REVIEW ARTICLE

Antiretroviral Therapy

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SUMMARY

The development of effective treatment strategies for human immunodeficiency virus (HIV) infection is a major achievement. Antiretroviral drugs inhibit key steps in the viral replication cycle and consist of six mechanistic classes: HIV entry inhibitors, reverse-transcriptase inhibitors (both nucleosides and nonnucleosides), capsid inhibitors, integrase inhibitors, and protease inhibitors. Antiretroviral therapy (ART) suppresses viral replication, thereby enhancing immune function, decreasing morbidity and mortality, and preventing viral transmission. Consequently, ART is recommended for all persons with HIV infection. On the basis of randomized clinical trials, the Food and Drug Administration has approved 36 antiretroviral drugs for the treatment of HIV infection since 1987; of these, 28 are currently available in the United States, and combination ART regimens are used. Initial preferred ART regimens are potent, convenient, and unlikely to cause side effects and consist of an HIV integrase inhibitor with a high barrier to resistance combined with one or two nucleoside reverse-transcriptase inhibitors. In the majority of patients using current ART regimens, viral replication is durably suppressed below detectable levels. Patients receiving ART are monitored for virologic response over time, and if virologic failure occurs, the next regimen is selected on the basis of treatment history and the results of drug-resistance testing; often, antiretroviral drugs from new classes are administered. Today, the life expectancy of someone with HIV infection who consistently takes ART approaches that of the general population.

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CME

The development of effective antiretroviral therapy (ART) for human immunodeficiency virus (HIV) infection ranks among the greatest achievements of modern medicine. The first cases of acquired immunodeficiency syndrome (AIDS) were reported in 1981,[1] and with no effective treatment, mortality due to AIDS was more than 50% at 1 year and 85% at 5 years.[2] The first antiretroviral drug shown to decrease mortality among persons with AIDS in randomized clinical trials was the nucleoside reverse-transcriptase inhibitor (NRTI) zidovudine,[3] which led to its approval in 1987 by the Food and Drug Administration (FDA). However, this benefit was short-lived, and the use of a single drug to treat HIV was accompanied by the emergence of drug-resistant viral strains.[4]

In the early 1990s, regimens combining two NRTIs showed clinical benefits over single-drug regimens in randomized clinical trials,[5,6] but these benefits were also transient. In the mid-1990s, the availability of quantitative HIV RNA testing and the development and evaluation of three-drug regimens — two NRTIs and an HIV protease inhibitor or nonnucleoside reverse-transcriptase inhibitor (NNRTI) — led to potent virologic suppression for the first time.[7,8] These three-drug regimens were associated with clinical benefits[9] in randomized clinical trials and quickly became standard care. Initial therapy with more than three antiretroviral drugs offered no additional benefits.[10,11] The first 10 years of HIV drug development established potent three-drug antiretroviral regimens, but these regimens were complex,

required taking up to 20 pills divided into three daily doses, and were associated with substantial side effects and toxic effects.

Consequently, the next 10 years saw the clinical development of three-drug regimens that were more convenient, less likely to be associated with unacceptable side effects, and less toxic, which led to FDA approval of the first one-pill, once-daily ART regimen in 2006 — coformulated tenofovir disoproxil fumarate, emtricitabine, and efavirenz[12,13] — and a number of subsequent drugs and coformulated regimens. These updated ART regimens controlled HIV infection and were associated with substantial clinical benefits that translated internationally, including decreased morbidity and mortality[14] and decreased HIV transmission.[15-18] In 2025, more than 32 million persons with HIV infection worldwide were receiving ART,[19] most commonly with a one-pill, once-daily three-drug regimen. Life expectancy for persons with HIV infection treated appropriately with ART now approaches that of the general population.[20] Notably, recent funding disruptions and withdrawals threaten these gains.[19,21-24]

WHEN TO START ART?

Current HIV treatment guidelines worldwide recommend that persons with HIV infection start ART regardless of symptoms, signs, clinical stage of disease, CD4 cell count, or HIV RNA level.[25-29] This strong recommendation follows from studies showing clinical benefits in persons with HIV infection as well as a reduction of HIV transmission to others.

The Strategic Timing of ART (START) trial was an international trial in which 4685 participants with HIV infection were randomly assigned to start ART immediately or delay ART.[30] All the participants had a CD4 cell count of more than 500 per microliter and had not previously received ART. Participants in the delayed-ART group were set to initiate ART if their CD4 cell count decreased to less than 350 per microliter or an AIDS-related event occurred. Clinical end points included both AIDS-defining events and serious non–AIDS-related events (e.g., cardiovascular events and non–AIDS-related cancers). The trial was stopped early because of a significant difference between the groups in clinical events, which occurred in 42 participants (1.8%) in the immediate-ART group and in 96 participants (4.1%) in the delayed-ART group, denoting a 57% reduction (hazard ratio, 0.43; 95% confidence interval [CI], 0.30 to 0.62; P<0.001). All the participants in the trial were then offered treatment and were followed for an additional 6 years. The participants in the immediate-ART group continued to benefit from treatment, with higher CD4 cell counts and fewer clinical events than the participants in the delayed-ART group, and the investigators concluded that a delay in starting ART confers persistent excess risk.[31]

