Antiretroviral Treatment of Adult HIV Infection 2012 Recommendations of the International Antiviral Society–USA Panel

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Since the first antiretroviral drug was approved 25 years ago, improvements in the potency, tolerability, simplicity, and availability of antiretroviral therapy (ART) have resulted in dramatically reduced numbers of opportunistic diseases and deaths where ART is accessible. New data show that viral suppression due to ART results in decreased human immunodeficiency virus (HIV) transmission on individual and population levels and that, when used consistently by HIV-uninfected persons, ART may also provide protection against HIV infection. Together, these developments have translated into newly articulated vi

Context New trial data and drug regimens that have become available in the last 2 years warrant an update to guidelines for antiretroviral therapy (ART) in human immunodeficiency virus (HIV)–infected adults in resource-rich settings.

Objective To provide current recommendations for the treatment of adult HIV infection with ART and use of laboratory-monitoring tools. Guidelines include when to start therapy and with what drugs, monitoring for response and toxic effects, special considerations in therapy, and managing antiretroviral failure.

Data Sources, Study Selection, and Data Extraction Data that had been published or presented in abstract form at scientific conferences in the past 2 years were systematically searched and reviewed by an International Antiviral Society–USA panel. The panel reviewed available evidence and formed recommendations by full panel consensus.

Data Synthesis Treatment is recommended for all adults with HIV infection; the strength of the recommendation and the quality of the evidence increase with decreasing CD4 cell count and the presence of certain concurrent conditions. Recommended initial regimens include 2 nucleoside reverse transcriptase inhibitors (tenofovir/emtricitabine or abacavir/lamivudine) plus a nonnucleoside reverse transcriptase inhibitor (efavirenz), a ritonavir-boosted protease inhibitor (atazanavir or darunavir), or an integrase strand transfer inhibitor (raltegravir). Alternatives in each class are recommended for patients with or at risk of certain concurrent conditions. CD4 cell count and HIV-1 RNA level should be monitored, as should engagement in care, ART adherence, HIV drug resistance, and quality-of-care indicators. Reasons for regimen switching include virologic, immunologic, or clinical failure and drug toxicity or intolerance. Confirmed treatment failure should be addressed promptly and multiple factors considered.

Conclusion New recommendations for HIV patient care include offering ART to all patients regardless of CD4 cell count, changes in therapeutic options, and modifications in the timing and choice of ART in the setting of opportunistic illnesses such as cryptococcal disease and tuberculosis.

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CME available online at www.jamaarchivescme.com and questions on p 413.

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subsequent therapy, ART management in the setting of special conditions, and new approaches to monitoring treatment success and quality. Discussion of the emerging area of antiretroviral pre-exposure prophylaxis for high-risk HIV-seronegative persons is included.

**METHODS**

A systematic literature review using PubMed and EMBASE was conducted to identify relevant evidence published since the last report. Data presented at scientific conferences in abstract form or released as safety reports by regulatory agencies or data and safety monitoring boards also were considered. Specified search terms included HIV and antiretroviral and treatment (or prevention or toxicity or monitoring) and filters included dates (July 1, 2010, to May 25, 2012), English, humans, adults, clinical trial OR meta-analysis OR guidelines OR editorials OR review, and full text OR free text OR abstracts. More than 600 potentially related articles were identified, of which 141 were determined to be relevant. Panel members conducted hand searches for newly published reports, abstracts from scientific conferences, and safety reports throughout the guideline development process; manufacturers of antiretroviral drugs provided lists of published, presented, and safety data, which were cross-checked with search results. Data that were not published or presented in a peer-reviewed setting were not considered.

