTIs

4. Coverage: HIV-1 and HIV-2; second-generation agents (bictegravir, dolutegravir) have a substantially higher genetic barrier to resistance than first-generation raltegravir. [7]

Major clinical uses

1. Drug: Bictegravir/emtricitabine/tenofovir alafenamide

1. Organism: HIV-1

1. Indication: Complete regimen for HIV-1 infection in treatment-naïve adults and pediatric patients weighing 14 kg or more, and in virologically suppressed patients switching regimens

1. Line: DHHS-preferred initial regimen component

1. Note: Carries a boxed warning on severe acute hepatitis B exacerbation after discontinuation in HIV/HBV-coinfected patients. [1]

2. Drug: Emtricitabine/tenofovir disoproxil fumarate

2. Organism: HIV-1

2. Indication: Combined with other antiretrovirals for HIV-1 treatment; also approved for HIV-1 pre-exposure prophylaxis (PrEP) in at-risk adults and adolescents confirmed HIV-negative

2. Line: backbone NRTI pair

2. Note: PrEP use requires confirmed HIV-negative status immediately before and every three months during use. [2]

3. Drug: Abacavir

3. Organism: HIV-1

3. Indication: Combined with other antiretrovirals for HIV-1 infection

3. Line: alternative NRTI backbone component

3. Note: Requires HLA-B*5701 testing before first use; contraindicated in HLA-B*5701-positive patients. [3]

4. Drug: Efavirenz

4. Organism: HIV-1

4. Indication: Combined with other antiretrovirals for HIV-1 infection, alone or as part of fixed-dose combinations

4. Line: NNRTI-based regimen component, less commonly first-line today

4. Note: Neuropsychiatric effects are dose-limiting for some patients; bedtime dosing on an empty stomach is used to reduce them. [6]

5. Drug: Darunavir with ritonavir

5. Organism: HIV-1

5. Indication: Treatment of HIV-1 infection in treatment-naïve and treatment-experienced adults and pediatric patients 3 years and older

5. Line: boosted-PI-based regimen component

5. Note: Dosing (once versus twice daily, with which ritonavir dose) depends on treatment history and darunavir resistance-associated substitutions. [5]

6. Drug: Dolutegravir

6. Organism: HIV-1

6. Indication: Combined with other antiretrovirals for HIV-1 infection, including as part of the two-drug dolutegravir/lamivudine regimen in selected patients

6. Line: DHHS-preferred initial regimen component

6. Note: Divalent/trivalent cation-containing products must be separated from dosing by hours because they impair its absorption. [4]

Pharmacokinetics

1. Drug: Tenofovir disoproxil fumarate / emtricitabine (Truvada)

1. Route: Oral

1. Absorption: Well absorbed orally

1. Csf Penetration: See prescribing reference

1. Metabolism: Minimal hepatic metabolism for either component

1. Elimination: Renal, largely as unchanged drug

1. Dose Adjust: Renal impairment is the principal dose-adjustment driver for both components [2]

2. Drug: Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy)

2. Route: Oral

2. Absorption: Well absorbed orally, taken with or without food per label

2. Csf Penetration: See prescribing reference

2. Metabolism: Bictegravir: hepatic, via CYP3A and UGT1A1

2. Elimination: Bictegravir predominantly hepatic/biliary; emtricitabine and tenofovir predominantly renal

2. Dose Adjust: Not recommended with severe renal impairment; avoid with rifampin (reduces bictegravir levels) and dofetilide (contraindicated combination) [1]

3. Drug: Dolutegravir
3. Route: Oral
3. Absorption: Well absorbed orally
3. Csf Penetration: See prescribing reference
3. Metabolism: Primarily via UGT1A1, minor CYP3A contribution
3. Elimination: Predominantly hepatic/biliary
3. Dose Adjust: Separate dosing from polyvalent cation-containing antacids/supplements by several hours; adjust with strong UGT1A1/CYP3A inducers [4]
4. Drug: Darunavir (with ritonavir)
4. Route: Oral, always with ritonavir or cobicistat boosting
4. Absorption: Well absorbed with food
4. Csf Penetration: See prescribing reference
4. Metabolism: Hepatic, via CYP3A4; ritonavir boosting is required to sustain adequate exposure
4. Elimination: Predominantly hepatic
4. Dose Adjust: Dose/frequency depends on treatment history and darunavir resistance-associated substitutions; must be taken with food [5]
1. This page gives no dose regimens by design. Regimen selection and dose adjustment depend on treatment history, resistance testing, renal and hepatic function, pregnancy, and concomitant medications, and belong in a current prescribing reference or the DHHS guidelines used by the treating clinician.
2. Cytochrome P450 and UGT drug-interaction potential is a major practical differentiator within this field: protease inhibitors and several NNRTIs are strong CYP3A4 substrates or modulators, while INSTIs interact mainly through UGT1A1 metabolism and, for the whole class, through chelation with polyvalent cations. [5][4]

