Special Communication

Antiretroviral Treatment of Adult HIV Infection
2014 Recommendations of the International Antiviral Society–USA Panel

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IMPORTANCE New data and antiretroviral regimens expand treatment choices in resource-rich settings and warrant an update of recommendations to treat adults infected with human immunodeficiency virus (HIV).

OBJECTIVE To provide updated treatment recommendations for adults with HIV, emphasizing when to start treatment; what treatment to start; the use of laboratory monitoring tools; and managing treatment failure, switches, and simplification.

DATA SOURCES, STUDY SELECTION, AND DATA SYNTHESIS An International Antiviral Society–USA panel of experts in HIV research and patient care considered previous data and reviewed new data since the 2012 update with literature searches in PubMed and EMBASE through June 2014. Recommendations and ratings were based on the quality of evidence and consensus.

RESULTS Antiretroviral therapy is recommended for all adults with HIV infection. Evidence for benefits of treatment and quality of available data increase at lower CD4 cell counts. Recommended initial regimens include 2 nucleoside reverse transcriptase inhibitors (NRTIs; abacavir/lamivudine or tenofovir disoproxil fumarate/emtricitabine) and a third single or boosted drug, which should be an integrase strand transfer inhibitor (dolutegravir, elvitegravir, or raltegravir), a nonnucleoside reverse transcriptase inhibitor (efavirenz or rilpivirine) or a boosted protease inhibitor (darunavir or atazanavir). Alternative regimens are available. Boosted protease inhibitor monotherapy is generally not recommended, but NRTI-sparing approaches may be considered. New guidance for optimal timing of monitoring of laboratory parameters is provided. Suspected treatment failure warrants rapid confirmation, performance of resistance testing while the patient is receiving the failing regimen, and evaluation of reasons for failure before consideration of switching therapy. Regimen switches for adverse effects, convenience, or to reduce costs should not jeopardize antiretroviral potency.

CONCLUSIONS AND RELEVANCE After confirmed diagnosis of HIV infection, antiretroviral therapy should be initiated in all individuals who are willing and ready to start treatment. Regimens should be selected or changed based on resistance test results with consideration of dosing frequency, pill burden, adverse toxic effect profiles, comorbidities, and drug interactions.

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JAMA. 2014;312(4):410-425. doi:10.1001/jama.2014.8722

Antiretroviral therapy (ART) consists of a combination of drugs targeting the human immunodeficiency virus (HIV) life cycle with the aim of stopping HIV replication and preserving or restoring immune function. Since publication of the last recommendations in 2012,[1] there is more evidence supporting the initiation of ART regardless of CD4 cell count. New cohort data provide compelling evidence for the effectiveness of treatment to prevent transmission in heterosexual and same-sex couples.[2-4] In addition, morbidity and mortality from non–AIDS-defining illness did not differ from that of the general population if CD4 cell counts of greater than 500/μL were achieved.[5] Several reports suggest that if ART is started early during acute infection, prolonged virologic suppression after discontinuation of ART may be achievable in rare cases.[6,7] New drugs with high potency, low toxicity, and good tolerability increase the feasibility of early, lifelong treatment. Even patients with prior treatment failure and multidrug resistance can usually be treated with suppressive ART. Recommendations provided herein for the optimal management of adults with HIV infection are based on the latest developments and available evidence.

Methods

These recommendations were developed by a volunteer, international panel of experts in HIV research and patient care selected by the International Antiviral Society–USA and vetted for suitability, expertise, conformance to the group's conflict of interest criteria, and ability to work toward consensus. The panel convened in person and by conference calls in 2013 and 2014. Section leaders and teams evaluated evidence and summarized draft recommendations for full-panel review.

Evidence used was published in the scientific literature, presented at major peer-reviewed scientific conferences, or released as safety reports by regulatory agencies or data and safety monitoring boards since 2012.[1] Literature searches in PubMed and EMBASE by reference librarians were designed to capture publications relevant to ART in HIV infection since the 2012 iteration[1] through June 2014. Approximately 400 relevant citations were identified. Relevant abstracts publicly presented at scientific conferences were identified by panel members. Manufacturers of antiretroviral drugs submitted lists of recent publications or abstracts meeting the established criteria.

These recommendations are focused on adults with HIV infection living in settings in which antiretroviral drugs are generally available (approved by regulatory bodies or in expanded access) or in late-stage development (new drug application filed). Recommendations were made by full-panel consensus and rated (**Table 1**). For areas in which recommendations have not changed substantially or no or few new data are available, the reader is referred to the previous report.[1] Further details about the process, the selection of panel members, the sponsor (International Antiviral Society–USA), and its policies are included in the eMethods, in eBoxes 1-4, and in eTables 1-3 in the Supplement.

Recommendations for When to Start

Additional evidence for initiating ART in all adults with HIV infection has emerged from continued observational cohort data,[5,9-11] the lack of demonstrated harm with early initiation, cost-effectiveness modeling, and data from a randomized clinical trial showing that ART reduced the likelihood of HIV transmission while providing clinical benefit to the individual.[2-4,12-15] Recommendations for when to start ART appear in **Box 1**. The strength of the recommendations and the quality of the evidence increase as CD4 cell counts decrease and in the presence of certain concurrent conditions. The World Health Organization recommends ART be initiated regardless of CD4 cell count for a number of clinical and programmatic indications.[16] The patient must be willing and ready to initiate therapy. Medication counseling and adherence support should be offered. However, patients who do not choose or are not ready to start ART should remain in clinical care with regular monitoring and ongoing discussion about the need for ART.

The evidence for initiating ART in patients termed *elite controllers* (ie, those with an HIV-1 RNA level of less than the level of detection without ART) is stronger than in the past,[17-19] but still insufficient to warrant recommending routine treatment.

Acute HIV Infection

ART is recommended for persons with acute HIV infection, and should be started as soon as possible to maximize benefit.[7] New data have demonstrated additional benefits of ART, namely reduction of proviral DNA and plasma viral load,[20,21] lower viral set point,[22] robust immune reconstitution,[21] and CD4 cell count increases greater than 900/μL.[23] Patients in these trials received ART for a limited period ranging from 12 to 60 months. None of the above benefits lasted for more than 24 months after treatment discontinuation.[24] ART did not prevent persistent T-cell activation,[25] but did reduce the generation of latently infected cells,[26] and in anecdotal cases, led to prolonged viral suppression after discontinuation of ART.[6,7]

ART should be offered to all patients with acute or early infection. Planned discontinuation of ART after a specific duration of treatment is not recommended except in research settings.

Table 1. Definitions for Strength of the Recommendation and the Quality of the Evidence[a]

	Definition
Strength of recommendation	
A	Strong support
B	Moderate support
C	Limited support
Quality of evidence	
Ia	Evidence from ≥1 RCTs published in the peer-reviewed literature
Ib	Evidence from ≥1 RCTs presented in abstract form at peer-reviewed scientific meetings
IIa	Evidence from non-RCTs, cohort, or case-control studies published in the peer-reviewed literature
IIb	Evidence from non-RCTs, cohort, or case-control studies presented in abstract form at peer-reviewed scientific meetings
III	Recommendation based on the panel's analysis of the accumulated available evidence

Abbreviation: RCT, randomized clinical trial.

[a] Adapted in part from the Canadian Task Force on Periodic Health Examination.[8]

Box 1. Recommendations for Antiretroviral Therapy (ART)[a]

When to Start ART

ART is recommended for the treatment of human immunodeficiency virus (HIV) infection and for the prevention of transmission of HIV (AIa).