Recommendations were developed by an international panel established initially by the IAS-USA in 1995 with planned member rotations. Members are experts in HIV research and clinical care and serve in a volunteer (noncompensated) capacity. Members do not participate in industry promotional activities such as speaker bureaus, lectures, or other marketing activities during their membership on the panel. The current panel convened in January 2012 and met twice weekly by teleconference. Section leaders (J.A.A., J.F.H., A.T., and P.A.V.) and teams were appointed to evaluate evidence and summarize panel discussions for each section. Prior to selection of teams and leaders, panel members declared and discussed potential conflicts of interests and recused themselves from serving as section leaders or team members, accordingly.

The panel limited recommendations to HIV-infected adults in international resource-rich settings with ART that was 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 according to the strength of the recommendation and the quality of the supporting evidence (eBox; available at http://www.jama.com). For areas in which recommendations have not changed substantially or no new data are available, the previous report is referenced.

### WHEN TO START

All adults with HIV infection should be offered ART regardless of CD4 cell count, based on recent observational cohort data that all patients may benefit from ART and data from a randomized controlled trial showing that ART reduces the likelihood of HIV transmission while providing clinical benefit to treated individuals. When prescribing ART, the following should be considered: (1) a patient must be ready and willing to adhere to ART, and adherence education and support should be offered; (2) the benefit of ART is unknown in elite controllers (HIV-1 RNA below the level of quantification without ART) and long-term nonprogressors (those with stable CD4 cell counts >500/µL and HIV-1 RNA <1000 copies/mL while not taking ART); (3) the benefit of ART in asymptomatic acute HIV infection is not as well studied as in symptomatic acute HIV infection; and (4) there is no CD4 cell count threshold at which starting therapy is contraindicated, but the strength of the recommendation and the quality of the evidence supporting initiation of therapy increase as the CD4 cell count decreases and when certain current conditions are present (Box 1).  

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point analysis was driven predominantly by TB.

In a registry of 20,775 HIV-infected and 215,158 uninfected persons, the incidence of most cancers was either no longer elevated in HIV-infected persons with CD4 cell counts at or above 500/µL compared with HIV-uninfected persons or was greatly decreased, also supporting earlier initiation of ART. Several cross-sectional studies examining the effect of CD4 cell count nadir on surrogate markers of cardiovascular risk suggest benefit for early therapy, although studies proving that ART can decrease this risk are lacking at this time.16-18

The concentration of HIV in both blood and seminal plasma correlates with the probability of transmission of HIV to a sexual partner. Reducing levels of HIV with ART decreases the probability of transmission, as confirmed in the HPTN 052 study, in which ART was 96% effective in reducing HIV transmission. Reduction of transmission has also been shown in high-risk men who have sex with men, although viral suppression in plasma does not guarantee suppression in semen, especially in the presence of inflammation. Additionally, other sexually transmitted infections such as hepatitis C virus (HCV) and syphilis continue to be reported at high rates, especially in men who have sex with men, underscoring the importance of continued condom use.

Several communities with high ART use have observed an association between reduced “community viral loads” and lower rates of new infections.24,25 The use of HIV treatment as prevention addresses an important public health objective, especially in the absence of a vaccine or additional inexpensive, highly effective prevention strategies other than condom use and male circumcision. Fortunately, the expanding recommendations for nearly universal treatment of HIV-infected persons in resource-rich countries and some middle-income countries render the recommendations for treatment of the individual concordant with public health goals. Challenges include limited financial and workforce resources, the need to implement broader testing, and the need for improved strategies to enhance engagement in HIV care and adherence to ART.

### Special Considerations

#### Pregnancy

ART is indicated for all pregnant women to prevent HIV transmission to the infant and for the mother’s health. Those not yet taking ART should start fully suppressive therapy as soon as possible. The potential for nonadherence due to morning sickness should not be an impediment to starting therapy.26,27 Women who conceive while already taking ART, including efavirenz or tenofovir, should continue the same therapy unless there is a need for change due to failure or intolerance. Therapy should not be discontinued post partum.

#### Opportunistic Infections

Early initiation of ART is recommended after starting active treatment of opportunistic infections. However, implementation may require focused educational and logistical support and consideration of the potential for drug interactions requiring dosage alterations.