Starting ART promptly not only benefits the person with HIV infection but reduces disease transmission to others. The international HIV Prevention Trials Network (HPTN) 052 trial enrolled 1763 couples in a stable relationship in which one partner had HIV infection and a CD4 cell count of 350 to 550 per microliter and the other did not have HIV infection.[15,32] The partners with HIV infection were randomly assigned to start ART immediately or to delay ART until their CD4 cell count decreased to less than 250 per microliter or AIDS-related symptoms developed. The primary end point was a new linked HIV infection in the partner without HIV infection. The final analysis showed 46 new phylogenetically linked cases during a follow-up period of more than 5 years: 3 cases in the immediate-ART group and 43 in the delayed-ART group, denoting a 93% reduction (hazard ratio, 0.07; 95% CI, 0.02 to 0.22).[33] Further analyses revealed that no linked HIV infections developed when the partner with HIV had a stably suppressed HIV RNA level while receiving ART.[33]

Three large international cohort studies — PARTNER1 (Partners of People on ART — A New Evaluation of the Risks),[16] Opposites Attract,[17] and PARTNER2[18] — included more than 2000 heterosexual and homosexual couples in which HIV status differed between the partners, the partner with HIV infection was receiving ART, and the couple practiced condomless vaginal or anal sex. With more than 144,000 reported sex acts, no linked HIV transmissions occurred when the partner with HIV infection receiving ART had an HIV RNA level of less than 200 copies per milliliter. The results of these studies support the concept of "U=U" (undetectable equals untransmittable — a person with HIV infection receiving ART with a viral load level suppressed below detection cannot transmit HIV to others) and reinforce the

recommendation that all persons with HIV infection start ART.

WHAT ART TO START?

Antiretroviral drugs target specific steps in the cycle of HIV replication (Fig. 1). In the first step of infection, HIV attaches to the CD4 receptor on the surface of the host target cell, the CD4+ T lymphocyte, and induces a conformational change that allows HIV to bind to a chemokine receptor, either CCR5 or CXCR4. This binding induces a second conformational change, which allows fusion of the viral and host membranes and extrusion of the virion contents into the cytoplasm of the cell. The viral capsid is transported to the nucleus of the cell while the virus-specific enzyme HIV reverse transcriptase transcribes viral RNA into a proviral DNA copy. The viral capsid next enters the cell nucleus and uncoats (i.e., breaks apart),[34] releasing the proviral DNA that is then integrated into the host-cell genome by a second HIV-specific enzyme, HIV integrase.

A fraction of infected cells may enter a latent period that can last for decades, establishing a long-lived cellular reservoir of HIV. However, a cell may be activated to transcribe the proviral DNA to genomic and messenger RNA (mRNA) and translate viral mRNA to produce viral proteins. These components then assemble into new immature viral particles that bud from the infected cell, incorporating a portion of the host-cell membrane. After separation, viral precursor proteins are cleaved by a third HIV-specific enzyme, HIV protease, to promote full maturation and infectiousness of the viral particles. Antiretroviral drugs target and inhibit specific steps of this viral replication cycle, thereby suppressing viral replication but not eradicating the virus. If ART is stopped, rapid virologic rebound occurs.

The FDA has approved 36 antiretroviral drugs for the treatment of HIV infection, 28 of which are currently available in the United States. These drugs block the steps of the viral replication cycle and are divided into six broad mechanistic classes: HIV entry inhibitors (CD4 attachment inhibitors, chemokine receptor inhibitors, and fusion inhibitors), HIV NRTIs, HIV NNRTIs, HIV capsid inhibitors, HIV integrase inhibitors, and HIV protease inhibitors (Table 1 and Fig. 2). Combinations of these drugs can enhance their virologic potency and prevent the emergence of drug-resistant virus to facilitate prolonged virologic suppression. Because up to 19% of persons with HIV infection in the United States who have not previously received ART may be infected with drug-resistant viral strains,[35] a baseline assessment of HIV genotype to test for substitutions in reverse transcriptase or protease is recommended (and integrase if transmission of integrase-inhibitor resistance is of concern or if the patient received the integrase inhibitor cabotegravir as preexposure prophylaxis) to assess preexisting drug resistance and guide ART choices.[25]

Most current HIV treatment guidelines recommend one standard initial regimen for most persons with HIV: one or two HIV NRTIs combined with an HIV integrase inhibitor that has a high barrier to resistance[25-29] (Tables 2 and 3). The specific preferred three-drug regimens are bictegravir with tenofovir alafenamide and emtricitabine or dolutegravir with tenofovir alafenamide (or tenofovir disoproxil fumarate) and emtricitabine (or lamivudine). Also recommended is a two-drug regimen of lamivudine with dolutegravir for persons who have an HIV RNA level of less than 500,000 copies per milliliter (although this restriction is under reconsideration on the basis of newer information[36]), have a known HIV genotype, and do not have hepatitis B coinfection. Alternative initial regimens include NNRTI-based or protease inhibitor-based regimens (pharmacologically boosted with cobicistat or ritonavir), although these are used less commonly today. Persons who received cabotegravir as HIV preexposure prophylaxis may have developed integrase-inhibitor resistance and should start a boosted protease inhibitor–based regimen while awaiting HIV genotype results.