ART is recommended regardless of CD4 cell count (AIa-BIII). The strength of the recommendation increases as the CD4 cell count decreases and in the presence of certain conditions, with the following ratings:

For CD4 cell counts of ≤500/μL: AIa

For CD4 cell counts of >500/μL: BIII

Ratings for specific conditions with CD4 cell counts of >500/μL:

Pregnancy: AIa

Chronic hepatitis B virus co-infection: AIIa

HIV-associated nephropathy: AIIa

ART is recommended and should be offered to persons during the acute phase of primary HIV infection, regardless of symptoms (BIII).

ART should be started as soon as possible, preferably within the first 2 weeks of diagnosis, in patients with opportunistic infections (AIa) and other opportunistic diseases and AIDS-defining illnesses (including all lymphomas and human papillomavirus–related cancers) (AIa-BIII).

The optimal timing for patients with cryptococcal meningitis is less certain, but initiating ART early during cryptococcal treatment should be considered when expert management of both cryptococcal and HIV infection is available (BIII).

ART is recommended in all HIV-infected persons with tuberculosis (TB) and should be started within 2 weeks of TB treatment when the CD4 cell count is <50/μL, and by 8 to 12 weeks for those with higher CD4 cell counts (AIa). The optimal timing for patients with TB meningitis is less certain, but ART should be started within the first 2 to 8 weeks of diagnosis and managed in consultation with experts (BIII).

Recommendations for ART Monitoring

HIV-1 RNA level should be monitored at about 4 weeks after treatment is initiated or changed, and then every 3 months to confirm suppression of viremia below the limit of quantification of sensitive commercial assays (AIa).

CD4 cell count should be monitored at least every 3 months after initiation of therapy, especially among patients with cell counts of <200/μL, to determine the need for initiation or discontinuation of primary opportunistic infection prophylaxis (BIII).

Once HIV-1 RNA level is suppressed for 1 year and CD4 cell count is stable at ≥350/μL, viral load and CD4 cell count can be monitored at intervals of ≤6 months in patients with dependable adherence (CIII).

Once viral load is demonstrated to be suppressed consistently for more than 2 years and CD4 cell counts are persistently >500/μL, monitoring CD4 cell counts is optional unless virologic failure occurs or there are intercurrent immunosuppressive treatments or conditions (CIII).

Detectable HIV-1 RNA level (>50 copies/mL) during therapy should be confirmed within 4 weeks in a subsequent sample prior to making management decisions (BIII).

HIV-1 RNA level >200 copies/mL should prompt evaluation of factors leading to failure and consideration of switching ART (AIIa).

Baseline genotypic testing for resistance should be performed in all treatment-naive patients (AIIa) and in cases of confirmed virologic failure (AIa).

Therapeutic drug monitoring is not recommended in routine care; however, selected patients might benefit from this intervention (BIII).

Laboratory monitoring for ART toxicity is recommended. In the absence of new abnormalities after week 16 of treatment, the frequency of monitoring, which is generally between 3 and 6 months, should be guided by the presence or absence of comorbidities, and by the components of the regimen (CIII).

Recommendations for Changing the ART Regimen in Treatment-Experienced Patients

Design of a new regimen should consider previous antiretroviral therapy exposure, previous resistance profile, drug interactions, and history of intolerance or toxic effects (AIIa).

Depending on the resistance profile, viral tropism, and options available for patients with multidrug resistance, inclusion of a boosted protease inhibitor and agents from newer drug classes (eg, an integrase strand transfer inhibitor or maraviroc) should be considered (AIa).

Monotherapy with a boosted protease inhibitor is not recommended when other options are available (AIa).

Maintenance of virologic suppression is paramount when switching the regimen to improve tolerability, reduce toxicity, and improve convenience (AIa).

Switching or regimen simplification in virologically suppressed individuals is generally safe if prior treatment and resistance profile are considered and full activity of the nucleoside reverse transcriptase inhibitors can be ensured for switches from a ritonavir-boosted protease inhibitor to drugs with low barriers to resistance (nonnucleoside reverse transcriptase inhibitors, unboosted protease inhibitors, or integrase strand transfer inhibitors) (AIa).

[a] Ratings of the strength of the recommendations and quality of evidence are described in Table 1.

The benefits of short-term ART are time limited, and treatment discontinuation with viral rebound is associated with transmission.[20,22,27]

Opportunistic Infections

The evidence for immediate initiation of ART during treatment for an acute opportunistic infection was reviewed previously,[1] although controversy continues on the best timing to start ART in persons with acute cryptococcal meningitis. An observational cohort study of 501 patients with cryptococcal meningitis treated in resource-limited settings found that time to initiation of ART was not associated with early or overall mortality.[28] A small randomized trial showed that early ART in the setting of cryptococcal meningitis did not improve cerebrospinal fluid fungal clearance, and was associated with increased risk of immune reconstitution inflammatory syndrome (IRIS) but not with increased mortality compared with delayed initiation of ART.[29] A Cochrane Database analysis reported no significant difference in mortality in early vs delayed ART (relative risk, 1.40; 95% CI, 0.42-4.68).[30] The recently published COAT trial demonstrated higher mortality in the 2- to 5-week period after randomization in those receiving early vs delayed ART, with the most pronounced difference observed in those with CD4 cell counts of less than 50/μL and severe cryptococcal meningitis with white blood cell counts of less than 5/μL in cerebrospinal fluid.[31] The excess mortality was not explained by other differences, including the occurrence of

Table 2. Recommended Initial Antiretroviral Regimens[a]

Type of Regimen	Antiretroviral Drug Combination	Rating	Comments
Integrase strand transfer inhibitor plus 2 nucleoside reverse transcriptase inhibitors	Dolutegravir[b] plus tenofovir/emtricitabine	AIa	Dolutegravir is dosed once daily. Associated with modest increases in creatinine level due to inhibition of creatinine secretion.
	Dolutegravir[b] plus abacavir[c]/lamivudine	AIa	No evidence that abacavir/lamivudine performs less well at HIV-1 RNA levels >100 000 copies/mL when given with dolutegravir. A fixed-dose combination is in late-stage development.
	Elvitegravir[b]/cobicistat/tenofovir/emtricitabine	AIa	Once-daily fixed-dose combination. Cobicistat is associated with modest increases in creatinine level due to inhibition of creatinine secretion; has similar drug interactions to ritonavir.
	Raltegravir[b] plus tenofovir/emtricitabine	AIa	Raltegravir is taken twice daily.
Nonnucleoside reverse transcriptase inhibitor plus 2 nucleoside reverse transcriptase inhibitors	Efavirenz[d]/tenofovir/emtricitabine	AIa	Efavirenz central nervous symptoms may persist beyond 2-4 weeks but is no longer contraindicated for use in pregnant women.
	Efavirenz[d] plus abacavir[c]/lamivudine[e]	AIa	Efavirenz central nervous symptoms may persist beyond 2-4 weeks but is no longer contraindicated for use in pregnant women.
	Rilpivirine[f]/tenofovir/emtricitabine	AIa	Once-daily fixed-dose combination. Rilpivirine-based therapy is not recommended in patients with baseline HIV-1 RNA levels >100 000 copies/mL.
Ritonavir-boosted protease inhibitor plus 2 nucleoside reverse transcriptase inhibitors	Atazanavir[g,h] plus tenofovir/emtricitabine	AIa	Atazanavir is associated with nephrolithiasis, cholelithiasis, and chronic kidney injury.
	Atazanavir[g,h] plus abacavir[c]/lamivudine[e]	AIa	Atazanavir is associated with nephrolithiasis, cholelithiasis, and chronic kidney injury.
	Darunavir[g] plus tenofovir/emtricitabine	AIa	During initial therapy, 800 mg of darunavir is given once daily with 100 mg of ritonavir given once daily.

[a] Regimen classes and drugs within these classes are listed in alphabetic order by the anchor (third) drug and not in order of preference. Ratings of the strength of the recommendations and quality of evidence are described in Table 1.