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**Box 1. Recommendations for When to Initiate Antiretroviral Therapy (ART)**

Patient readiness for treatment should be considered when deciding to initiate ART. Clinicians should engage supportive services as needed to assist with ART education and to address barriers to adherence (AIII).

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

- For CD4 cell count of 500/µL and below: AIIa
- For CD4 cell count above 500/µL: BIII

Ratings for specific conditions are as follows:

- Pregnancy: AIIa
- Chronic hepatitis B virus (HBV) coinfection: AIIa
- Hepatitis C virus (HCV) coinfection: AIIa (however, coinfection with CD4 cell count > 500/µL may delay ART until after completion of HCV treatment)
- Age older than 60 years: BIIa
- Human immunodeficiency virus (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 (AIIa). The optimal timing for patients with cryptococcal meningitis is less certain, but initiating ART early during cryptococcal treatment may be associated with higher mortality; therefore, ART initiation in these patients should be managed in consultation with experts (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 below 50/µL and by 8 to 12 weeks for those with higher CD4 cell counts (AIIa). 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).

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Recent data have raised concerns about the timing of ART initiation during cryptococcal meningitis. In a randomized clinical trial conducted in Zimbabwe, ART was begun within 72 hours after diagnosis of cryptococcal meningitis or delayed until completion of 10 weeks of antifungal treatment with 800 mg/d of fluconazole alone. The risk of death was 2.85 times higher in the early ART group. Immune reconstitution inflammatory syndrome (IRIS) occurred in patients in both groups and did not explain the increased mortality. The increased mortality seen in the early ART treatment group is concordant with the recent announcement of the cessation of randomization in the COATS trial following data and safety monitoring board review. Antifungal therapy consisted of fluconazole alone in the former study and amphotericin B plus fluconazole during induction followed by fluconazole alone in the COATS study. These data suggest that persons with HIV and cryptococcal meningitis should be closely monitored after starting ART and managed in consultation with experts, particularly if CD4 cell counts are below 50/µL.

Three randomized trials evaluating when to start ART during TB treatment demonstrated that early ART improved AIDS-free survival compared with initiation after completion of TB treatment. The greatest benefit was achieved in persons with CD4 cell counts below 50/µL, and for this subgroup, the optimal time of ART initiation was within the first 2 weeks of TB treatment. Those with higher CD4 cell counts who deferred ART until 8 to 12 weeks after starting TB treatment had lower rates of IRIS and other adverse events. In all 3 studies, trends toward improved AIDS-free survival were observed across all CD4 cell count strata. Benefit was greatest in those with the most advanced immunosuppression, as were rates of IRIS. Deaths attributable to IRIS were few. In a randomized trial of 253 patients with HIV and TB meningitis, initiation of ART within 2 vs 8 weeks of TB treatment was not associated with improved survival, and those in the immediate ART group had significantly more severe adverse events. Whether these results also can be generalized is unclear because the patient population included a high proportion of injection drug users with underlying viral hepatitis; most deaths occurred in the first month of treatment, before an effect of ART could be observed; and risk of death was related to severity of TB meningitis. Therefore, early initiation of ART should be considered in persons with HIV and TB meningitis, but with close monitoring and management in consultation with experts, particularly if CD4 cell count is below 50/µL.

**Hepatitis B Virus.** The risk of liver-related morbidity and mortality is increased in persons dually infected with HIV and hepatitis B virus (HBV). Although there are conflicting data as to whether HBV adversely affects the natural history of HIV, the potential to treat both infections with the same medications provides a compelling argument for treatment of all HIV- and HBV-coinfected persons who otherwise have no contraindications to therapy.