These recommendations follow directly from the results of large, comparative, randomized clinical trials involving persons with HIV infection who had not previously received ART. These trials showed superiority of integrase inhibitor–based regimens over NNRTI- or protease inhibitor–based regimens[37-39] along with the similarity between bictegravir- and dolutegravir-based regimens[40,41] and the similarity between dolutegravir-based regimens with one NRTI and those with two NRTIs.[42] ART adherence is key to continued virologic suppression.[43] Current initial ART regimens are associated with durable virologic suppression for 5 years and beyond.[44] Patients

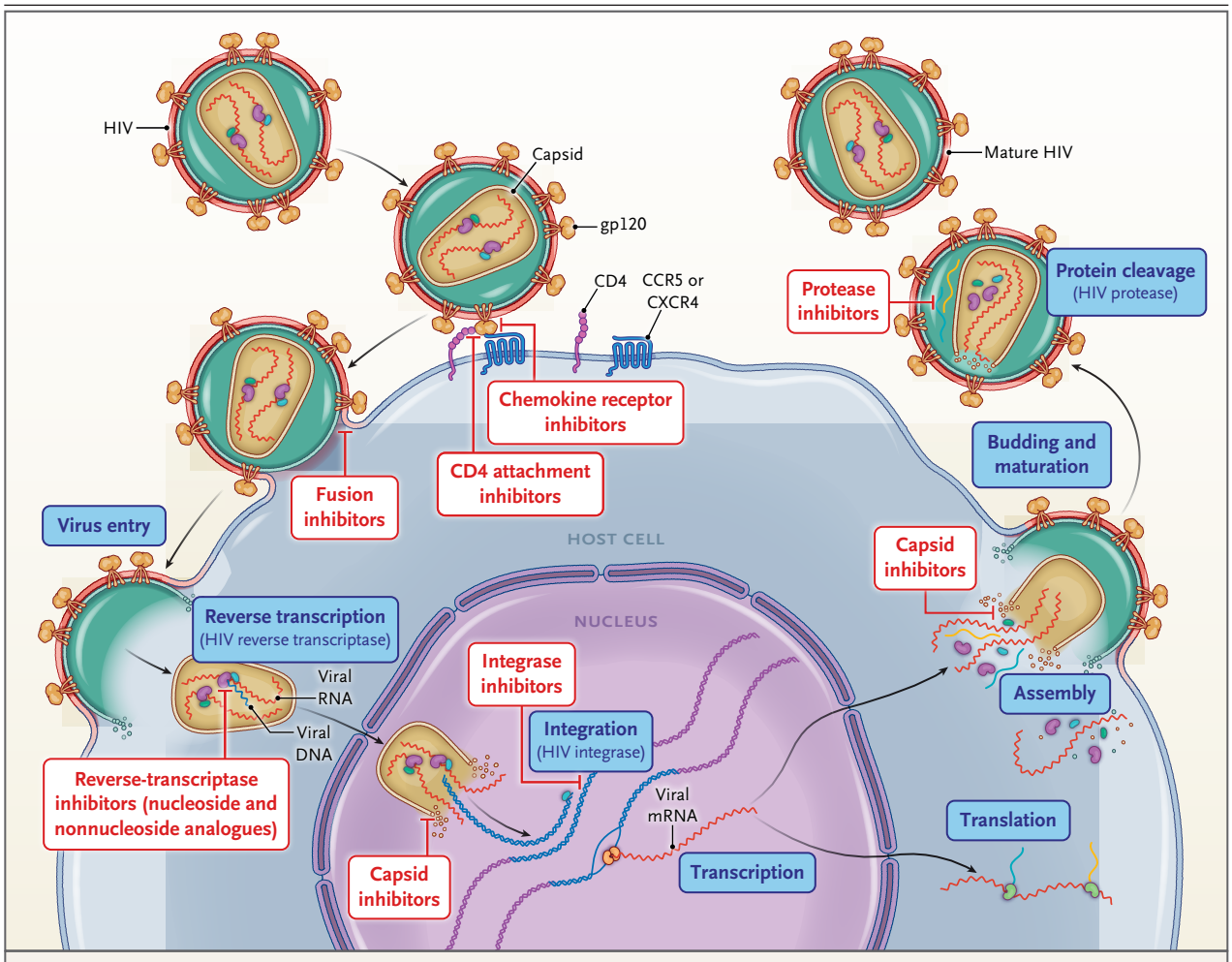

Figure 1. Cycle of HIV Replication and Antiretroviral Mechanisms of Action.

Human immunodeficiency virus (HIV) replicates in the host CD4+ T lymphocyte through a series of steps (blue boxes): HIV attachment to the cell with fusion of membranes and entry into the cell, reverse transcription of viral RNA into viral DNA, migration to the nucleus, uncoating of the capsid, integration of transcribed viral DNA into the host-cell DNA, transcription of host-cell and viral RNA, translation of viral messenger RNA (mRNA) into viral proteins, assembly into new viral particles that bud off the cell, and then postbudding cleavage of viral precursor proteins for full maturation and infectiousness. Antiretroviral drugs (red boxes) work by inhibiting the specific steps and enzymes of the HIV replication cycle. The abbreviation gp120 denotes glycoprotein 120.

with virologic suppression who are receiving a stable ART regimen typically undergo monitoring with assessment of HIV RNA levels at least every 6 months.[25]

WHEN TO CHANGE ART?

In the context of virologic suppression with ART, common reasons to consider changing the regimen are access and cost, side effects and toxic effects, drug–drug or drug–food interactions, pill burden, pregnancy, and regimen simplification.[25] The fundamental principle when changing ART is to maintain virologic suppression. The clinical approach is to review the ART history, previous ART toxic effects, and cumulative drug-resistance test results. ART changes are usually successful in maintaining virologic suppression if a potent, convenient regimen that is unlikely to be associated with unacceptable side effects is selected and drug resistance does not develop.