[b] Simultaneous administration with antacids or other medications with divalent cations (Ca^{2+}, Mg++, Al++, Fe++) should be avoided due to chelation of the integrase strand transfer inhibitor by the cation, thereby reducing absorption.

[c] Abacavir has been associated with increased cardiovascular risk, although data are conflicting; use with caution in patients with high cardiovascular risk. Should only be used in HLA-B*5701–negative patients.

[d] Should be taken on an empty stomach, and preferably at bedtime.

[e] The combination of abacavir and lamivudine was less efficacious with baseline HIV-1 RNA level above 100 000 copies/mL than the combination of tenofovir and emtricitabine when these agents were given with efavirenz or ritonavir-boosted atazanavir.

[f] Rilpivirine should not be given with proton pump inhibitors and should be taken consistently with a full meal.

[g] Should be taken with food.

[h] Co-administration with H2-blockers or proton pump inhibitors should be avoided if possible and, if not, specific doses and dose separation schedules are recommended as per prescribing information.

IRIS between the 2 groups. Most deaths were attributed to progressive cryptococcal meningitis, although it was not possible to differentiate IRIS from progressive cryptococcal disease. These data suggest that caution when initiating ART in the setting of cryptococcal meningitis is warranted. Earlier initiation of ART (before 5 weeks) might be considered in settings in which there is access to appropriate antifungal therapy (including flucytosine),[32] frequent monitoring, appropriate management of high intracranial pressure, and careful management of other underlying conditions that might influence mortality.

Cost

The cost of ART varies globally, but even in resource-rich countries ART is highly cost-effective.[33-35] In the United States, cost of care for patients with more advanced disease (eg, CD4 cell count <50/μL) is 2.5-fold higher (expenditure/patient/year) than for those with higher (>350/μL) CD4 cell counts.[36] In resource-limited settings, ART is even more cost-effective because of much lower medication costs.[13]

In the next 4 years, more than 20 drugs are expected to become available in generic form (eTable 4 in the Supplement). A modeling study has estimated substantial reductions in expenditures and improved cost-effectiveness will occur when generic drugs are used.[14] However, some of the newer agents have efficacy or tolerability advantages over drugs that will soon become generic. In addition, the use of generic drugs may require that patients switch from single-tablet regimens to multiple-pill regimens, which could adversely affect adherence.

Recommendations for What Treatment to Start

Data that inform choices for initial ART continue to accrue, and options for ART-naive patients include several single-tablet regimens and other efficacious regimen choices (**Table 2** and **Table 3**). Large studies have expanded knowledge of ART anchored by integrase strand transfer inhibitors (INSTIs),[37-45] and several INSTI-based regimens are now recommended. At present, ART is considered lifelong, and sustained viral suppression is the foundation for immune recovery, optimal health, and prevention of resistance and transmission. Thus, maximizing adherence and minimizing toxicity is paramount; the goal is to treat with an effective therapy that is well tolerated and convenient, and has limited drug interactions and effects on comorbid conditions. In

Table 3. Alternatives to Recommended Initial Regimens[a]

Type of Regimen	Alternative Antiretroviral Drug Combinations	Rating	Comments
Integrase strand transfer inhibitor plus 2 nucleoside reverse transcriptase inhibitors	Raltegravir[b] plus abacavir[c]/lamivudine	BIa	No evidence that abacavir/lamivudine performs less well at HIV-1 RNA levels >100 000 copies/mL when taken with raltegravir.
Nonnucleoside reverse transcriptase inhibitor (NNRTI) plus 2 nucleoside reverse transcriptase inhibitors	Nevirapine plus 2 nucleoside reverse transcriptase inhibitors	BIa	Severe hepatotoxicity may occur in initial therapy when CD4 cell count is >250/μL in women and >400/μL in men. Severe rash is more common than with other NNRTIs.
	Rilpivirine[d] plus abacavir[c]/lamivudine	AIa	Rilpivirine-based therapy is not recommended in patients with baseline HIV-1 RNA levels >100 000 copies/mL.
Protease inhibitor plus 2 nucleoside reverse transcriptase inhibitors	Atazanavir[e]/cobicistat[f] with 2 nucleoside reverse transcriptase inhibitors	BIa	Atazanavir plus cobicistat as a fixed-dose combination achieves atazanavir levels similar to those with ritonavir boosting. As separate agents, they were noninferior to ritonavir-boosted atazanavir, both in combination with tenofovir/emtricitabine.
	Darunavir[e]/cobicistat[f] with 2 nucleoside reverse transcriptase inhibitors	BIII	Darunavir plus cobicistat as a fixed-dose combination achieves darunavir levels similar to those with ritonavir boosting.
	Darunavir[e,g] plus abacavir[c]/lamivudine	BIb	Comparative clinical data from a subset of patients from a single, randomized study.
	Lopinavir[g] fixed-dose combination with 2 nucleoside reverse transcriptase inhibitors	BIa	Main advantage is fixed-dose combination. May have increased cardiovascular risk and be less tolerable than recommended options.
Nucleoside reverse transcriptase inhibitors limiting or sparing[h]	Darunavir[e,g] plus raltegravir	BIb	Raltegravir taken twice daily, ritonavir-boosted darunavir taken once daily. Less effective at CD4 cell counts of <200/μL and possibly HIV-1 RNA levels >100 000 copies/mL.
	Lopinavir[g] plus lamivudine	BIa	Single study; comparator nucleoside reverse transcriptase inhibitor included zidovudine (53.9%), tenofovir (36.6%), and abacavir (9.4%), each with lamivudine.
	Lopinavir[g] plus raltegravir	BIa	Both medications taken twice daily; single study with relatively small sample size and low baseline plasma HIV-1 RNA level.

[a] Regimen classes and drugs within these classes are listed in alphabetic order by the anchor (third) drug and not in order of preference. Ratings of the strength of the recommendations and quality of evidence are described in Table 1.

[b] Simultaneous administration with antacids or other medications with divalent cations (Ca^{2+}, Mg++, Al++, Fe++) should be avoided due to chelation of the integrase strand transfer inhibitor by the cation, thereby reducing absorption.

[c] Abacavir has been associated with increased cardiovascular risk, although data are conflicting; use with caution in patients with high cardiovascular risk. Should only be used in HLA-B*5701–negative patients.

[d] Rilpivirine should not be given with proton pump inhibitors and should be taken consistently with a full meal.

[e] Should be taken with food.

[f] US Food and Drug Administration approval of the fixed-dose combination is anticipated in 2014.

[g] Ritonavir-boosted regimen.

[h] Only in certain circumstances (see the NRTI-Sparing Therapy section in text for full explanation).

resource-rich regions, individualization of therapy is common,[46] whereas in resource-limited settings, a public health approach as described in the World Health Organization guidelines[47] has been adopted. Ideally, definitive studies to determine the optimal regimen for the majority of ART-naive patients would simplify treatment strategies. However, such studies would be costly and are unlikely to be conducted. Wider availability of effective generic drugs[14] and the development of comorbid conditions as patients age will have a strong influence on initial ART choice.

Initial ART, selected based on baseline resistance testing and patient characteristics and preference, continues to be based on a combination of 2 nucleoside reverse transcriptase inhibitors (NRTIs) and a third agent, either an INSTI, a nonnucleoside reverse transcriptase inhibitor (NNRTI), or a boosted protease inhibitor (PI). Since the 2012 recommendations,[1] several large trials have expanded and refined initial ART choices.[37-44,48-51] In addition, data from well-powered comparative studies of combinations that limit or spare NRTI exposure[52,53] provide evidence for ART choices when inclusion of an NRTI poses a substantial toxic effect risk. In settings in which the use of generic drugs is not required, 3 (and soon to be 4) co-formulated, once-daily, single-tablet regimens are now available. Recommended and alternative regimens are listed in Table 2 and Table 3. The clinical situations in which alternative regimens are needed are limited.