**Hepatitis C Virus.** Infection with HIV also increases the risk of liver-related morbidity and mortality in persons dually infected with HCV. Early treatment has been associated with improved survival, and those with higher CD4 cell counts who deferred ART until after completion of HCV treatment had lower rates of CD4 cell decline after treatment interruptions of 6 to 15 months compared with deferred treatment. A substantial proportion of ongoing HIV transmission is attributable to individuals with acute infection. These individuals may have markedly higher HIV-1 RNA levels in plasma and genital secretions, which increases the risk of transmission per sexual encounter. Thus, offering persons with acute HIV infection early treatment represents a high priority in ART-for-prevention strategies.

**WHAT TO START**

The options for initial therapy for treatment-naïve adults with confirmed drug-susceptible virus continue to expand, with new drugs and coformulations (Table 1 and Table 2). Because therapy is expected to be sustained indefinitely, regimen choice must consider patient convenience, potential toxicities, and tolerability that may affect adherence. The aim of therapy continues to be maximal, lifelong, and continuous suppression of HIV replication to prevent emergence of resistance, facilitate optimal immune recovery, and improve health. Interactions among ART drugs and with other medications are a growing challenge as per-
sions with HIV age and require additional medications for comorbid conditions.46-51 The cost of therapy is expected to be an increasingly important issue as part of a larger movement to control health care expenditures. Generic ART drugs may reduce program costs and allow for treatment of more individuals, but it will be crucial to ensure that any resulting medication choices do not revert to older and more toxic drugs no longer recommended in指南.

Table 1. Recommended and Alternative Initial Antiretroviral Regimens, Including Strength of Recommendations and Quality of Evidencea

<table>
<thead>
<tr>
<th>Recommended Regimens</th>
<th>Alternative Regimensb</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>NNRTI plus NRTIs</td>
<td></td>
<td></td>
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<tr>
<td>Efavirenz/tenofovir/emtricitabine (AIa)</td>
<td>Nevirapine plus tenofovir/emtricitabine or abacavir/lamivudine (Bla)</td>
<td>Severe hepatotoxicity and rash with nevirapine are more common in initial therapy when CD4 cell count is &gt;250/µL in women and &gt;400/µL in men.</td>
</tr>
<tr>
<td>Efavirenz plus abacavir/lamivudine (AIa) in HLA-B*5701-negative patients with baseline plasma HIV-1 RNA &lt;100,000 copies/mL</td>
<td>Rilpivirine/tenofovir/emtricitabine (or rilpivirine plus abacavir/lamivudine) (Bla)</td>
<td></td>
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<tr>
<td>PI/r plus NRTIsc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darunavir/r plus tenofovir/emtricitabine (Ala)</td>
<td>Darunavir/r plus abacavir/lamivudine (Bil)</td>
<td>Other alternative PIs include fosamprenavir/r and saquinavir/r but indications to use these options for initial treatment are rare.</td>
</tr>
<tr>
<td>Atazanavir/r plus tenofovir/emtricitabine (Ala)</td>
<td>Lopinavir/r plus tenofovir/emtricitabine (Bla) (or abacavir/lamivudine) (Bla)</td>
<td></td>
</tr>
<tr>
<td>Atazanavir/r plus abacavir/lamivudine (Ala) in patients with plasma HIV-1 RNA &lt;100,000 copies/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>InSTI plus NRTIsd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir plus tenofovir/emtricitabine (Ala)</td>
<td>Raltegravir plus abacavir/lamivudine (Bla) Elvitegravir/cobicistat/tenofovir/emtricitabine (Bil)</td>
<td>Raltegravir is given twice daily; experience with elvitegravir/cobicistat/tenofovir/emtricitabine is limited to 48-week data.</td>
</tr>
</tbody>
</table>

Abbreviations: InSTI, integrase strand transfer inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; /r, ritonavir-boosted.

* Ratings of the strength of the recommendations and quality of evidence are described in the eBox. Fixed-dose combinations are recommended when available and appropriate.