In the context of ongoing viremia, often due to suboptimal adherence, the potential for virologic failure and the emergence of drug resistance must be assessed.[25] Among persons with HIV RNA levels of less than 200 copies per milliliter, the risk

Table 1. Current Food and Drug Administration–Approved Antiretroviral Drugs According to Mechanistic Class.*

Generic Drug Name	Common Trade Names	Common Coformulations	Date of Approval
HIV capsid inhibitors			
Lenacapavir (LEN)	Sunlenca		2022
HIV entry inhibitors			
Fostemsavir (FTR)	Rukobia		2020
Ibalizumab (IBA)	Trogarzo		2018
Maraviroc (MVC)	Selzentry		2007
HIV integrase inhibitors			
Bictegravir (BIC)	Biktarvy	Bictegravir, tenofovir alafenamide, and emtricitabine	2018
Cabotegravir (CAB)	Vocabria, Cabenuva	Cabotegravir and rilpivirine (Cabenuva)	2021
Dolutegravir (DTG)	Tivicay, Triumeq, Dovato	Dolutegravir, abacavir, and lamivudine (Triumeq); dolutegravir and lamivudine (Dovato)	2013
Elvitegravir (EVG)	Vitekta, Stribild, Genvoya	Elvitegravir, cobicistat, tenofovir disoproxil fumarate, and emtricitabine (Stribild); elvitegravir, cobicistat, tenofovir alafenamide, and emtricitabine (Genvoya)	2012
Raltegravir (RAL)	Isentress		2007
HIV NNRTIs			
Doravirine (DOR)	Pifeltro, Delstrigo	Doravirine, tenofovir disoproxil fumarate, and lamivudine (Delstrigo)	2018
Efavirenz (EFV)	Sustiva		1998
Etravirine (ETR)	Intelence		2008
Nevirapine (NVP)	Viramune		1996
Rilpivirine (RPV)	Edurant, Complera, Odefsey	Rilpivirine, tenofovir disoproxil fumarate, and emtricitabine (Complera); rilpivirine, tenofovir alafenamide, and emtricitabine (Odefsey)	2011
HIV NRTIs			
Abacavir (ABC)	Ziagen, Kivexa	Abacavir and lamivudine (Kivexa)	1998
Emtricitabine (FTC)	Emtriva		2003
Islatravir (ISL)	Idvynso	Islatravir and doravirine	2026
Lamivudine (3TC)	Epivir		1995
Tenofovir alafenamide (TAF)	Vemlidy, Descovy	Tenofovir alafenamide and emtricitabine (Descovy)	2015
Tenofovir disoproxil fumarate (TDF)	Viread, Truvada, Cimduo	Tenofovir disoproxil fumarate and emtricitabine (Truvada); tenofovir disoproxil fumarate and lamivudine (Cimduo)	2001
Zidovudine (ZDV and AZT)	Retrovir		1987
HIV protease inhibitors			
Atazanavir (ATV)	Reyataz, Evotaz	Atazanavir and cobicistat (Evotaz)	2003
Darunavir (DRV)	Prezista, Prezcobix, Symtuza	Darunavir and cobicistat (Prezcobix); darunavir, cobicistat, tenofovir alafenamide, and emtricitabine (Symtuza)	2006
Lopinavir (LPV)	Kaletra	Lopinavir and ritonavir	2000
Nelfinavir (NFV)	Viracept		1997
Ritonavir (RTV)	Norvir		1996
Tipranavir (TPV)	Aptivus		2005

* Food and Drug Administration–approved antiretroviral drugs that are no longer marketed are amprenavir, delavirdine, didanosine, enfuvirtide, indinavir, saquinavir, stavudine, and zalcitabine. HIV denotes human immunodeficiency virus, NNRTI nonnucleoside reverse-transcriptase inhibitor, and NRTI nucleoside reverse-transcriptase inhibitor.

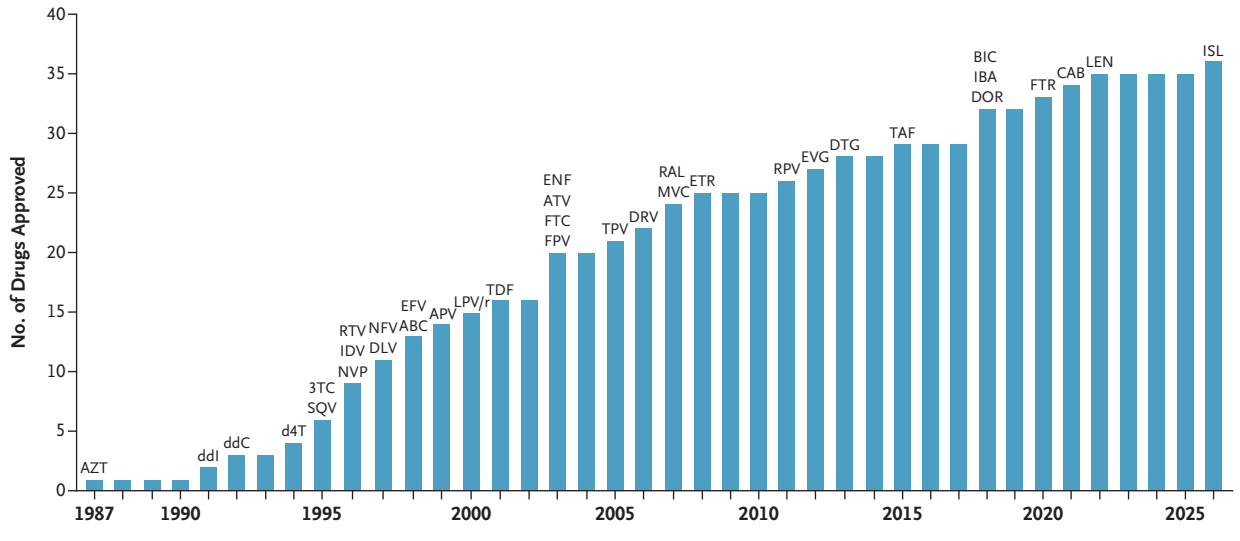

Figure 2. Food and Drug Administration Approval of Antiretroviral Drugs from 1987 through 2026.

