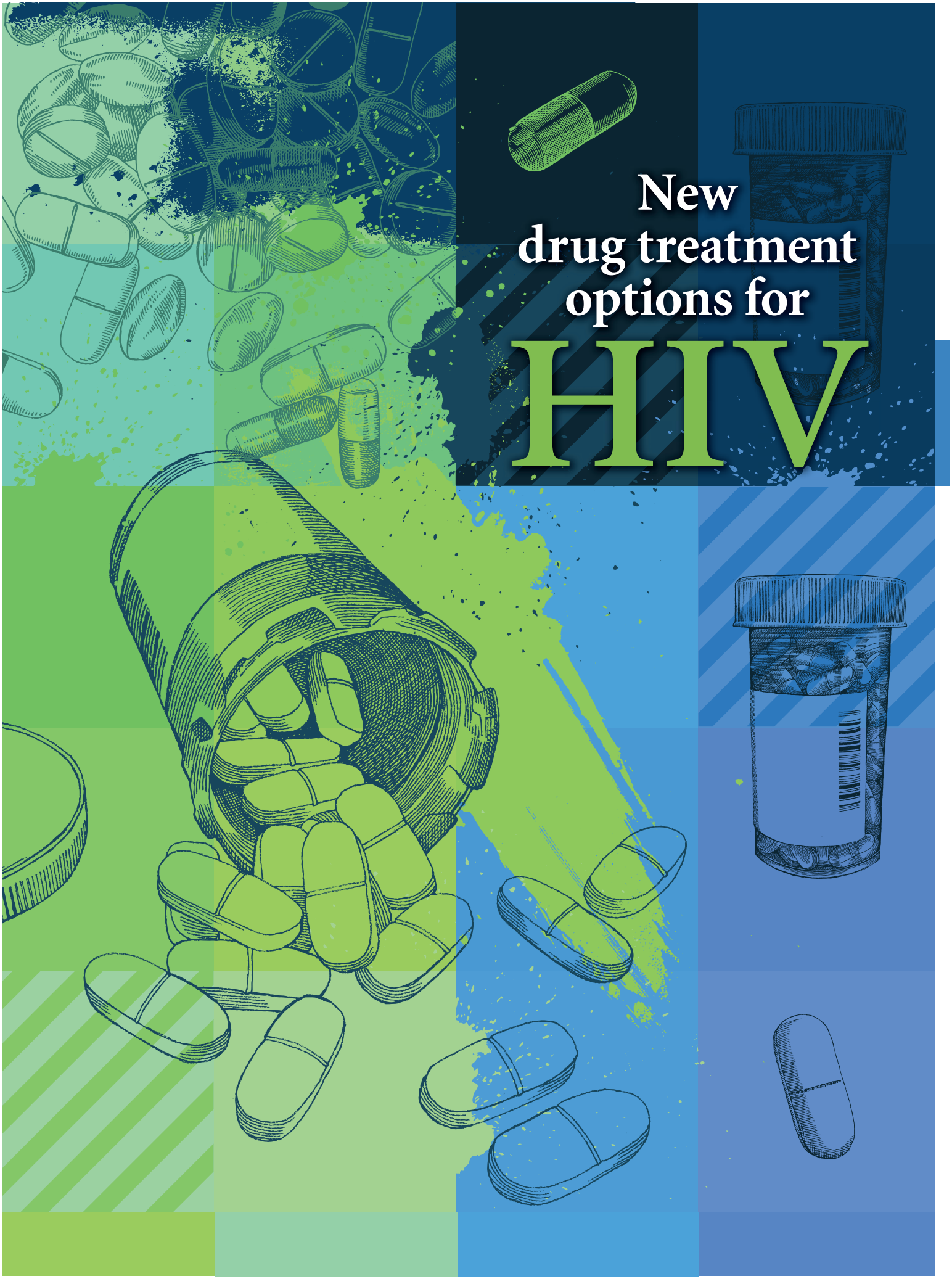

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Abstract: Current treatments for patients with HIV are not only effective at controlling viral replication but are also associated with a more favorable adverse reaction profile, may often be taken once daily, and are increasingly available in combination single-tablet regimens. This article provides an overview and prescribing considerations for several primary drugs currently recommended by the US Department of Health and Human Services.

antiretroviral therapy

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Treatment options for persons living with HIV (PLWH) have improved over the past decade. Current treatments are not only effective at controlling viral replication but are also associated with a more favorable adverse reaction profile, may often be taken once daily, and are increasingly available in combination single-tablet regimens (STRs). With these newer treatment options, adherence to antiretroviral therapy (ART) has improved and more patients are able to achieve undetectable viral loads.[1] This article provides an overview and prescribing considerations for several primary drugs currently recommended by the US Department of Health and Human Services (DHHS) guidelines for the treatment of adults and adolescents living with HIV-1 infection, the most common strain of HIV infection in the US.[2]