Adverse effects

1. Effect: Gastrointestinal upset
1. Detail: Nausea, diarrhea and headache are commonly reported across most oral antiretrovirals, including BIKTARVY. [1]
2. Effect: Neuropsychiatric symptoms with efavirenz
2. Detail: Dizziness, abnormal dreams, insomnia and, less commonly, hallucination or euphoria occur in roughly half of patients, usually most pronounced in the first one to two weeks. [6]
3. Effect: Insomnia, fatigue and headache with dolutegravir
3. Detail: The most common adverse reactions of at least moderate intensity reported with TIVICAY. [4]
1. Effect: Abacavir hypersensitivity reaction
1. Detail: A multi-organ syndrome typically involving two or more of fever, rash, gastrointestinal symptoms, constitutional symptoms and respiratory symptoms; can occur even in HLA-B*5701-negative patients, though at much lower frequency.
1. Action: Screen for HLA-B*5701 before starting; discontinue abacavir immediately if hypersensitivity is suspected and never rechallenge with abacavir or any abacavir-containing product. [3]
2. Effect: Renal impairment and Fanconi syndrome with tenofovir
2. Detail: Acute renal failure and Fanconi syndrome have been reported with tenofovir disoproxil fumarate, particularly with concurrent nephrotoxic drugs.
2. Action: Baseline and periodic monitoring of renal function is part of routine care with any tenofovir-containing regimen. [2]
3. Effect: Decreased bone mineral density with tenofovir
3. Detail: Decreases in bone mineral density have been observed in both HIV-infected and HIV-uninfected individuals taking tenofovir disoproxil fumarate; osteomalacia associated with renal tubular injury has also been reported.
3. Action: Bone monitoring is considered in patients with a history of pathologic fracture or risk factors for bone loss. [2]

4. Effect: Severe acute hepatitis B exacerbation after stopping an HBV-active antiretroviral
4. Detail: Patients coinfectd with HIV and HBV who discontinue emtricitabine- or tenofovir-containing regimens (or BIKTARVY as a whole) can experience severe, sometimes fatal, hepatitis B flares.
4. Action: HBV status is tested before starting and hepatic function is monitored closely for several months after any such regimen is stopped. [1][2]
5. Effect: Hypersensitivity and hepatotoxicity with dolutegravir
5. Detail: Hypersensitivity reactions with rash, constitutional findings and sometimes organ dysfunction including liver injury have been reported; patients with underlying hepatitis B or C may be at increased risk of transaminase elevation.
5. Action: Discontinue promptly if hypersensitivity is suspected; monitor liver enzymes in HBV/HCV-coinfectd patients. [4]
6. Effect: Serious psychiatric symptoms with efavirenz
6. Detail: Severe depression, suicidal ideation and other serious psychiatric symptoms have been reported.
6. Action: Immediate medical evaluation is recommended for new or worsening severe psychiatric symptoms. [6]
1. Drug: Abacavir
1. Effect: The only antiretroviral in routine use with a labelled pharmacogenomic contraindication (HLA-B*5701 positivity) rather than a purely clinical one. [3]
2. Drug: Darunavir (boosted)
2. Effect: Must always be co-administered with ritonavir or cobicistat and with food; unboosted use is not an approved option. [5]
3. Drug: Efavirenz
3. Effect: The class-defining neuropsychiatric adverse-effect profile among NNRTIs, distinct from the largely renal/bone concerns of the NRTI backbone drugs. [6]