On the basis of the results of clinical trials, the Food and Drug Administration (FDA) approved 36 antiretroviral drugs between 1987 and 2026 for the treatment of HIV infection. FDA-approved antiretroviral drugs that are no longer marketed are amprenavir (APV), delavirdine (DLV), didanosine (ddI), enfuvirtide (ENF), indinavir (IDV), saquinavir (SQV), stavudine (d4T), and zalcitabine (ddC). 3TC denotes lamivudine, ABC abacavir, ATV atazanavir, AZT zidovudine, BIC bictegravir, CAB cabotegravir, DOR doravirine, DRV darunavir, DTG dolutegravir, EFV efavirenz, ETR etravirine, EVG elvitegravir, FPV fosamprenavir, FTC emtricitabine, FTR fostemsavir, IBA ibalizumab, ISL islatravir, LEN lenacapavir, LPV/r lopinavir with ritonavir, MVC maraviroc, NFV nelfinavir, NVP nevirapine, RAL raltegravir, RPV rilpivirine, RTV ritonavir, TAF tenofovir alafenamide, TDF tenofovir disoproxil fumarate, and TPV tipranavir.

of the emergence of drug resistance is low. Persons with HIV RNA levels above the limit of detection but less than 200 copies per milliliter (low-level viremia) should have their levels checked again within 3 months. Virologic failure is defined as a confirmed HIV RNA level of more than 200 copies per milliliter — a level that increases the risk of the emergence of drug resistance and that warrants clinical intervention.

WHAT ART TO CHANGE TO?

In the context of virologic suppression, a number of ART regimens have shown continued suppression, including two-drug oral regimens such as coformulated dolutegravir with lamivudine,[45] dolutegravir with rilpivirine,[46] and doravirine with islatravir.[47,48] A novel two-drug regimen is the long-acting, fully injectable ART regimen of the integrase inhibitor cabotegravir with the NNRTI rilpivirine. Large, comparative, randomized clinical trials involving participants with virologic suppression showed that the percentage of participants who maintained suppression with cabotegravir and rilpivirine was similar to that with standard oral ART regimens.[49-51] The fully injectable regimen of cabotegravir and rilpivirine is currently administered as two 3-ml injections in the buttocks every 2 months (or two 2-ml injections every month) in a health care setting, which poses logistical challenges for both patients and facilities.[52] In addition, the long half-lives of cabotegravir and rilpivirine result in prolonged drug concentrations even after treatment discontinuation,[53] which increases the risk of the emergence of drug-resistant viral strains if suppressive ART is not administered.

In the context of virologic failure, the approach is to review the treatment history, with an assessment of adherence, acceptability of side effects, adverse drug–drug interactions, and drug resistance and to conduct drug-resistance testing with

Table 2. Guidelines of the Department of Health and Human Services for Initial Antiretroviral Regimens in Adults and Adolescents.*[25]

Mechanistic Class	No. of Pills per Day	Selected Considerations
Recommended for most people		
INSTI plus 2 NRTIs		
Bictegravir, tenofovir alafenamide, and emtricitabine†	1	
Dolutegravir plus tenofovir (either alafenamide or disoproxil fumarate) plus either emtricitabine or lamivudine‡	2 or 3	
INSTI plus 1 NRTI		
Dolutegravir and lamivudine§	1	Not currently recommended for patients with HIV RNA level >500,000 copies/ml,¶ with concomitant hepatitis B infection, or without an HIV genotype result available
Recommended for people previously treated with cabotegravir as preexposure prophylaxis		
Pharmacologically boosted PI plus 2 NRTIs		
Cobicistat-boosted darunavir plus tenofovir alafenamide and emtricitabine‖	1	Drug–drug interactions with cobicistat
Cobicistat-boosted darunavir** or ritonavir-boosted darunavir plus tenofovir (either alafenamide or disoproxil fumarate) plus either emtricitabine or lamivudine‡	2 to 4	Drug–drug interactions with cobicistat or ritonavir
Alternative for certain clinical scenarios		
INSTI plus 2 NRTIs		
Dolutegravir, abacavir, and lamivudine††	1	Do not use if HLA-B*5701 is present
NNRTI plus 2 NRTIs		
Doravirine, tenofovir disoproxil fumarate, and lamivudine‡‡	1	
Doravirine plus tenofovir alafenamide and emtricitabine‡	2	
Rilpivirine, tenofovir alafenamide, and emtricitabine§§	1	Do not use if HIV RNA level is >100,000 copies/ml or CD4 count is <200 cells/μl
Pharmacologically boosted PI plus 2 NRTIs		
Cobicistat-boosted darunavir plus tenofovir alafenamide and emtricitabine‖	1	Drug–drug interactions with cobicistat
Cobicistat-boosted darunavir** or ritonavir-boosted darunavir plus tenofovir (either alafenamide or disoproxil fumarate) plus either emtricitabine or lamivudine‡ or abacavir and lamivudine¶¶	2 to 4	Drug–drug interactions with cobicistat or ritonavir