Drug classes and mechanism of action

All HIV ART works by altering or inhibiting viral replication. To review, HIV is a single-stranded RNA retrovirus that utilizes the CD4+ lymphocyte as the site of replication.[3] As with other retroviruses, HIV uses a process called reverse transcription to integrate into the host's CD4+ lymphocytes.[3] This process allows HIV to create a DNA template, which in turn results in the creation of more HIV RNA strands. Once these additional RNA strands are created, the genetic material is then cleaved into smaller segments, reencapsulated into new viral particles, and released into the bloodstream.[3] This process results in the destruction of the CD4+ lymphocyte.[3] Over time, the rate of CD4+ destruction surpasses production and individuals experience a decline in their CD4+ lymphocytes, leading to immunosuppression.[3]

Current classes of ART are designed to control this process and include:

- nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
- nonnucleoside reverse transcriptase inhibitors (NNRTIs)
- integrase strand transfer inhibitors (INSTIs)
- protease inhibitors (PIs)
- entry inhibitors.[4]

The NRTI and NNRTI classes function in a similar way by stopping the enzyme reverse transcriptase (RT). By preventing RT from working, HIV is unable to create key amino acids required for replication. The INSTI class blocks the integrase enzyme, resulting in the inability of the virus to integrate its genetic material into the host cell's DNA. PIs block the protease

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Keywords: antiretroviral therapy, antiretrovirals, HIV, immunosuppression, persons living with HIV, PLWH, retrovirus, single-tablet regimens, US Department of Health and Human Services

enzyme, preventing newly formed virions from maturing and infecting other cells. Entry inhibitors refer to antiretrovirals that prevent HIV from entering the host cell. The entry inhibitor class includes fusion inhibitors, postattachment inhibitors, and a chemokine CCR5 receptor antagonist.

Viral resistance and drug efficacy

One characteristic of HIV is its ability to mutate and change its genetic structure as it replicates. This can occur as part of the natural replication process or in the setting of suboptimal drug levels.[5] A key consideration when selecting an ART regimen is the ability of the drugs to retain efficacy even if the virus has mutated. HIV antiretrovirals are often described by their "*genetic barrier to resistance.*"[6] This refers to the number of mutations HIV must develop before a medication loses its efficacy. Drugs with a high barrier to resistance require multiple mutations before losing efficacy. Drugs with a low barrier to resistance, such as some early generation NNRTIs, only require one mutation to render them ineffective.[6] Most of the PIs and newer INSTIs have high barriers to resistance, making them ideal for people with drug-resistant HIV, or for individuals whose inability to adhere to daily therapy puts them at risk for developing drug resistance.[2]

Initial HIV antiretroviral combinations[2]

Recommended combinations for most patients

- bictegravir/tenofovir AF/emtricitabine (**AI**)
- dolutegravir/abacavir/lamivudine (**AI**) (*if HLA-B*5701 negative*)
- dolutegravir + emtricitabine[a] + tenofovir[b] (**AI**)
- dolutegravir/lamivudine (**AI**) (*except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available*)
- raltegravir + emtricitabine[a] + (tenofovir AF (**BII**) or tenofovir DF (**BI**))

Recommended initial combinations in certain clinical situations

INSTI + 2 NRTIs

- elvitegravir/cobicistat/emtricitabine/tenofovir[b] (**BI**)

Boosted PI + 2 NRTIs

- (darunavir/cobicistat or darunavir/ritonavir) + tenofovir[b] + emtricitabine[a] (**AI**)
- (atazanavir/cobicistat or atazanavir/ritonavir) + tenofovir[b] + emtricitabine[a] (**BI**)
- (darunavir/cobicistat or darunavir/ritonavir) + abacavir/lamivudine (**BII**) (*if HLA-B*5701 negative*)

NNRTI + 2 NRTIs

- doravirine/tenofovir DF/lamivudine (**BI**) or doravirine + tenofovir AF/emtricitabine (**BIII**)
- efavirenz 600 mg + tenofovir DF + emtricitabine[a] (**BI**)
- efavirenz 400 mg/tenofovir DF/lamivudine (BI)
- efavirenz 600 mg + tenofovir AF/emtricitabine (BII)
- rilpivirine/tenofovir[b]/emtricitabine (**BI**) *(if HIV RNA <100,000 copies/mL and CD4+ cell count >200 cells/mm^3)*

Regimens to consider when abacavir and tenofovir AF or tenofovir DF cannot be used or are not optimal:

- dolutegravir/lamivudine (**AI**) *(except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available)*
- darunavir/ritonavir + raltegravir BID (**CI**) *(if HIV RNA <100,000 copies/mL and CD4+ cell count >200 cells/mm^3)*
- darunavir/ritonavir once daily plus lamivudine (**CI**)

Rating of recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = Data from randomized controlled trials;
II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = expert opinion
[a] may substitute lamivudine
[b] tenofovir alafenamide (tenofovir AF) or tenofovir disoproxil fumarate (tenofovir DF)

Principles of HIV treatment

Three-drug vs. two-drug therapy

Combination therapy with at least two different classes of ART is considered the standard of care in patients with HIV.[2] Until recently, the accepted practice was to use three different drugs as the foundation of treatment (two NRTIs combined with another class of medication). However, studies using two-drug, two-class regimens have shown to be an effective alternative for certain patients.[7] The benefits of dual therapy versus triple therapy include potentially fewer drug-drug interactions and a lower risk of adverse events such as lactic acidosis, renal impairment, and myocardial infarction (MI).[2,5] Given the emerging evidence supporting two-drug regimens, the most recent clinical guidelines now include a two-drug, two-class option as an initial treatment choice for most people newly diagnosed with HIV.[2]

Initiating ART in treatment-naive patients

Whether a patient is prescribed two or three drugs, the primary goal of treating HIV is to suppress viral replication. DHHS guidelines

recommend initiating ART at the time of diagnosis, regardless of CD4+ lymphocyte count or HIV viral load.[2] The guidelines utilize two broad categories for its recommendations: treatment recommended for most individuals, and treatment recommended for individuals with certain clinical conditions. (See *Initial HIV antiretroviral combinations* for a list of initial therapy options for PLWH.)

NRTIs with an INSTI is recommended for most patients. The selection of ART should be guided by several factors, including baseline drug resistance and comorbidities such as cardiovascular disease, renal impairment, chronic hepatitis B, or advanced liver disease.[2] Other considerations include pregnancy status and desire for pregnancy, concomitant medications or supplements (such as H2 blockers, proton pump inhibitors (PPIs), steroids, and statins), antiretroviral adverse reactions, baseline viral load, pill burden, and dosing preferences (once daily versus twice daily; with meals or without meals).[2]

Lab assessment

Prior to prescribing ART, the clinician must obtain baseline lab studies. (See *Lab assessment in HIV ART management.*) Testing includes CD4+ count, HIV viral load, HIV genotype for drug resistance, renal and hepatic function, hepatitis serologies (in particular hepatitis B and C), and pregnancy status.[2] Follow-up assessment of renal and hepatic function as well as viral load is recommended 2 to 8 weeks after treatment initiation.[2] Clinicians should monitor the viral load every 4 weeks until undetectable, and then repeat every 3 to 6 months.[2] Patients who are stable on ART can be followed every 6 months.[2]

Lab assessment in HIV ART management[2]

Test	Frequency of testing
CD4+ cell count	• Prior to beginning ART • Every 3 to 6 months for the first 2 years of treatment • Annually after the first 2 years of treatment if CD4+ cell count is between 300 and 500 cells/mm^3 • Continue to monitor every 3 to 6 months if viremia develops or if CD4+ cell counts are <300 • If CD4+ cell count is >500, monitoring is not required
HIV viral load	• Prior to beginning ART • Every 4 to 8 weeks until viral load is <200 copies/mL • Every 3 to 6 months once viral load is <200 copies/mL
Comprehensive metabolic panel, including renal and hepatic function	• Prior to beginning ART • Repeat in 2 to 8 weeks after treatment initiation or modification • Monitor every 3 to 6 months while on ART
Complete blood cell count with differential	Repeat every 3 to 6 months or if CD4+ cell count is done
Fasting lipid profile	Repeat every 6 months if abnormal at last measurement or if normal, may repeat annually
Fasting glucose or hemoglobin A1C	Repeat every 6 months if abnormal at last measurement or if normal, may repeat annually
Urinalysis	Repeat every 6 months if on tenofovir DF or tenofovir AF, otherwise may repeat annually
HIV genotype	Repeat if evidence of virologic failure or inadequate response to ART
Hepatitis B serology (HBsAb, HBsAg, HBcAb total)	• May repeat if patient is nonimmune and does not have chronic HBV infection • Vaccinate those who are nonimmune
Hepatitis C screening	Repeat screening for patients at risk for acquiring hepatitis C virus infection
Pregnancy test	Repeat if clinically indicated
HLA-B*5701 test	If considering abacavir therapy as part of a new regimen