Contraindications, precautions and interactions

1. Abacavir: known HLA-B*5701-positive status, or a prior hypersensitivity reaction to abacavir. [3]
2. BIKTARVY: coadministration with dofetilide (risk of serious cardiac effects) or rifampin (reduces bictegravir concentrations, risking treatment failure and resistance). [1]
1. HIV/HBV coinfection requires caution around stopping any emtricitabine- or tenofovir-containing regimen because of the risk of severe hepatitis B exacerbation. [2][1]
2. Pre-existing renal impairment is a caution for tenofovir-containing regimens, given the drug's renal elimination and nephrotoxicity signal. [2]
3. TRUVADA for PrEP requires confirmed HIV-negative status immediately before starting and retesting at least every three months during use, because undetected acute infection risks selecting drug-resistant HIV-1 variants. [2]
1. With: Polyvalent cation-containing antacids, laxatives, sucralfate, or iron/calcium supplements
1. Effect: Reduce dolutegravir absorption; dosing must be separated by two hours before or six hours after. [4]
2. With: Rifampin and other strong CYP3A/UGT1A1 inducers
2. Effect: Can reduce bictegravir or dolutegravir concentrations enough to risk virologic failure. [1]
3. With: Other CYP3A4 substrates
3. Effect: Ritonavir- or cobicistat-boosted protease inhibitors have extensive CYP3A4-mediated interaction potential with many other drug classes. [5]

Resistance mechanisms

Intro: HIV's reverse transcriptase lacks proofreading activity, generating roughly one new mutation per genome per replication cycle; combined with a very high daily replication rate, this means resistance mutations arise constantly and are selected for whenever drug pressure is incomplete - the core reason for combination therapy.

1. Mechanism: NRTI resistance via chain-terminator discrimination or excision
1. Detail: Mutations such as M184V reduce incorporation of emtricitabine/lamivudine by the enzyme, while

thymidine-analogue mutation pathways allow excision of an already-incorporated NRTI, restoring chain elongation. [7]

2. Mechanism: NNRTI resistance via altered binding-pocket residues

2. Detail: Single point mutations in the NNRTI-binding pocket of reverse transcriptase can markedly reduce first-generation NNRTI binding; the low genetic barrier of this class is a recognised limitation. [7]

3. Mechanism: Protease inhibitor resistance via stepwise accumulation of mutations

3. Detail: High-level PI resistance typically requires accumulation of multiple mutations in the protease gene, which is part of why boosted PIs are considered to have a relatively high genetic barrier to resistance. [7]

4. Mechanism: INSTI resistance, first- versus second-generation

4. Detail: Raltegravir (first-generation) has a comparatively low genetic barrier to resistance; bictegravir and dolutegravir (second-generation) require multiple mutations to lose full activity, giving them a substantially higher genetic barrier. [7]

Comparison tables

Title: Five classes, one replication cycle, five different failure points

Caption: Each class blocks a different step; combining classes closes off more resistance pathways than any one class can alone.

1. Key: class

1. Label: Class

1. Is Row Header: true

2. Key: target

2. Label: Molecular target

3. Key: example

3. Label: Example drug

4. Key: signature_issue

4. Label: Signature safety/use issue

1. Class: NRTI

1. Target: Reverse transcriptase active site (chain termination)

1. Example: Tenofovir, emtricitabine, abacavir

1. Signature Issue: Abacavir: HLA-B*5701 hypersensitivity; tenofovir: renal/bone effects [3][2]

2. Class: NNRTI

2. Target: Reverse transcriptase allosteric pocket

2. Example: Efavirenz, rilpivirine

2. Signature Issue: Efavirenz: neuropsychiatric effects [6]

3. Class: Protease inhibitor

3. Target: HIV protease (polyprotein cleavage)

3. Example: Darunavir (boosted)

3. Signature Issue: Must be pharmacokinetically boosted; extensive CYP3A4 interactions [5]

4. Class: INSTI

4. Target: Integrase (strand transfer)

4. Example: Dolutegravir, bictegravir

4. Signature Issue: Chelation by polyvalent cations reduces absorption [4]

5. Class: Entry/fusion/capsid

5. Target: Co-receptor binding, membrane fusion, or capsid protein

5. Example: Maraviroc, enfuvirtide, lenacapavir

5. Signature Issue: Reserved mainly for multidrug-resistant disease; several require injection [7]

High-yield exam pearls

1. Pearl: HIV is never treated with monotherapy, and outside a few specifically studied two-drug regimens, not with two

drugs from one class either.