* INSTI denotes integrase strand-transfer inhibitor, NNRTI nonnucleoside reverse-transcriptase inhibitor, NRTI nucleoside reverse-transcriptase inhibitor, and PI protease inhibitor.
† Bictegravir, tenofovir alafenamide, and emtricitabine are available as a fixed-dose combination.
‡ Tenofovir alafenamide and emtricitabine, tenofovir disoproxil fumarate and emtricitabine, and tenofovir disoproxil fumarate and lamivudine are available as fixed-dose combinations.
§ Dolutegravir and lamivudine are available as a fixed-dose combination.
¶ This restriction is under reconsideration owing to newer information.[36]
‖ Cobicistat-boosted darunavir plus tenofovir alafenamide and emtricitabine are available as a fixed-dose combination.
** Cobicistat-boosted darunavir is available as a fixed-dose combination.
†† Dolutegravir, abacavir, and lamivudine are available as a fixed-dose combination.
‡‡ Doravirine, tenofovir disoproxil fumarate, and lamivudine are available as a fixed-dose combination.
§§ Rilpivirine, tenofovir alafenamide, and emtricitabine are available as a fixed-dose combination.
¶¶ Abacavir and lamivudine are available as a fixed-dose combination.

Table 3. International Guidelines for Initial Antiretroviral Regimens Recommended for Most Adults and Adolescents.

Guideline	Three-Drug Regimens	Two-Drug Regimens
U.S. Department of Health and Human Services, 2026[25]	Bictegravir, tenofovir alafenamide, and emtricitabine* Dolutegravir plus either tenofovir alafenamide or tenofovir disoproxil fumarate and either emtricitabine or lamivudine†	Dolutegravir and lamivudine‡
International Antiviral Society–USA Panel, 2024[26]	Bictegravir, tenofovir alafenamide, and emtricitabine* Dolutegravir plus either tenofovir alafenamide or tenofovir disoproxil fumarate and either emtricitabine or lamivudine†	Dolutegravir and lamivudine‡
British HIV Association, 2025[27]	Bictegravir, tenofovir alafenamide, and emtricitabine* Dolutegravir plus either tenofovir alafenamide or tenofovir disoproxil fumarate and either emtricitabine or lamivudine†	Dolutegravir and lamivudine‡
European AIDS Clinical Society, 2025[28]	Bictegravir, tenofovir alafenamide, and emtricitabine* Dolutegravir plus tenofovir (either alafenamide or disoproxil fumarate) plus either emtricitabine or lamivudine† Doravirine plus tenofovir alafenamide and emtricitabine; or doravirine plus tenofovir disoproxil fumarate and either emtricitabine or lamivudine†§	Dolutegravir and lamivudine‡ or dolutegravir and emtricitabine
World Health Organization, 2025[29]	Dolutegravir, tenofovir alafenamide or tenofovir disoproxil fumarate, and emtricitabine or lamivudine†¶	None

* Bictegravir, tenofovir alafenamide, and emtricitabine are available as a fixed-dose combination.
† Tenofovir alafenamide and emtricitabine, tenofovir disoproxil fumarate and emtricitabine, and tenofovir disoproxil fumarate and lamivudine are available as fixed-dose combinations.
‡ Dolutegravir and lamivudine are available as a fixed-dose combination.
§ Doravirine, tenofovir disoproxil fumarate, and lamivudine are available as a fixed-dose combination.
¶ Dolutegravir, tenofovir disoproxil fumarate, and lamivudine are available as a fixed-dose combination in many low- and middle-income countries.

the goal of selecting an active regimen that addresses the reasons for virologic failure.[25] Persons with virologic failure due to suboptimal adherence benefit from adherence counseling and may restore viral suppression by improving adherence to their current regimen. Persons with drug-resistant virus benefit from adding new active drugs while optimizing the background ART regimen on the basis of the treatment history and the results of drug-resistance testing. The goal is to maximally suppress the HIV RNA level, which is best accomplished with an ART regimen that contains two or three fully active drugs.[25]

New active drugs that are used to treat drug-resistant virus often come from new mechanistic classes of ART. For example, persons with virologic failure while receiving initial integrase inhibitor–based therapy often benefit from a change to a boosted protease inhibitor–based regimen. Persons with multidrug-resistant HIV infection will benefit from consultation with an HIV expert who may consider new classes of drugs such as the HIV entry inhibitors maraviroc (for persons with R5 virus documented with a tropism assay),[54] ibalizumab,[55] or fostemsavir[56] or the HIV capsid inhibitor lenacapavir.[57] For example, a phase 2–3 trial that enrolled 36 heavily treated participants who were randomly assigned to receive lenacapavir or placebo together with an optimized background ART showed that lenacapavir was superior to placebo; virologic suppression was reported in 88% of the participants in the lenacapavir group and 17% of those in the placebo group at day 15.[57] After optimization of the background regimen, durable virologic suppression in the lenacapavir group lasted from week 26[57] through 3 years.[58]

SIDE EFFECTS AND TOXIC EFFECTS

Most currently used ART regimens are associated with few side effects or long-term toxic effects. Contemporary clinical trials that tested recommended initial ART regimens in participants with HIV infection showed that fewer than 5% of the participants had treatment-limiting side effects.[38-42] Adverse effects seen with older antiretroviral drugs (e.g., cytopenias, diarrhea, lactic acidosis, lipoatrophy, lipohypertrophy, pancreatitis, peripheral neuropathy, and vivid dreams) are rare with contemporary drugs.