Nucleoside Reverse Transcriptase Inhibitors

Two fixed-dose, NRTI combinations (in alphabetic order), abacavir/lamivudine and tenofovir disoproxil fumarate/emtricitabine, were generally chosen as the NRTI components in randomized trials of initial therapy in the recent past.

Recommended

Abacavir should only be used in HLA-B*5701–negative individuals. Whether this drug carries an increased risk of myocardial infarction (MI) remains uncertain. An association of abacavir with MI has been demonstrated in some observational studies,[54,55] but not in others.[56] A US Food and Drug Administration meta-analysis of randomized clinical trials found no appreciable risk of MI compared with alternative NRTIs in patients with low cardiovascular risk initiating abacavir-containing therapy with a median follow-up of 1.5 years.[57] An updated analysis from the cohort collaboration that originally reported the association of abacavir with MI in 2008 recently reconfirmed the results with data updated through 2012, despite evidence that those at higher risk for cardiovascular disease were less

likely to have been prescribed abacavir since the original report.[58] Paired with efavirenz or ritonavir-boosted atazanavir, abacavir/lamivudine had lower rates of viral suppression in persons with baseline HIV-1 RNA levels of greater than 100 000 copies/mL than did tenofovir/emtricitabine.[59] However, this difference was not observed with abacavir/lamivudine paired with dolutegravir or raltegravir.[37-39,60]

Tenofovir and emtricitabine are available in 3 single-tablet regimens in addition to the fixed-dose combination of the 2 NRTIs. This combination is well tolerated but, as outlined in the previous recommendations, long-term use of tenofovir is associated with increased risk of kidney injury, which is accentuated by concomitant use of boosted PIs and is typically but not always reversible with discontinuation if detected early.[61] Patients should be monitored regularly for glomerular and tubular injury. Although most ART regimens are associated with an early and nonprogressive decrease in bone mineral density (BMD), this decrease is more pronounced with tenofovir. Long-term efficacy and safety data have continued to accumulate for emtricitabine, and no new or unexpected adverse events have been reported.

Alternative

Twice-daily fixed-dose combination zidovudine/lamivudine may be considered for the individual who is unable to receive abacavir or tenofovir for tolerability or safety reasons and for whom an NRTI is considered necessary.

Integrase Strand Transfer Inhibitors

Dolutegravir once daily, elvitegravir with cobicistat once daily, and raltegravir twice daily are potent antiretroviral drugs that are well tolerated in combination with NRTIs. Compared with NNRTI-based or boosted PI-based regimens, these agents have consistently shown higher rates of viral suppression, which in several studies reached statistical superiority.[37,44,62] The drugs are discussed in alphabetic order.

Recommended

Dolutegravir is a once-daily INSTI that does not require pharmacological boosting and has similar activity and safety to raltegravir when combined with tenofovir/emtricitabine or abacavir/lamivudine.[38,39] Dolutegravir plus abacavir/lamivudine was superior to the fixed-dose combination of efavirenz/tenofovir/emtricitabine with the difference driven by nonvirologic end points.[37,63] Dolutegravir was superior to ritonavir-boosted darunavir in an open-label study when combined with either recommended NRTI combination.[45] Dolutegravir appears to have a higher barrier to resistance than raltegravir or elvitegravir. Resistance to INSTIs has not yet been reported in trials of dolutegravir in treatment-naive individuals. A fixed-dose combination with abacavir/lamivudine is expected to be available in the near future.

Elvitegravir has only been studied as initial therapy in a fixed-dose combination with cobicistat/tenofovir/emtricitabine, which has comparable efficacy with efavirenz-based and ritonavir-boosted atazanavir–based therapies over 3 years,[40-43] with similar rates of resistance as raltegravir and 2 NRTIs. Variants of HIV resistant to raltegravir or elvitegravir should be considered cross-resistant. Cobicistat, a pharmacokinetic booster with no antiretroviral activity, has drug interactions similar to ritonavir. Cobicistat causes a reversible small increase in serum creatinine level because it inhibits tubular creatinine secretion, but does not affect glomerular filtration.[64] Other drugs, including dolutegravir, rilpivirine, and ritonavir, also decrease tubular creatinine secretion.

Raltegravir has durable efficacy, superior to efavirenz at 4 years and 5 years,[62] with similar overall rates of resistance as those observed with efavirenz-based therapy. Over 96 weeks, twice-daily raltegravir was superior to once-daily ritonavir-boosted darunavir and ritonavir-boosted atazanavir when each third agent was combined with once-daily tenofovir/emtricitabine.[44]

Nonnucleoside Reverse Transcriptase Inhibitors

Efavirenz and rilpivirine are each available as a single pill for once-daily use and are available in fixed-dose combinations with tenofovir and emtricitabine.

Recommended

Efavirenz has long-term efficacy and safety data but is inferior to some INSTI-based regimens,[37,62] predominantly because of tolerability. The more recent blinded trials show that the early central nervous system adverse effects of efavirenz[37,42] may persist longer than initially thought. An analysis of patients randomized to efavirenz-containing vs non–efavirenz-containing regimens found a 2.3-fold increased risk of suicidality (suicidal ideation, suicide attempt, or completed suicide) with efavirenz.[65] However, an analysis of spontaneous adverse event reports to the US Food and Drug Administration did not show a strong signal for an association between efavirenz use and suicidality.[66]

Rilpivirine in a fixed-dose combination with tenofovir/emtricitabine is recommended for individuals with pretreatment plasma HIV-1 RNA levels of less than 100 000 copies/mL.[50,51] Risk of NRTI- and NNRTI-class resistance with virologic failure is greater with failure of rilpivirine-based than with efavirenz-based therapy, and rilpivirine-resistant variants are likely to be cross-resistant to all available NNRTIs.[67]

Alternatives

Rilpivirine with abacavir/lamivudine is an alternative regimen. A 400-mg dose of efavirenz may have reduced adverse effects with similar efficacy.[68] Nevirapine-based ART remains an alternative if baseline CD4 cell count criteria are met.[1]

Protease Inhibitors

Protease inhibitors are used in combination with 2 NRTIs for initial ART. In most cases, co-administration with either ritonavir or cobicistat is required to boost PI levels through inhibition of the cytochrome P450 3A4 (CYP3A4) enzyme. As a class, PIs are associated with mild to moderate nausea, diarrhea, and dyslipidemia. However, these adverse effects occur less frequently with newer PIs. All PIs may be associated with cardiac conduction abnormalities, particularly PR prolongation.[69]

Recommended

Ritonavir-boosted atazanavir is used in initial therapy once daily. The atazanavir-boosted regimen blocks bilirubin conjugation, resulting in an elevation in unconjugated (indirect) bilirubin, which can cause jaundice in some individuals but does not represent hepatotoxicity. Unboosted atazanavir has reduced potency and is generally not

recommended, although unlike darunavir, atazanavir can be given without boosting in patients who are unable to tolerate ritonavir or cobicistat, if tenofovir is not used. Atazanavir can cause cholelithiasis[70] and nephrolithiasis,[71] and has been associated with renal impairment.[61,72] It is the only ritonavir-boosted PI shown to be noninferior to efavirenz in a large randomized trial[73] and was not associated with MI in a large cohort analysis.[74] However, ritonavir-boosted atazanavir was inferior to ritonavir-boosted darunavir and raltegravir in a large randomized open-label trial, primarily because of discontinuations due to increased bilirubin.[44]

Ritonavir-boosted darunavir is used once daily in initial regimens. Darunavir contains a sulfa moiety, and rashes occurred in approximately 10% of patients during clinical trials. Darunavir should be used with caution in patients with severe sulfa allergies.