1. Why: HIV's error-prone reverse transcriptase generates resistance mutations constantly; combining classes with different resistance pathways is what keeps a regimen durable. [7]
2. Pearl: Abacavir hypersensitivity is screened for genetically (HLA-B*5701), not managed by dose reduction.
2. Why: It is one of the few antiretroviral toxicities with a mandated pre-treatment pharmacogenomic test rather than a purely clinical monitoring plan. [3]
3. Pearl: Boosted protease inhibitors are always given with ritonavir or cobicistat.
3. Why: Unboosted PI regimens are not an approved option for agents like darunavir - the booster is required to reach adequate plasma exposure, not optional for tolerability. [5]
4. Pearl: Second-generation INSTIs (bictegravir, dolutegravir) have a much higher genetic barrier to resistance than first-generation raltegravir.
4. Why: This is why current guidelines favour bictegravir- or dolutegravir-based regimens as initial therapy. [8][7]
5. Pearl: Stopping an emtricitabine- or tenofovir-containing regimen in a patient coinfectd with HBV can trigger a severe hepatitis flare.
5. Why: Both drugs are also active against HBV, so withdrawing them removes HBV suppression as well as HIV suppression, and hepatic function needs monitoring for months afterward. [2][1]

Common exam traps

1. Trap: Assuming any two-drug HIV regimen is inadequate.
1. Correction: Specifically studied two-drug regimens such as dolutegravir/lamivudine are now guideline-supported for selected patients - the general rule against under-treating HIV is about resistance barrier and trial evidence, not an absolute drug count. [8]
2. Trap: Treating ritonavir as primarily an antiretroviral in modern regimens.
2. Correction: At the low doses used today, ritonavir functions mainly as a CYP3A4-inhibiting pharmacokinetic booster for another protease inhibitor, not as the regimen's antiviral backbone. [5]
3. Trap: Assuming abacavir hypersensitivity cannot occur in an HLA-B*5701-negative patient.
3. Correction: The label explicitly notes hypersensitivity reactions have occurred in patients who do not carry the allele, so a negative test lowers but does not eliminate the risk, and any suspected reaction still means permanent discontinuation. [3]
4. Trap: Assuming NNRTIs work the same way as NRTIs because both act on reverse transcriptase.
4. Correction: NRTIs are incorporated into the growing DNA chain and terminate it; NNRTIs are not incorporated at all and instead bind an allosteric pocket that blocks the enzyme's necessary conformational change. [7]

Self-test questions

1. Question: Why is HIV treated with combination antiretroviral therapy rather than a single drug?
1. Because no single antiretroviral is potent enough to suppress viral load
2. Because HIV's error-prone reverse transcriptase generates resistance mutations quickly, and combining classes closes off more resistance pathways than any one class can alone
3. Because combination pills are easier to manufacture
4. Because single-drug regimens are more expensive
1. Explanation: HIV's high mutation rate under drug pressure means a single agent is quickly overcome by resistant variants; combining agents from different classes with different resistance pathways is what keeps suppression durable. [7]
2. Question: What distinguishes the mechanism of NNRTIs from NRTIs?
1. NNRTIs terminate the DNA chain like NRTIs but at a different nucleotide
2. NNRTIs bind an allosteric pocket on reverse transcriptase and block its conformational change, without being incorporated into the DNA chain

3. NNRTIs act on integrase rather than reverse transcriptase
4. NNRTIs and NRTIs have an identical mechanism
2. Explanation: NRTIs are incorporated into viral DNA and terminate the chain because they lack a 3'-hydroxyl group; NNRTIs instead bind an allosteric site and block the enzyme's necessary movement without becoming part of the DNA. [7]
3. Question: Before starting abacavir, which test is specifically required by the drug's labelling?
 1. CD4 count only
 2. HLA-B*5701 genetic testing
 3. Liver biopsy
 4. Tropism testing
3. Explanation: Abacavir carries a labelled requirement for HLA-B*5701 screening because patients who carry the allele are at markedly higher risk of a serious multi-organ hypersensitivity reaction. [3]
4. Question: Why must darunavir be co-administered with ritonavir or cobicistat?
 1. To improve its taste
 2. To boost darunavir's plasma exposure via CYP3A4 inhibition, which is required to achieve the intended antiviral effect
 3. Because darunavir has no antiviral activity alone
 4. To reduce pill burden
4. Explanation: The PREZISTA label states darunavir must be co-administered with ritonavir (or cobicistat) and food to achieve the desired antiviral effect; boosting is required, not optional. [5]
5. Question: Which class does dolutegravir belong to, and what is a key drug-interaction concern with it?
 1. Protease inhibitor; interacts with grapefruit juice
 2. Integrase strand transfer inhibitor; polyvalent cation-containing products (antacids, iron, calcium) reduce its absorption
 3. NNRTI; interacts with St John's wort only
 4. Fusion inhibitor; no significant interactions
5. Explanation: Dolutegravir is an INSTI, and its label specifies separating dosing from cation-containing antacids, supplements or laxatives by two hours before or six hours after to avoid reduced absorption. [4]
6. Question: What can happen if a patient coinfectd with HIV and hepatitis B stops a tenofovir- or emtricitabine-containing regimen?
 1. Nothing of clinical significance
 2. A severe, sometimes fatal, acute exacerbation of hepatitis B
 3. Immediate HIV cure
 4. Improved renal function only
6. Explanation: Both drugs are active against HBV as well as HIV; stopping them removes HBV suppression and can trigger a severe hepatic flare, so hepatic function is monitored closely for months afterward. [2][1]