As a class, the most common side effect of ART is gastrointestinal (dyspepsia), which may be addressed by treating the symptom or taking ART with food. Some other side effects are worth noting. Tenofovir disoproxil fumarate is associated with proximal renal tubular dysfunction and loss of bone mineral density; these toxic effects are rare with tenofovir alafenamide.[59] Abacavir and some protease inhibitors are associated with cardiovascular events,[60,61] and abacavir, tenofovir alafenamide, efavirenz, and boosted protease inhibitors are associated with dyslipidemia.[25] A more recently appreciated side effect, weight gain, is associated with tenofovir alafenamide or HIV integrase inhibitors, particularly in women and Black persons,[62,63] although this finding is controversial.[64]

DRUG INTERACTIONS

Preferred NRTIs (e.g., emtricitabine, lamivudine, and tenofovir) have few serious drug–drug interactions. Integrase inhibitors may be bound by compounds containing divalent cations such as aluminum, calcium, iron, magnesium, or zinc (e.g., some antacids and nutritional supplements),[65] and strategies such as staggered dose administration or taking the treatments with food are warranted. Bictegravir and dolutegravir inhibit organic cation transporter 2, which leads to a modest increase in the serum creatinine level that does not indicate a decrease in the glomerular filtration rate.[66] Dolutegravir increases metformin concentrations by 69 to 79%, and when these drugs are given together, the metformin dose should be adjusted to achieve glycemic control.[25]

Some antiretroviral drugs interact with the cytochrome P-450 3A4 (CYP3A4) hepatic enzyme system and can affect other drugs. The NNRTIs efavirenz and etravirine induce CYP3A4, potentially reducing the levels of some other drugs (e.g., bictegravir, dolutegravir, some azole antifungals, some antidepressants, and some antipsychotics). The pharmacologic enhancers (i.e., boosters) cobicistat and ritonavir strongly inhibit CYP3A4, which increases the levels of some other drugs including the HIV protease inhibitors, some antidepressants, and some antipsychotics. Some drugs pose particular challenges, and interactions with ART should be carefully assessed, including interactions with apixaban, clarithromycin, clopidogrel, glucocorticoids (systemic, inhaled, and injected), rifamycins (rifabutin, rifampin, and rifapentine) used in the treatment and prevention of tuberculosis, older anticonvulsants (carbamazepine, phenobarbital, and phenytoin), and some statins (lovastatin and simvastatin). Resources for assessing drug–drug interactions with ART can be found in the guidelines of the Department of Health and Human Services[25] and on the University of Liverpool HIV Drug Interactions website.[67]

SPECIAL POPULATIONS

EARLY HIV INFECTION

Persons with acute or recent HIV infection benefit from starting ART promptly to reduce acute symptoms, signs, and HIV RNA levels and decrease the risk of transmission. HIV genotypic testing should be performed, and a standard ART regimen should be started while these results are awaited.[25] When results become available, the regimen can be adjusted if necessary.

HIV CONTROLLERS

A small proportion of persons with HIV infection maintain low or undetectable levels of HIV RNA without ART.[68] Because ongoing HIV replication, immune activation, inflammation, and clinical events can occur in this group[69] and pilot data suggest benefits of ART,[70] starting ART is generally recommended,[25] although definitive data are lacking.

ADOLESCENTS

Although standard ART regimens are recommended for adolescents,[25] this group of patients may have lower rates of virologic suppression and higher rates of loss to follow-up.[71] Treatment with one pill once daily or with fully injectable ART regimens improves adherence and virologic response.[72]

PREGNANCY

Current guidelines recommend starting ART during pregnancy as early as possible, both for the health of the pregnant person and to decrease the risk of transmission to the baby; if the person is receiving suppressive ART, it should be continued.[73] In general, most ART is safe to use during pregnancy, with an incidence of adverse outcomes that is similar to that in the general population.[74] The selection of specific antiretro-

viral drugs depends on the previous findings regarding use during pregnancy, and standard three-drug ART regimens are recommended. Preferred regimens include combinations of the NRTIs tenofovir (tenofovir alafenamide or tenofovir disoproxil fumarate) with emtricitabine or lamivudine together with an integrase inhibitor (bictegravir or dolutegravir).[73] Other drugs, including the two-drug combination of dolutegravir and lamivudine, some NNRTIs, and ritonavir-boosted protease inhibitors, are considered to be alternatives. Cobicistat is not recommended because of substantially decreased drug levels during pregnancy. Other drugs (doravirine, HIV entry inhibitors, and HIV capsid inhibitors) are not generally recommended because of limited data during pregnancy, although they may be used in some clinical situations.