Alternative

Ritonavir-boosted lopinavir is an alternative that has more adverse effects than darunavir or atazanavir and is associated with increased cardiovascular risk.[1] Following the expected availability of cobicistat as a stand-alone booster, it will be possible to use it as an alternative to ritonavir to boost darunavir and atazanavir, and coformulations of cobicistat with either PI are expected to follow. In a randomized trial comparing cobicistat with ritonavir as boosters for atazanavir, efficacy and tolerability were comparable.[75]

NRTI-Sparing Therapy

There are clinical situations in which minimizing or eliminating NRTI exposure is desirable (eg, a patient with high risk of cardiovascular disease or a positive HLA-B*5701 assay who also has chronic kidney disease or osteoporosis). Results from well-powered, controlled studies comparing NRTI-sparing or NRTI-limiting regimens with standard combination therapy are now available.

Alternatives

Ritonavir-boosted darunavir once daily with raltegravir twice daily was noninferior to ritonavir-boosted darunavir plus tenofovir/emtricitabine in a large randomized study.[53] However, in patients with CD4 cell counts of less than 200 cells/μL, ritonavir-boosted darunavir plus raltegravir was less efficacious.[53] Twice-daily ritonavir-boosted lopinavir plus lamivudine was compared with ritonavir-boosted lopinavir plus lamivudine and another NRTI, and demonstrated comparable viral suppression at 48 weeks.[52] Of the patients in the comparator group, 53.9% received zidovudine as the second NRTI, which limits the study's applicability to resource-rich settings. Twice-daily ritonavir-boosted lopinavir with raltegravir is an NRTI-sparing alternative that had similar efficacy to ritonavir-boosted lopinavir with tenofovir/emtricitabine in a small trial in which only 16.5% of patients had HIV-1 RNA levels of greater than 100 000 copies/mL.[76] A large study comparing ritonavir-boosted darunavir plus maraviroc with ritonavir-boosted darunavir plus tenofovir/emtricitabine was stopped due to the inferior efficacy of the maraviroc group,[77] a reminder that any NRTI-sparing regimen must be evaluated carefully.

Special Considerations

Pregnancy

ART should be initiated in all HIV-infected women who became pregnant. The rate of congenital birth defects following exposure to ART during pregnancy is not higher than that reported in the general population and is not greater with exposure during the first trimester than later during the pregnancy. Enough first trimester exposure data have accrued on numerous individual antiretroviral drugs, including efavirenz and tenofovir, to detect a 2-fold increase in risk, but no such increases have yet been detected.[78] Clinical experience and pharmacokinetic data support initiation with zidovudine/lamivudine plus either ritonavir-boosted lopinavir or ritonavir-boosted atazanavir. Total plasma drug concentrations decline during pregnancy, but free drug concentrations of PIs are not reduced to the same degree, suggesting that dose adjustment during pregnancy may not be necessary,[79,80] except possibly with ritonavir-boosted atazanavir given with tenofovir or acid reducers. Tenofovir/emtricitabine is a better-tolerated alternative NRTI, although BMD in infants may be lowered,[81] and efavirenz may have fewer adverse effects and result in faster virologic suppression than PI-based therapy.[82]

Comorbid Diseases

The choice of initial regimens is influenced by chronic and acute comorbid conditions. Specific antiretroviral drugs may exacerbate comorbid conditions or increase the risk of negative clinical outcomes. Comorbidities may increase the likelihood of antiretroviral drug toxicity, and treatment for these conditions may have substantial 1- or 2-way interactions with ART.

Cardiovascular, Renal, and Bone Diseases

As noted in the 2012 recommendations,[1] consideration should be given to avoiding use of abacavir, ritonavir-boosted lopinavir, and ritonavir-boosted fosamprenavir in persons at high risk for cardiovascular disease because these regimens have been associated with increased risk of cardiovascular events in some studies. In a large randomized trial of treatment-naive patients, raltegravir had less adverse effects on lipids than either ritonavir-boosted atazanavir or ritonavir-boosted darunavir combined with tenofovir/emtricitabine.[83] Similarly, dolutegravir plus abacavir/lamivudine was associated with fewer adverse lipid changes than efavirenz/tenofovir/emtricitabine,[37] and elvitegravir/cobicistat/tenofovir/emtricitabine had less effect on lipids than efavirenz/tenofovir/emtricitabine.[40] Taken together, these data suggest that INSTI-based regimens may be a good option for patients with preexisting dyslipidemia.

Patients with reduced renal function should generally avoid tenofovir, especially in combination with a boosted PI.[61,84] Initiation of elvitegravir/cobicistat/tenofovir/emtricitabine is not recommended for patients with an estimated creatinine clearance of less than 70 mL/min, and discontinuation is recommended if creatinine clearance is less than 50 mL/min.[85]

As noted in the 2012 recommendations,[1] the prevalence of osteoporosis and incidence of fragility fracture are increased with HIV infection. Initiation of ART generally results in a 2% to 6% loss of BMD over the following 1 to 2 years. Loss of BMD is greater with tenofovir than with abacavir,[86] and less with raltegravir than with ritonavir-boosted atazanavir or ritonavir-boosted darunavir when combined with tenofovir/emtricitabine.[87] In a randomized, placebo-controlled trial, supplementation with calcium carbonate and vitamin D attenuated the loss of BMD with initiation of efavirenz/tenofovir/emtricitabine.[88] Whether supplementation is

efficacious with other ART regimens and whether both vitamin D and calcium are necessary are not known. In patients at elevated risk for fracture (eg, postmenopausal women, known osteoporosis, or chronic hepatitis C virus [HCV] infection), avoiding tenofovir, especially in combination with a boosted PI, may be prudent.

Opportunistic Infections

Drug interactions and tolerability are important considerations when determining which antiretroviral drugs to use in the context of acute opportunistic infections. Azole antifungals and rifamycins are of principal concern. When starting ART in the setting of rifampin-based tuberculosis (TB) therapy, a standard 600 mg dose of efavirenz plus 2 NRTIs is recommended.[89-94] If efavirenz cannot be used, rifabutin-based therapy with a boosted PI plus 2 NRTIs is an alternative. Recent data indicate that rifabutin should be given in a daily dose of 150 mg in this setting.[95-97] Rifampin decreases raltegravir concentrations, and an increase in the dose of raltegravir to 800 mg twice daily has been suggested. However, in a randomized clinical trial of raltegravir given at 400 mg or 800 mg twice daily in patients with TB and receiving rifampin, virologic response was similar to that seen with efavirenz in combination with 2 NRTIs.[98] Dolutegravir may be used together with rifampin or rifabutin based on a pharmacokinetic study of rifamycin administered with 50 mg of dolutegravir given twice daily in healthy volunteers.[99] However, dolutegravir has not been studied in HIV-infected individuals with active TB. There are no data on elvitegravir/cobicistat with rifamycin drugs, but these drugs should not be used together because of a likely interaction.

A 3-month, once-weekly regimen of isoniazid with rifapentine for treatment of latent TB infection is as effective as 9 months of isoniazid alone.[100] This regimen has now also been shown to be equally effective in HIV-infected individuals.[101] As with rifampin, pharmacokinetic data from an ongoing study indicate that high-dose daily rifapentine can be safely administered with efavirenz, suggesting that the 3-month regimen of weekly isoniazid and rifapentine for latent TB infection can also be given together with efavirenz-based ART.[102]

Bedaquiline, a diarylquinoline antimycobacterial drug, has recently been approved by the US Food and Drug Administration for treatment of multidrug-resistant TB,[103] in combination with other active agents. There are no data on bedaquiline use in HIV-infected persons receiving ART. If bedaquiline use is anticipated in an HIV-infected patient receiving ART, expert consultation is recommended.