Immune reconstitution inflammatory syndrome

In patients with more advanced immune suppression (typically with CD4+ cell counts under 100 cells/mm^3) who are newly starting ART, clinicians should monitor for immune reconstitution inflammatory syndrome (IRIS).[8] IRIS is an inflammatory reaction that can occur in a small percentage of patients during the first few weeks after treatment initiation and is a paradoxical reactivation or unmasking of an underlying infection (such as mycobacterial infection, cytomegalovirus, hepatitis B or C, herpes simplex virus, or *Pneumocystis jirovecii*).[8] ART treatment does not need to be

discontinued in most cases. Patients experiencing IRIS should be treated for the underlying infection; the addition of steroids may be warranted for patients who experience severe symptoms.[8]

Nucleoside/nucleotide reverse transcriptase inhibitors

The preferred NRTIs recommended for most PLWH include one or more of the following: tenofovir alafenamide (AF), tenofovir disoproxil fumarate (DF), emtricitabine, abacavir, or lamivudine. The selection and choice of NRTIs depends on drug resistance, manufacturer-derived coformulations, and other comorbidities. For patients with chronic hepatitis B, tenofovir AF, tenofovir DF, emtricitabine, or lamivudine are preferred.[2] For patients with renal impairment, consider limiting tenofovir DF-containing products due to renal effects from the drug.[2] For patients with cardiovascular disease, consider avoiding abacavir due to association of increased cardiovascular events.[2] Other NRTIs, including earlier generation drugs such as zidovudine, didanosine, and stavudine, are not used as first-line agents due to greater adverse reactions such as anemia, peripheral neuropathy, lipoatrophy, and mitochondrial toxicity.

Combination therapy with at least two different classes of ART is considered the standard of care in patients with HIV.

Precautions with NRTIs

Lactic acidosis and hepatomegaly with steatosis. In general, the current NRTIs are well tolerated. Common adverse reactions such as nausea are typically associated with treatment initiation and can be managed with supportive care or use of medications that address specific symptoms, such as antiemetics. NRTIs have class-associated precautions of lactic acidosis and hepatomegaly with steatosis.[9,10] Although rare and seen primarily with early-generation NRTIs, the prescribing information for all NRTIs still list these as a potential risk.[2] Patients on NRTI-containing regimens exhibiting signs or symptoms consistent with lactic acidosis (such as body aches, abdominal pain, malaise, and elevated lactate) should be evaluated for possible NRTI-related lactic acidosis.[2]

Hepatic flare. The NRTIs emtricitabine, lamivudine, tenofovir AF, and tenofovir DF also have activity against hepatitis B virus (HBV).[2] In PLWH with chronic HBV infection, clinicians should use caution when discontinuing or switching ART that contains one of these NRTIs because patients may experience a reactivation of their chronic HBV.[2] Close monitoring of hepatic function is recommended, and in some instances, the addition of a non-HIV antiviral that specifically treats HBV may be required.[2]

Tenofovir

Both available forms of tenofovir (AF and DF) are identical in their mechanism of interrupting viral replication. Additionally, both of these medications have potential adverse reactions, which include effects on renal function and bone mineral density.[2] However, tenofovir AF has greater intracellular penetration and less impact on renal function and bone mineral density compared with tenofovir DF.[10,11] Both tenofovir AF and tenofovir DF are available as individual agents but are also found in several combination products. (See *Currently available STRs for treating HIV-1 infection.*) Given that tenofovir AF has less effect on renal function, it is approved for use in patients with a creatine clearance (CrCl) of 30 mL/min or higher without dose adjustment versus the 50 mL/min limitation used for tenofovir DF.[2] Both forms of tenofovir are typically paired with either emtricitabine or lamivudine.

Abacavir

Abacavir is another NRTI that is listed as part of the DHHS guidelines and is typically paired with lamivudine.[2] Abacavir has been associated with a life-threatening hypersensitivity reaction.[12] This reaction, characterized by rash, fever, and gastrointestinal and/or respiratory symptoms, occurs in individuals who have the genetic allele HLA-B*5701. Therefore, prior to prescribing abacavir-containing products, clinicians must order HLA-B*5701 blood testing. People found to be HLA-B*5701 positive should not be prescribed abacavir.[2] Abacavir is available as a single agent (Ziagen) or as part of a combination with lamivudine (Epzicom), as part of triple NRTI combination with lamivudine and zidovudine (Trizivir), or as an STR with lamivudine and the INSTI dolutegravir (Triumeq).