Frequently asked questions

1. Question: Why can't HIV be treated with just one antiretroviral drug?
 1. Answer: HIV's reverse transcriptase makes frequent copying errors, and combined with the virus's very high daily replication rate, drug-resistant variants arise constantly. A single drug leaves an escape route open; combining agents from at least two classes closes off enough of those routes to keep viral suppression durable, which is why standard therapy uses at least three drugs from at least two classes. [7]
 2. Question: Is a two-drug HIV regimen ever appropriate?
 2. Answer: Yes, but only for specifically studied combinations rather than as a general shortcut. Current DHHS guidelines support dolutegravir plus lamivudine as an option in selected patients, based on dedicated trial evidence for that pairing - it is a defined exception, not a general retreat from the combination-therapy principle. [8]

3. Question: Why does abacavir require a genetic test before it's prescribed?

3. Answer: Abacavir can cause a serious, potentially fatal multi-organ hypersensitivity reaction, and carrying the HLA-B*5701 allele substantially raises that risk. The FDA label requires screening for this allele before starting abacavir and contraindicates the drug in patients who test positive; anyone in whom hypersensitivity is ever suspected, regardless of test result, must stop it permanently and never restart it. [3]

4. Question: What is the main safety concern with tenofovir?

4. Answer: Both forms of tenofovir (disoproxil fumarate and the newer alafenamide prodrug) carry renal and bone-density warnings. Acute renal failure and Fanconi syndrome have been reported, particularly with concurrent nephrotoxic drugs, and decreases in bone mineral density have been observed in treated patients. Baseline and periodic monitoring of renal function is standard with any tenofovir-containing regimen. [2]

References

- [1] BIKTARVY (bictegravir, emtricitabine, and tenofovir alafenamide) - prescribing information. DailyMed, U.S. National Library of Medicine . <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=664cb8f0-1f65-441b-b0d9-ba3d798be309>
- [2] TRUVADA (emtricitabine and tenofovir disoproxil fumarate) - prescribing information. DailyMed, U.S. National Library of Medicine . <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=54e82b13-a037-49ed-b4b3-030b37c0ecdd>
- [3] ZIAGEN (abacavir) - prescribing information. DailyMed, U.S. National Library of Medicine . <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ca73b519-015a-436d-aa3c-af53492825a1>
- [4] TIVICAY (dolutegravir) - prescribing information. DailyMed, U.S. National Library of Medicine . <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=807b0cd2-093c-4353-a4a5-2e1f264616ba>
- [5] PREZISTA (darunavir) - prescribing information. DailyMed, U.S. National Library of Medicine . <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4cde01bb-230b-42d8-a9e1-4c7da1a01b76>
- [6] SUSTIVA (efavirenz) - prescribing information. DailyMed, U.S. National Library of Medicine . <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=04b5c345-c446-43a4-83f0-509bc287e10b>
- [7] HIV Antiretroviral Therapy. StatPearls Publishing / NCBI Bookshelf 2026. <https://www.ncbi.nlm.nih.gov/books/NBK513308/>
- [8] What to Start: Initial Combination Antiretroviral Regimens for the Antiretroviral-Naive Patient. Panel on Antiretroviral Guidelines for Adults and Adolescents, U.S. Department of Health and Human Services (clinicalinfo.HIV.gov) . <https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/what-start-initial-combination-regimens>

For education only. This guide does not replace professional medical advice. Do not use it to choose or change treatment.