Hepatitis B Virus Infection

Recommended ART for persons co-infected with HIV and hepatitis B virus includes tenofovir and emtricitabine (or lamivudine) as the fundamental NRTI. If a co-infected patient has moderate kidney disease (creatinine clearance, 30-49 mL/min/1.73 m^2), then tenofovir/emtricitabine may be used every other day provided the kidney injury is not secondary to tenofovir. Entecavir is an alternative to tenofovir if used with suppressive ART.

Malignancy and Immunosuppressive Treatment

Anticancer and immunosuppressive drugs (including long-acting corticosteroids) and ART often have overlapping toxic effects, and there is potential for substantial drug interactions. Because of their favorable drug interaction profiles, dolutegravir- or raltegravir-based regimens are recommended in this setting.

Hepatitis C Virus Infection

In the setting of co-infection with HIV and HCV, selection of optimal ART is determined by potential drug interactions between ART and HCV treatments. Drug interactions between ART and direct-acting antivirals for HCV are common because many of these drugs are substrates of CYP450 or membrane transporters such as P-glycoprotein. Also, many of these agents are either inhibitors or inducers of these systems, leading to increased or decreased plasma concentrations.[104] With numerous new direct-acting antiviral drugs becoming available for the treatment of HCV, it is beyond the scope of this analysis to make specific recommendations. Instead, guidance from the American Association for the Study of Liver Diseases, the Infectious Diseases Society of America, and the International Antiviral Society–USA, which is frequently updated,[105] should be followed. In addition, a list of known drug interactions among HIV and HCV agents is maintained by the Liverpool HIV and Hepatitis Pharmacology Group.[106]

Recommendations for Monitoring

Specific recommendations for patient monitoring appear in Box 1. Suppression of plasma HIV-1 RNA levels to below detection limits (<20-75 copies/mL) should occur by 24 weeks regardless of prior treatment experience. Level of HIV-1 RNA is the primary marker of treatment success[107] and adherence.[108] A retrospective evaluation indicated that persons with HIV-1 RNA levels of less than 200 copies/mL and CD4 cell counts of greater than 300/μL had a 97% probability of maintaining durable CD4 cell counts of greater than 200/μL for 4 years.[109] Other data[110] suggest that CD4 cell count can be monitored yearly or not at all in patients with documented viral suppression and a high CD4 cell count,[107] a change that could lead to substantial cost savings.[111] Assays to detect HIV-1 RNA levels can report qualitative RNA detection below the limit of quantification. The concordance between commercial assays is lower at low HIV-1 RNA levels.[112,113] Research-based assays identify many treated patients with residual viremia of 1 to 10 copies/mL despite optimal ART adherence.[114]

Studies using observational databases suggest that patients with HIV-1 RNA levels of less than 40 copies/mL but with detectable viremia have poorer virologic outcomes than those with no detectable HIV-1 RNA.[115,116] However, other studies indicate that individuals with at least 2 reported HIV-1 RNA levels of 20 to 50 copies/mL during 1 year of follow-up did not have higher rates of failure than fully suppressed patients.[117] Persistent HIV-1 RNA levels of 50 to 200 copies/mL were associated with increased risk of virologic failure,[118] although not in a recent large observational study.[119] A first detectable HIV-1 RNA level of greater than 50 copies/mL during therapy should be confirmed in a subsequent sample within 4 weeks to exclude treatment failure prior to making management decisions. There are insufficient data to make general recommendations for the management of patients with sustained viremia of 50 to 200 copies/mL. Whether to alter therapy in this situation should be considered carefully and may depend on individual patient characteristics, treatment history, current ART regimen, and resistance data.

New resistance mutations were detected in 16% to 65% of participants with persistent HIV-1 RNA levels of less than 1000 copies/mL.[1,120] Drug resistance in that setting is strongly associated with subsequent virologic failure.[121] Genotyping of low-level viremia samples can be performed with a reasonably high success rate,[122,123] which has led some to recommend resistance testing in such circumstances.[123]

All newly diagnosed patients should have reverse transcriptase and protease resistance performed as soon as possible after diagnosis and before initiation of ART. Transmitted resistance may be underestimated if testing is not performed early after infection.[124] Patients with mutations detected prior to ART initiation have a 3- to 5-fold greater risk of virologic failure if a drug to which the virus is resistant is used.[125] Routine integrase genotyping is not generally recommended but should be considered if there is widespread use of this drug class and a lack of surveillance data for primary integrase resistance. For confirmed virologic failure, resistance testing is essential and should be performed while the patient is still receiving the failing regimen when possible.

Routine use of therapeutic drug monitoring is not recommended. However, measurement of drug concentrations may help evaluate treatment response or toxicity[126] in some settings, including in pregnant women,[127] children,[128] patients with organ dysfunction, and in cases of potential drug interactions. Therapeutic drug monitoring may serve to confirm nonadherence in cases of virologic failure without resistance.[129] Target values for the therapeutic range can be found in eTable 5 in the Supplement. Despite early promise, few applications of pharmacogenetics have reached clinical care; screening for HLA-B*5701 prior to abacavir use is a notable exception.

Monitoring for toxic effects due to treatment is recommended during ART generally every 3 to 6 months. However, with safer drugs, there is interest in less frequent monitoring. A recent study found that among patients within normal ranges within 1 year prior to ART initiation, new abnormalities decreased after week 16 of treatment. Taiwo et al[130] concluded that subsequent monitoring should be guided by the presence or absence of comorbidities. However, the components of the ART regimen should be considered because extending monitoring intervals could delay detection of late-occurring toxic effects. Retrospective analyses concluded that clinicians are able to make appropriate decisions to safely extend follow-up intervals in virologically suppressed patients.[131] Clinicians should actively contribute pharmacovigilance-relevant information.[132] As the prognosis of HIV infection continues to improve, patients should also be monitored for relevant age- and sex-specific health problems. Evidence-based guidelines on general monitoring have been recently published.[133] Specific recommendations for ART monitoring are summarized in Box 1.

Treatment-Experienced Patients

Management of Virologic Failure

Recommendations for changing the regimen in treatment-experienced patients appear in Box 1. With increased availability of new drugs and regimens, the goal of sustained suppression should be achievable in most individuals. The principles and approach to virologic failure are unchanged from the 2012 guidelines.[1] When constructing a new regimen in the setting of virologic failure, the potential reasons for failure should be considered, including adverse effects, exacerbation of comorbidities, drug interactions, pill burden, and dosing frequency, all of which can affect adherence. New regimens are constructed based on treatment history, reasons for nonadherence, and the results of previous and current resistance tests. Interpretation of mutations and cross-resistance can be complex and expert advice should be sought.

Failure of Initial ART Regimen

The approach to virologic failure of an initial NNRTI-based or PI-based regimen has been addressed previously.[1] The approach to initial failure of an INSTI-based regimen is similar, but an integrase genotype (or combined genotype) should be included prior to discontinuation of the INSTI. Raltegravir- and elvitegravir-based regimens should be discontinued as soon as virologic failure is confirmed and resistance testing ordered to minimize accumulation of further mutations that may cause cross-resistance to dolutegravir.[134]

Rates of virologic failure are comparable at 1 year for NNRTI and boosted PI regimens; however, NNRTI-based regimens were associated with more NNRTI and NRTI mutations than PI-based regimens.[135,136] Higher rates of treatment failure were also reported in patients receiving a second regimen,[137] suggesting that patients receiving second-line therapy were often nonadherent to their initial regimen. The second regimen should generally include a boosted PI because of the high barrier to resistance, especially when there is evidence of a compromised NRTI backbone. A boosted PI should be used with at least 1 fully active agent (NRTI, INSTI, or NNRTI). New evidence emerged for the use of an active NRTI backbone plus a boosted PI, an INSTI plus a boosted PI, or an INSTI plus a boosted PI after initial failure of an NNRTI-based regimen.[138,139]

Multidrug Resistance

Multidrug resistance typically occurs after failure of several regimens, especially after extensive treatment with older, less potent antiretroviral drugs. Transmission of multidrug-resistant HIV is rare. Because thymidine analog NRTIs and unboosted PIs are rarely used today, extensive NRTI and PI resistance has become uncommon.