Currently available STRs for treating HIV-1 infection[2]

Generic drug names	Trade name	Comments
2 NRTIs + INSTI		
abacavir + lamivudine + dolutegravir	Triumeq	• Use only in HLA-B*5701 negative individuals • Do not use if CrCl <50 mL/min
tenofovir AF + emtricitabine + bictegravir	Biktarvy	• Do not use if CrCl <30 mL/min
tenofovir AF + emtricitabine + elvitegravir + cobicistat	Genvoya	• Administer with food • Multiple drug-drug interactions due to cobicistat • Do not use if CrCl <30 mL/min
tenofovir DF + emtricitabine + elvitegravir + cobicistat	Stribild	• Administer with food • Multiple drug-drug interactions due to cobicistat • Use in patients with CrCl <70 mL/min not recommended • Discontinue if CrCl <50 mL/min
2 NRTIs + PI		
tenofovir AF + emtricitabine + darunavir + cobicistat	Symtuza	• Caution in patients with sulfa allergy • Administer with food • Multiple drug-drug interactions due to cobicistat • Do not use if CrCl <30 mL/min
1 NRTI + INSTI		
lamivudine + dolutegravir	Dovato	• Approved for treatment-naive individuals • Do not use in patients with HIV viral load >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available • Do not use if CrCl <50 mL/min
2 NRTIs + NNRTI		
tenofovir AF + emtricitabine + rilpivirine	Odefsey	• Administer with a meal • Avoid use of PPIs • Do not use if pretreatment HIV viral load >100,000 copies/mL • Do not use if CrCl <30 mL/min
tenofovir DF + emtricitabine + efavirenz	Atripla	• May cause vivid dreams, depression • Recommend dosing at night on an empty stomach • Do not use if CrCl <50 mL/min
tenofovir DF + emtricitabine + rilpivirine	Complera	• Administer with a meal • Avoid use of PPIs • Do not use if pretreatment HIV viral load >100,000 copies/mL • Do not use if CrCl <50 mL/min
tenofovir DF + lamivudine + doravirine	Delstrigo	• Only for treatment-naive individuals • Administer with or without food • No drug-drug interaction with acid-lowering agents • Do not use if CrCl <50 mL/min
tenofovir DF + lamivudine + efavirenz	Symfi SymfiLo	• Symfi contains 600 mg of efavirenz • SymfiLo contains 400 mg of efavirenz • May cause vivid dreams, depression • Recommend dosing at night on an empty stomach • Do not use if CrCl <50 mL/min
INSTI + NNRTI		
dolutegravir + rilpivirine	Juluca	• Only to replace therapy in patients with HIV RNA <50 copies/mL for at least 6 months and no previous drug resistance to dolutegravir or rilpivirine. • Administer with a meal • Avoid use of PPIs • In patients with severe renal impairment (CrCl <30 mL/min), increased monitoring is recommended.

Recent data have found abacavir to be associated with a higher incidence of MI.[13] In a recent systematic review of abacavir use and cardiovascular disease, an elevated risk of cardiovascular events was seen with abacavir use.[13] Clinicians should consider using alternatives to abacavir in patients with preexisting cardiovascular disease and in those at high risk for MI.

Lamivudine and emtricitabine

The NRTIs lamivudine and emtricitabine are similar in both their mechanism of action and renal and hepatic effects, as well as their resistance profile. Both medications are generally well tolerated, and as noted earlier, have activity against chronic HBV. Dose adjustment is required in patients with a CrCl under 50 mL/min. DHHS guidelines state that these two medications are interchangeable and should not be prescribed together in the same regimen.[2] They are available as single agents or as part of combination tablets.

Integrase strand transfer inhibitor therapy

The INSTI class of medications is considered the preferred class to use in combination with the NRTIs for most patients initiating HIV-1 treatment. The INSTI class also provides an option for treatment simplification in some virologically suppressed patients.[2] Four INSTIs are FDA-approved: bictegravir, dolutegravir, elvitegravir, and raltegravir. Bictegravir and dolutegravir have higher barriers to drug resistance than elvitegravir and raltegravir.[2] The benefits of INSTIs include their tolerability as well as their ability to rapidly reduce viral load, which is a critical factor in decreasing the risk of viral transmission.[2]

More recent data have shown that INSTIs may be associated with greater weight gain than other classes of ART; in particular, dolutegravir has been associated with more weight gain than other INSTIs.[14] The weight gain seen in these cases is different than the body fat changes seen with PIs. INSTI weight gain is more generalized with increased waist circumference compared with the dorsocervical fat accumulation and visceral fat seen with early-generation PI-based treatment.[14]

Key drug interactions across the INSTI class include interactions with polyvalent cation-containing agents (such as aluminum-containing antacids and oral supplements containing iron or calcium).[2] These agents lower the therapeutic dose of the INSTI due to similar metabolic pathways. Dose separation or coadministration with food may address these issues.[2] Clinicians should refer to the prescribing information of the specific INSTI to verify dosing recommendations.