ACUTE OPPORTUNISTIC INFECTIONS

Persons with acute opportunistic infections benefit from starting ART promptly to decrease the risk of clinical progression and death.[75] This strategy does not increase the incidence of virologic breakthrough, drug side effects, or immune reconstitution inflammatory syndrome. However, in persons starting treatment for acute central nervous system opportunistic infections such as cryptococcal or tuberculous meningitis, ART may provoke immune reconstitution inflammatory syndrome, which can lead to adverse clinical outcomes and death[76,77]; therefore, ART is generally deferred for at least 2 weeks after the start of treatment for these central nervous system opportunistic infections.[25]

COINFECTIONS

Persons with certain coinfections merit special consideration with respect to ART. Some antiretroviral drugs (e.g., emtricitabine, lamivudine, and tenofovir) also have potent activity against hepatitis B virus. Current guidelines recommend treating both hepatitis B virus and HIV infections, with two active antiviral drugs for hepatitis B virus and three active antiretroviral drugs for HIV.[25] Hepatitis C antiviral drugs may have interactions with ART. Tuberculosis treatment or prevention with rifamycin-containing regimens complicates the use of ART because of serious drug–drug interactions that may warrant dose adjustment. In some cases, the use of certain antiretroviral drugs may be contraindicated.

SUBOPTIMAL ADHERENCE

Some persons find ART adherence to be challenging, even with single-pill, once-daily oral regimens. The LATITUDE (Long-Acting Therapy to Improve Treatment Success in Daily Life) trial enrolled 453 participants with a history of suboptimal adherence to oral ART who were given monetary incentives to take oral ART to achieve virologic suppression.[78] A total of 306 participants with virologic suppression were then randomly assigned to continue their oral regimen or change to injectable cabotegravir and rilpivirine. The investigators found that the injectable regimen was superior with respect to virologic suppression. Case series involving persons with HIV infection and suboptimal adherence or ongoing viremia have suggested that injectable ART regimens of cabotegravir and rilpivirine[79] or cabotegravir and lenacapavir[80] can be effective, although more definitive data are needed. Guidelines recommend consideration of fully injectable regimens in patients with suboptimal adherence in certain clinical scenarios.[25,26]

FUTURE DIRECTIONS

Strategies to enhance adherence to long-term ART regimens by further improving the convenience of these regimens are currently under investigation. A weekly oral regimen of the HIV nucleoside analogue reverse-transcriptase translocation inhibitor islatravir combined with the HIV capsid inhibitor lenacapavir was tested in a phase 2 study involving persons with HIV infection and virologic suppression who were receiving standard, daily, three-drug, bictegravir-based ART; the study showed that the weekly regimen maintained virologic suppression through 48 weeks.[81] Studies using a single weekly coformulated tablet of islatravir with lenacapavir and other weekly oral regimens are underway.

Although the current fully injectable ART regimen of cabotegravir and rilpivirine is FDA-approved for administration every 2 months in persons with HIV infection and virologic suppression receiving ART, newer approaches are under investigation. Alternative formulations of cabotegravir with longer dose-administration intervals are under clinical evaluation.[82] Investigational, extended-release prodrugs of cabotegravir were tested in studies in animals, and data suggested that yearly administration could be possible.[83]

KEY POINTS

ANTIRETROVIRAL THERAPY

- Antiretroviral therapy (ART) is recommended for all persons with human immunodeficiency virus (HIV) infection, both for their own health and to prevent HIV transmission to others.
- Current first-line ART regimens are potent, convenient, and unlikely to be associated with unacceptable side effects and consist of one or two nucleoside reverse-transcriptase inhibitors together with an integrase inhibitor administered as one- or two-pill, once-daily therapy.
- In persons with suppressed HIV RNA levels, changing ART regimens (e.g., for regimen simplification or because of toxic effects) is usually successful if there is no drug resistance.
- In persons with virologic failure, changing ART regimens warrants a review of the ART history and results of drug-resistance testing to design a new regimen, optimally with two or three fully active drugs.
- Today, the life expectancy of a person with HIV infection appropriately managed with ART is approaching that of the general population.
- Future ART innovations include once-weekly oral regimens, longer-acting fully injectable therapy, and novel delivery systems such as implants and patches.

Currently, lenacapavir can be administered parenterally every 6 months[57]; in an early clinical study, a newer parenteral formulation achieved target concentrations for a year.[84]

A number of investigational antiretroviral agents are in development, both in existing classes (HIV NNRTIs, integrase inhibitors, and capsid inhibitors) and in newer classes, including HIV broadly neutralizing monoclonal antibodies (bNAbs) that prevent viral attachment. A notable pilot study enrolled persons with HIV infection and virologic suppression receiving standard ART who had viral strains susceptible to two HIV bNAbs, teropavimab and zinlirvimab.[85] Participants were given a single injection of lenacapavir with single infusions of the two bNAbs and had durable virologic suppression for 6 months. This every-6-month parenteral ART regimen was explored further in a phase 2 trial of 80 participants with HIV infection and virologic suppression receiving oral ART, 53 of whom were randomly assigned to change to the parenteral regimen and 27 of whom were assigned to continue their suppressive oral ART; at 26 weeks, all but 1 of the 80 participants continued to have virologic suppression.[86] Also under study are novel delivery strategies for ART including other unique injectable regimens, implants, and patches.[87]

CONCLUSIONS

ART is recommended for all persons with HIV infection to control viremia, enhance immune function, decrease morbidity and mortality, and prevent transmission. The optimal choice of an ART regimen depends on consideration of virologic potency, convenience, side-effect profile, drug–drug interactions, patient factors, coinfections and coexisting conditions, and access. Currently recommended initial ART consists of two- or three-drug, coformulated, once-daily, oral regimens that are potent, convenient, and unlikely to be associated with unacceptable side effects. Newer innovations include weekly oral regimens, fully injectable regimens, and newer strategies of administration including infusions, implants, and patches. Persons with HIV infection who start ART promptly and take it consistently and whose treatment is managed appropriately have a life expectancy approaching that of the general population and do not transmit HIV to others.

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