There are 5 classes of antiretroviral drugs from which to select a regimen with at least 2 fully active drugs. In the setting of multidrug resistance, inclusion of a potent boosted PI in the new regimen is recommended because of its higher barrier to resistance. In most cases, this regimen will be either 800 mg of darunavir with 100 mg of ritonavir (once daily) if there are no darunavir-associated mutations or 600 mg of darunavir with 100 mg of ritonavir (twice daily) if there are major darunavir-associated mutations.[140] Alternatively, ritonavir-boosted tipranavir may have a role in the regimen based on resistance test results. Some patients, especially those who previously experienced treatment failure with unboosted amprenavir or fosamprenavir, may have cross-resistance to darunavir but susceptibility to tipranavir. However, tipranavir is less well tolerated, requires boosting with 200 mg of ritonavir twice daily, and has complex

Box 2. Summary of Selected New Recommendations and Those for Which Strength or Quality of Evidence Has Changed Substantially[a]

Changes in Recommendations for When to Start ART

Antiretroviral therapy (ART) is recommended for the treatment of HIV infection and for the prevention of transmission of HIV regardless of CD4 cell count (AIa-BIII).

ART should be started as soon as possible, preferably within the first 2 weeks of diagnosis, in patients with opportunistic infections (AIa) and other opportunistic diseases and AIDS-defining illnesses (including all lymphomas and human papillomavirus–related cancers) (AIa-BIII).

Optimal timing of ART initiation in patients with cryptococcal meningitis is less certain, but initiating ART early during cryptococcal treatment should be considered when expert management for both cryptococcal and HIV infection is available (BIII).

Changes in Recommendations for What Treatment to Start

Dolutegravir-based regimens and co-formulated elvitegravir/cobicistat/tenofovir/emtricitabine have been added to the list of recommended regimens for initial ART (AIa).

Co-formulated rilpivirine/tenofovir/emtricitabine has been added as an initial recommended ART regimen in patients with HIV-1 RNA levels <100 000 copies/mL (AIa).

Raltegravir plus abacavir/lamivudine has been added as an alternative initial regimen (BIa).

Atazanavir/cobicistat plus 2 nucleoside reverse transcriptase inhibitors was added as an alternative initial regimen (BIa).

Darunavir/cobicistat plus 2 nucleoside reverse transcriptase inhibitors was added as an alternative initial regimen (BIII).

Ritonavir-boosted darunavir plus abacavir/lamivudine was added as an alternative initial regimen (BIb).

Ritonavir-boosted darunavir plus raltegravir has been added as an nucleoside reverse transcriptase inhibitor–sparing alternative regimen only to be used in certain circumstances (BIb).

Ritonavir-boosted lopinavir plus lamivudine has been added as an nucleoside reverse transcriptase inhibitor–limiting alternative regimen only to be used in certain circumstances (BIb).

Changes in Recommendations for Monitoring

Level of HIV-1 RNA should be monitored approximately 4 weeks after treatment is initiated or changed, and then every 3 months to confirm suppression of viremia below the limit of quantification of sensitive commercial assays (AIa).

Once viral load has been suppressed consistently for >2 years and CD4 cell counts are consistently >500/μL, monitoring CD4 cell counts is optional unless virologic failure occurs or there are intercurrent immunosuppressive treatments or conditions (CIII).

Level of HIV-1 RNA of >200 copies/mL should prompt evaluation of factors leading to failure and consideration of switching ART (AIIa).

Laboratory monitoring for ART toxicity is recommended. In the absence of new abnormalities after week 16 of treatment, the frequency of monitoring, which is generally between 3 and 6 months, should be guided by the presence or absence of comorbidities, and by the components of the regimen (CIII).

Changes in Recommendations for Treatment-Experienced Patients

Depending on resistance, viral tropism, and available options, inclusion of a boosted protease inhibitor and agents from newer drug classes should be considered in patients with multidrug resistance (AIa).

Maintenance of virologic suppression is paramount when switching the regimen to improve tolerability, reduce toxicity, and improve convenience (AIa).

Switching or regimen simplification in virologically suppressed individuals is generally safe if prior treatment and resistance profile are considered. Full activity of the nucleoside reverse transcriptase inhibitors is important when switching from a boosted ritonavir-boosted protease inhibitor to a drug with a lower barrier to resistance (AIa).

[a] Ratings of the strength of the recommendations and quality of evidence are described in Table 1. The recommendations described herein were chosen because the recommendation is new compared with the 2012 recommendations or the recommendation has changed in some substantial way, including strength or quality of rating, compared with the 2012 recommendations.

drug interactions.[141] Dolutegravir should be dosed twice daily when combined with tipranavir, regardless of prior INSTI use.

ART drugs typically used with a boosted PI in regimens for multidrug-resistant HIV include etravirine,[142] dolutegravir, maraviroc, and in exceptional circumstances the fusion inhibitor enfuvirtide. Susceptibility of etravirine is predicted by genotype or phenotype. Etravirine retains good activity against HIV with the K103N mutation, similar to activity against wild-type virus, but the presence of 3 or more etravirine mutations substantially reduces its activity, particularly the Y181C mutation. Specific mutation-weighted scoring systems to predict etravirine activity should be used.[143,144] Dosing of uncommon combinations should be checked against drug interactions and prescribing information for each drug.

Studies have confirmed a role for INSTIs in patients with virologic failure and triple-class–resistant virus (ie, NRTI, NNRTI, and PI). Elvitegravir and raltegravir have comparable activity in treatment-experienced, INSTI-naive patients.[145,146] Dolutegravir has better activity than raltegravir in ART-experienced, INSTI-naive patients, and is dosed once daily.[147] Dolutegravir should be dosed twice daily in patients who experienced treatment failure with a raltegravir- or elvitegravir-containing regimen.[148] Activity of dolutegravir is substantially reduced in the presence of the Q148 mutation plus additional INSTI mutations, including the G140 mutation.[148,149]

If maraviroc is being considered, tropism should be determined because maraviroc is only active against exclusively CCR5-tropic virus. If CXCR4 or dual-mixed tropism is present, maraviroc is not suitable.[150] Maraviroc dosing varies depending on the other antiretroviral drugs in the regimen because of its metabolism by hepatic CYP 3A4 enzymes; the dose should be determined using drug interaction resources.[106]

Including NRTIs with partial or no anticipated activity in a new regimen has been a common practice, but recent data suggest that omitting NRTIs from the regimen, guided by results from resistance testing, does not compromise regimen efficacy if the phenotypic susceptibility score of the drugs in the regimen is greater than 2.[151] There is no role for adding a single active agent to a failing regimen.

Switching Regimens for Toxicity, Tolerability, or Convenience

Several ART switch strategies are available to reduce or prevent toxicity and improve adherence in suppressed individuals. Switching 1

agent to reduce or prevent toxicity (eg, switching from efavirenz for central nervous system effects, or switching from a boosted PI for hyperlipidemia and high cardiovascular risk) is generally safe and effective in virologically suppressed patients.[1] Studies using a switch strategy from a boosted PI to raltegravir have shown substantial improvement in lipids and a small but substantial increase in BMD.[152-155]

Switching from a multiple-tablet regimen to a fixed-dose combination pill is likely to improve convenience and maintain adherence and may also reduce cost to the patient (eg, lower co-payments). However, not all switches are successful because the activity of the accompanying drugs is a key determinant of outcome. The major consideration in switching is maintenance of potency and suppression; knowledge of archived resistance is crucial, as demonstrated in switch studies from a boosted PI to raltegravir, in which a compromised NRTI backbone increased the risk of treatment failure.[156] Although switching for reduced pill burden to fixed-dose combinations generally maintains virologic suppression, there is a risk of adverse effects from the new regimen; patients require close monitoring after the switch.