Bictegravir is a once-daily INSTI available as an STR combined with tenofovir AF and emtricitabine (Biktarvy). It is approved for use in adult and pediatric patients weighing 25 kg or more with a CrCl of 30 mL/min or more who are newly starting ART or for those who have had an undetectable viral load and have no previous history of resistance to components of Biktarvy.[15] It is contraindicated in patients taking dofetilide or rifampin. Due to the common metabolic pathway, these two drugs lower bictegravir levels to suboptimal therapeutic levels.[15] There are insufficient data on the use of bictegravir in pregnancy, so it is recommended that clinicians discuss the risk and benefits of using Biktarvy in patients of childbearing potential.[15] Patients who become pregnant while using bictegravir should be included in the antiviral pregnancy registry.[15]

Dolutegravir is approved for the treatment of HIV in patients who are newly starting ART or those switching from another ART.[16] It is also recommended as one of the agents for postexposure prophylaxis.[17] Dolutegravir comes as a single agent (Tivicay) or combined into several different STR formulations. As an STR, dolutegravir can be found paired with two NRTIs, abacavir and lamivudine (Triumeq), with lamivudine alone (Dovato), or with the NNRTI rilpivirine (Juluca). The STR Dovato is currently FDA-approved for treatment-naive individuals, while Juluca is approved for patients currently suppressed on ART with no previous resistance to either dolutegravir or rilpivirine.[18,19] Juluca provides an option for treatment-experienced patients who desire or need to modify therapy or who are unable to take an NRTI.[19]

Dosing of dolutegravir is once daily in INSTI-naive individuals or those who are virologically suppressed. In PLWH with evidence of certain INSTI resistance mutations or those taking certain medications that are metabolized by the cytochrome 3A (CYP3A) system (such as rifampin), the dosing of dolutegravir is twice daily.[6] Clinicians should consult with the full prescribing information or consult a pharmacist to verify drug-drug interactions.

For PLWH with renal impairment, dolutegravir can be safely administered as a single agent or if combined with rilpivirine (Juluca).[18] However, if dolutegravir

is prescribed in the STR-containing lamivudine and abacavir (Triumeq), there is a renal dosing restriction due to the lamivudine component. Triumeq should not be administered to patients with a CrCl under 50 mL/min.[20]

Initial reports from a study conducted in Botswana found increased rates of neural tube defects associated with dolutegravir, which prompted the FDA to issue a warning on the use of dolutegravir in pregnancy in May of 2018.[21] However, more recent data found the rates to be less frequent than initially reported, leading to a revision by the World Health Organization and the DHHS Guidelines to include dolutegravir as a preferred INSTI in pregnant women.[2,22,23]

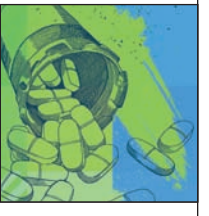
Raltegravir is the only INSTI that is not combined with another agent. It must be taken with at least one other class of ART. Raltegravir is available as film-coated tablets dosed twice daily or as a 600 mg high-dose formulation that requires patients to take two tablets once daily.[24] Both forms may be taken with or without food. Raltegravir has been shown to have a lower barrier to drug resistance than dolutegravir or bictegravir, meaning it may be less potent in people with resistant virus.[2]

Raltegravir is safe to use in PLWH with end-stage renal disease.[24] There are no dosing limitations; however, patients on dialysis should dose raltegravir after dialysis. For patients with mild-moderate liver disease, raltegravir is safe to use with no dose adjustment, but no data are available for the high-dose version so raltegravir high-dose is not recommended in patients with hepatic impairment.[24] For patients who are currently taking rifampin, the high-dose version is not recommended, and the dose of raltegravir should be increased to twice daily.[24]

Elvitegravir is the only INSTI requiring coadministration with cobicistat, a pharmacokinetic boosting agent.[25,26] Elvitegravir has a shorter half-life and requires a boosting agent to increase drug levels to allow for once-daily dosing. Elvitegravir is currently available in a once-daily, fixed-dose STR with cobicistat, emtricitabine, and either tenofovir AF (Genvoya) or tenofovir DF (Stribild). Both forms are dosed as one tablet once daily with food.[25,26] Because elvitegravir requires pharmacologic boosting with cobicistat, there are more drug-drug interactions than the other INSTIs. A careful review of concomitant medications that induce or inhibit CYP3A is important in patients receiving cobicistat-boosted elvitegravir.