When switching therapy in patients with virologic suppression, the pretreatment viral load is less important than in ART-naive patients. Switching from efavirenz/tenofovir/emtricitabine to rilpivirine/tenofovir/emtricitabine to relieve efavirenz-associated central nervous system adverse effects appears safe in suppressed individuals, without loss of virologic control despite the potential for subtherapeutic rilpivirine concentrations from the effect of efavirenz on CYP 3A4 enzymes in the first 2 weeks of treatment change.[157] Switches to improve dosing convenience in treatment-experienced patients include twice-daily raltegravir or a boosted PI-based or efavirenz-based regimen to once-daily elvitegravir/cobicistat/tenofovir/emtricitabine[158-160] or rilpivirine/tenofovir/emtricitabine single-tablet regimens.[161] Switching a twice-daily boosted PI to once-daily boosted darunavir (800 of darunavir with 100 mg of ritonavir) is safe in suppressed individuals with no baseline darunavir mutations.[140,162]

Treatment Simplification Strategies

Few data support the efficacy of induction-maintenance strategies in which treatment is deintensified after virologic suppression has been achieved. Selection criteria for boosted PI monotherapy applied to a clinic population in Spain identified only 17% of patients suitable for this approach.[163] Some studies have demonstrated maintenance of virologic suppression with boosted PI monotherapy after suppression with a standard regimen, but others have shown increased low-level viremia, virologic failure, and detectable virus in the cerebrospinal fluid.[164-168] Therefore, boosted PI monotherapy is not recommended for initial or maintenance therapy. In addition, dual-therapy strategies intended to take advantage of drug interactions, such as the combination of unboosted atazanavir and raltegravir, are still investigational and not recommended for clinical practice.

Conclusions and Future Directions

New recommendations or those with increased strength, compared with the 2012 recommendations,[1] are summarized in **Box 2**. Despite the success of ART and its potential for reduction of HIV transmission, the incidence of new infections in resource-rich settings remains relatively stable.[169] To date, 30% to 35% of newly diagnosed patients in high-income countries present with a CD4 cell count of less than 200/μL at diagnosis.[170] Therefore, to fully exploit the potential of ART, efforts are needed to diagnose and treat HIV infection as early as possible. In particular, diagnosis and treatment of acute and recent infection is crucial because it is a major driver of the epidemic.[171-173] The availability of new, less toxic drugs with convenient dosing facilitates widespread acceptance of early therapy. In addition, new strategies must be pursued to eliminate the HIV-associated stigma and discrimination that persist in many countries and are partially responsible for delayed care. The ultimate goal is global availability of ART for everyone in need. This is the prerequisite to reduce HIV morbidity and mortality on a global scale and to achieve control of the pandemic. Early, intensified, widespread, and uninterrupted treatment has the greatest potential to control the pandemic because a vaccine and cure are not yet within reach.

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Author Contributions: Dr Günthard had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition, analysis, or interpretation of data: Günthard, Aberg, Eron, Hoy, Telenti, Benson, Burger, Cahn, Glesby, Reiss, Saag, Jacobsen, Volberding.
Drafting of the manuscript: Günthard, Aberg, Eron, Hoy, Telenti, Benson, Burger, Cahn, Gallant, Glesby, Saag, Jacobsen, Volberding.
Critical revision of the manuscript for important intellectual content: Günthard, Aberg, Eron, Hoy, Telenti, Benson, Burger, Cahn, Gallant, Glesby, Reiss, Saag, Thomas, Volberding.
Administrative, technical, or material support: All authors.
Study supervision: All authors.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Günthard reported receiving research grants from Swiss National Science Foundation, the Yvonne Jacob Foundation, ZPHI, University of Zurich, the Vontobel Foundation, the Hartmann-Müller Foundation, the European Commission, and Gilead Sciences; receiving personal fees for serving on data and safety monitoring committees for EuroSida and Merck and for being a member of the research council of the Swiss National Science Foundation; serving as a medical advisor and consultant (all money went to the University of Zurich, not to Dr Günthard) to Gilead Sciences, ViiV, Bristol-Myers Squibb, and Janssen; and receiving travel grants from Bristol-Myers Squibb, Gilead Sciences, and Janssen. Dr Aberg reported receiving personal fees for serving on scientific advisory boards for AbbVie, Merck, and Janssen. Dr Eron reported receiving grants and personal fees from Merck, Bristol-MyersSquibb, ViiV Healthcare, and GlaxoSmithKline; and personal fees from Gilead, Janssen, and AbbVie. Dr Hoy reported her institution was paid by ViiV HealthCare, Merck Sharp & Dohme, and Gilead Sciences for participation on advisory boards. Dr Benson

reported that her spouse, Robert T. Schooley, MD, has received research support from Bristol-Myers Squibb and Boehringer Ingelheim Pharmaceuticals Inc; served as a scientific advisor to CytoDyn and Merck & Co Inc; served as a scientific advisory board member for Gilead Sciences Inc, GlobeImmune Inc, and Monogram Biosciences; served as a member of data and safety monitoring committees for Axio and Gilead Sciences Inc; and has stock in GlobeImmune Inc. Dr Burger reported receiving research grants, educational grants, and/or honoraria for participation in advisory boards or as a speaker at symposia from Merck, Bristol-Myers Squibb, Janssen/Tibotec, GlaxoSmithKline/ViiV, Gilead, AbbVie, and Roche (all payments went to Radboud University Medical Center, not to Dr Burger). Dr Cahn reported receiving grant support and other for serving on advisory boards for Merck, ViiV, Gilead, and Tibotec; and receiving grant funding from Merck. Dr Gallant reported receiving grants and personal fees from Bristol-Myers Squibb, Gilead Sciences, and Merck & Co; personal fees from Takara Bio Inc and Janssen Therapeutics; and grants from Sangamo BioSciences, Vertex Pharmaceuticals, ViiV Healthcare, and AbbVie. Dr Glesby reported receiving grant funding from Pfizer; and personal fees from Pfizer, UpToDate, Clinical Care Options, and International Antiviral Society–USA. Dr Reiss reported receiving other from Gilead Sciences and Janssen Pharmaceutica; and grants from Gilead Sciences, Janssen Pharmaceutica, Merck & Co, Bristol-Myers Squibb, and ViiV Healthcare. Dr Saag reported receiving consulting fees from Gilead, Merck, ViiV, and Bristol-Myers Squibb; and receiving institutional grants from Bristol-Myers Squibb, Merck, Boehringer Ingelheim, Pfizer, Gilead, Janssen, and ViiV. Dr Volberding reported receiving personal fees from Bristol-Myers Squibb and Gilead Sciences. Drs Telenti and Thomas and Ms Jacobson did not report any disclosures. During the last 5 years, the International Antiviral Society–USA reported receiving grants for selected continuing medical education activities that are pooled (ie, no single company supports any single effort) from Abbott Laboratories, AbbVie, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen Therapeutics, Merck & Co, Mylan, Pfizer, Salix Pharmaceuticals, Tibotec Therapeutics, Vertex Pharmaceuticals, and ViiV Healthcare.

Funding/Support: This work was supported and funded by the International Antiviral Society–USA, a mission-based, nonmembership, 501(c)(3) not-for-profit organization. No private sector or government funding was used to support the effort. Panel members are not compensated for participation.

Role of the Sponsors: The International Antiviral Society–USA had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank Rachel D. Lastra, BA (International Antiviral Society–USA), for administrative and editorial support; Evans Whitaker, MD, MLIS (University of California San Francisco [UCSF]), for conducting the PubMed literature search; and Gloria Y. Won, MLIS (UCSF Medical Center at Mount Zion), for conducting the EMBASE literature search.

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