Elvitegravir can be used as an initial ART regimen or as a treatment simplification option for people who are virologically controlled on another ART regimen. Although elvitegravir itself does not have a dosing restriction for patients with renal or hepatic impairment, the currently available STRs have renal dose restrictions based on the form of tenofovir used. Stribild should not be used in patients with a CrCl of under 70 mL/min, and Genvoya should not be used in patients with a CrCl under 30 mL/min.[25,26]

A careful review of concomitant medications that induce or inhibit CYP3A is important in patients receiving cobicistat-boosted elvitegravir.



Protease inhibitor therapy

PIs are a potent class of medications that provide a high barrier to drug resistance.[2] Examples when PI therapy may be considered include individuals who have a history of inconsistent medication adherence, or individuals who have developed drug resistance from the failure of other ART regimens.

Pharmacologic boosting agents are required for most PI-based therapies. These boosting agents increase drug levels allowing for once-a-day dosing. The most commonly used boosting agent is ritonavir (Norvir). The other boosting agent that can be used is cobicistat. Given that PI-based therapy is coadministered with a boosting agent, there is a greater potential for drug-drug interactions, particularly those that are processed via the cytochrome P450 pathway.[2]

Darunavir is one of the PIs recommended in the current DHHS guidelines and is available as a single agent (Prezista), as a paired agent with cobicistat (Prezcobix), and as an STR with tenofovir AF, emtricitabine, and cobicistat (Symtuza). All forms of darunavir may be used in both treatment-naive individuals or as part of a combination regimen for patients on ART wishing to switch or simplify treatment.[27-29] One of the components of darunavir contains a sulfa moiety, so caution should be used in patients with a sulfa allergy.[27]

Because darunavir must be administered with a pharmacologic booster (either ritonavir or cobicistat), clinicians should be mindful of potential drug-drug

interactions. It is important to note that boosted darunavir may be administered with cation-containing supplements as well as PPIs and H2 blockers.[28,29] The use of certain statins (simvastatin and lovastatin) is contraindicated with boosted darunavir.[28,29] Atorvastatin and rosuvastatin are safe to use with boosted darunavir, although careful monitoring for statin-associated toxicity or adverse reactions is recommended.[28,29]

Boosted darunavir is one of the preferred PIs for PWLH who are pregnant.[30] Pregnant individuals are usually placed on two NRTIs plus a PI. Due to potential decreased serum concentrations during pregnancy, twice-daily dosing during pregnancy is recommended.[30]

Atazanavir is another PI that is recommended for both treatment-naive and treatment-experienced patients.[2] Atazanavir is only available as a single agent and does not come in an STR. Similar to other PIs, atazanavir is typically administered with a pharmacologic booster daily with food.[31] For treatment-naive individuals with normal or mild liver disease, unboosted atazanavir daily may be prescribed.[31]

One of the adverse reactions of atazanavir is hyperbilirubinemia that results in scleral icterus. This is more of a cosmetic issue and does not reflect hepatic injury.[31] The icterus is reversible with drug discontinuation.

Review patients' HIV drug resistance reports to ensure new ARTs will provide adequate coverage for archived drug resistance mutations.

There are several drug-drug interactions with atazanavir, but an important one for clinicians to be aware of is the interaction of atazanavir with acid-reducing medications. These medications can lower the concentration of atazanavir. If a patient must take an H2 blocker, the dose of atazanavir and the H2 blocker should be separated by at least 10 hours; PPIs should be spaced at least 12 hours apart from atazanavir.[31]

In treatment-naive pregnant patients, atazanavir can be safely used daily with ritonavir and two NRTIs. In treatment-experienced patients or those on H2 blockers or tenofovir DF, atazanavir should be dosed with ritonavir and two NRTIs.[31]

In postmarketing reports of patients prescribed atazanavir, cases of renal disease and nephrolithiasis have been reported.[31] Although there are no dose adjustments for individuals with renal disease, it is recommended that clinicians obtain baseline renal function testing and ongoing monitoring while on therapy.[31] For patients with progressive or worsening renal function, atazanavir should be discontinued.

Nonnucleoside reverse transcriptase inhibitor therapy

NNRTI therapy is an option for patients who may be unable to take INSTIs or PIs, or who prefer the adverse reaction or dosing profile of NNRTI therapy. NNRTIs can be coadministered with NRTIs or INSTIs and do not require a booster. A common class-associated adverse reaction includes rash.[2] Most individuals can be treated through this rash, but in patients with more severe rash or Stevens-Johnson reaction, the NNRTI should be discontinued.[2] Other disadvantages of this class of ART are the lower barrier to resistance and the prevalence of NNRTI-drug resistance in treatment-naive individuals.[2]

Rilpivirine is a once-daily NNRTI available in a combined STR with emtricitabine and either tenofovir DF (Complera) or tenofovir AF (Odefsey); combined with dolutegravir (Juluca); or as a single agent (Edurant). All forms of rilpivirine, except for Juluca, are currently FDA-approved for treatment-naive individuals or treatment-experienced patients with no known resistance to components of rilpivirine or other drugs it may be paired with in an STR. Juluca is only approved for patients on a stable regimen with an undetectable viral load for at least 6 months or longer who wish to switch therapy.[19] A newer long-acting injectable formulation of rilpivirine is under FDA review for both HIV treatment and prevention when paired with a new injectable integrase inhibitor, cabotegravir.[32]

Rilpivirine must be taken with food to improve absorption of the medication.[33] There is a drug-drug interaction with PPIs, so PPI use is contraindicated. Antacids containing aluminum, magnesium, or calcium carbonate should be spaced at least 2 hours before or 4 hours after rilpivirine.[31] H2 blockers can be used but must be taken 12 hours before or 4 hours after rilpivirine.[33] In clinical trials, the virologic efficacy of rilpivirine was reduced in PLWH with pretreatment viral loads over 100,000 copies/mL; therefore, rilpivirine is not recommended for patients with pretreatment viral loads over 100,000 copies/mL.[33]

Doravirine is the newest NNRTI and is available as a single agent (Pifeltro) or in an STR paired with tenofovir DF and lamivudine (Delstrigo). Doravirine provides a treatment option for PLWH who may have drug resistance to other NNRTIs. Additional advantages of doravirine compared with other NNRTIs include the ability to be taken with or without food, fewer neuropsychiatric adverse reactions, fewer drug interactions, and can be used in patients with high pretreatment viral loads.[34,35]

Efavirenz, one of the first NNRTIs, has been shown to be highly effective in controlling HIV. It is available as an individual agent (Sustiva) to be used in combination with other ART and comes as part of several STRs (paired with tenofovir DF and either emtricitabine [Atripla] or lamivudine [Symfi, SymfiLo]). Efavirenz has been associated with central nervous system (CNS) adverse reactions, including vivid dreams and depression.[2] Patients starting efavirenz should be counseled to take it prior to bedtime which helps minimize the CNS-associated effects.[36] Efavirenz was previously contraindicated in pregnancy because of concern for teratogenicity, but newer data resulted in the perinatal guidelines recommending efavirenz as an option during pregnancy.[30] Patients taking efavirenz who are virologically controlled and who are found to be pregnant should continue on their prescribed ART.[30] Data have demonstrated that efavirenz metabolites in urine can cause false reactivity to benzodiazepines on urine drug screening tests.[37] Patients on efavirenz-containing regimens who may need to be drug-screened should be advised of this potential cross-reactivity.

SymfiLo is an STR containing tenofovir DF, lamivudine, and efavirenz. This STR provides an option for individuals who are new to treatment or who wish to switch or simplify their existing regimen and who have no previous history of drug resistance to components of SymfiLo.[38]

Switching or simplifying therapy for patients on ART

For PLWH who are virologically suppressed on earlier-generation ART combinations or who are on multipill or multidose regimens, simplification to an STR or a once-daily dosed regimen may be an option. Prior to switching ART, clinicians should review the patient's HIV drug resistance reports to ensure that the new ART option will provide adequate coverage for archived drug resistance mutations.[2] For clinicians not familiar with interpreting resistance data or who may not have extensive clinical experience managing heavily treated PLWH, a consult with an HIV expert may be prudent. Additionally, it is important to check for potential drug-drug interactions and any dosing limitations (such as renal or hepatic function).

Injectable therapy

Long-acting injectable ART is being evaluated for use in clinical practice. Cabotegravir, an injectable INSTI, has been studied for ART as well as for prevention of HIV.[39] In clinical trials, cabotegravir has been paired with the NNRTI rilpivirine, and dosing intervals of 4 weeks and 8 weeks have been evaluated.[32,39] Outcomes from these studies found good virologic response, and study participants preferred injectable options to oral ART.[39,40] The most common adverse reaction of injectable cabotegravir and rilpivirine was injection-site reaction.[39] The FDA is currently evaluating the data on cabotegravir/rilpivirine.

Implications for practice

HIV treatment continues to evolve and improve. New formulations of effective and well-tolerated drugs, novel delivery options, and an increase in the number of STRs are helping PLWH achieve virologic control of HIV. An understanding of preferred ART, dosing considerations, and common ART drug-drug interactions is critical for clinicians. NPs in primary care and specialty care should become familiar with these newer treatment options in order to educate and provide patients with the best options available to treat and manage this chronic condition.

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