Current fixed-dose combinations available are efavirenz/tenofovir/emtricitabine; tenofovir/emtricitabine; abacavir/lamivudine; rilpivirine/tenofovir/emtricitabine; lopinavir/ritonavir; zidovudine/lamivudine; and, if approved, elvitegravir/cobicistat/tenofovir/emtricitabine.

Zidovudine/lamivudine is an alternative NRTI component of NNRTI-, PI/r-, and raltegravir-based regimens, but the toxicity profile of zidovudine reduces its utility.

†H-BA*-5701 screening is recommended before abacavir administration to reduce the risk of hypersensitivity reaction.

Avoiding the use of abacavir or lopinavir/ritonavir might be considered for patients with or at high risk of cardiovascular disease.

ªNew Drug Application for this combined formulation has been filed with regulatory authorities. Approval decisions pending.

Table 2. CCR5 Antagonist–Based and NRTI-Sparing Initial Regimens That Can Be Considered Only in Special Circumstances, Including Strength of Recommendations and Quality of Evidencea

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCR5 antagonist plus NRTIs (NNRTI-, PI-, and InSTI-sparing)</td>
<td>Tropism assay to confirm R5 virus should be done before prescribing maraviroc. Maraviroc is not effective in persons who have X4 or dual/mixed X4/R5 virus infection. Few data are available for maraviroc with tenofovir/emtricitabine or abacavir/lamivudine.</td>
</tr>
<tr>
<td>Maraviroc plus tenofovir/emtricitabine or abacavir/lamivudine (Cill)</td>
<td></td>
</tr>
<tr>
<td>P/r plus InSTI (NRTI-sparing)</td>
<td>Darunavir/ritonavir plus raltegravir (Bla) Lopinavir/ritonavir plus raltegravir (Bla) Data emerging for these regimens. Clinical trial evidence needed before formal recommendation can be made.</td>
</tr>
</tbody>
</table>

Abbreviations: CCR5, C5 chemokine receptor 5; InSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; /r, ritonavir-boosted.

* Ratings of the strength of the recommendations and quality of evidence are described in the eBox.

Nucleos(t)ide Reverse Transcriptase Inhibitors

Three 2-drug NRTI FDCs are currently available. In some cases, these FDCs are coformulated with another potent drug, adding to the overall regimen convenience.

Recommended. Tenofovir disoproxil fumarate and emtricitabine are available in a once-daily FDC with no food restrictions. Tenofovir is well tolerated but has been associated with kidney injury, which appears to increase in incidence with long-term administration and concurrent P/r use.16,35,36

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Renal function should be assessed before use and monitored over time, dosing adjusted according to the package insert in the case of renal impairment (estimated glomerular filtration rate [eGFR] < 50 mL/min), and tenofovir discontinued when eGFR is below 30 mL/min. Tenofovir causes a decrease in bone mineral density in the spine and hip, the long-term progression of which currently remains ill defined. Emtricitabine is similar to lamivudine in mechanism of action, potency, toxicity, and patterns of resistance.

An abacavir and lamivudine FDC offers once-daily administration, no food restriction, and minimal subjective toxicity. Screening for HLA-B*57:01 markedly reduces the risk of potentially life-threatening hypersensitivity reaction to abacavir. In some studies, but not in others, abacavir has been associated with a higher risk of acute myocardial infarction.

Initial regimens containing abacavir/ lamivudine had lower rates of viral suppression in persons with baseline HIV-1 RNA levels above 100,000 copies/mL than regimens containing tenofovir/emtricitabine. However, in a second randomized trial, this difference was not observed. Lamivudine is extremely well tolerated.

Alternatives. A zidovudine and lamivudine FDC must be used twice daily. Zidovudine commonly causes headache, nausea, anemia, neutropenia, and progressive and persistent peripheral lipatrophy. Its use should be reserved for individuals unable to use abacavir or tenofovir.

Nonnucleoside Reverse Transcriptase Inhibitors

Nevirapine, efavirenz, and rilpivirine are each available as a single pill for once-daily use; the 2 latter drugs are available in FDCs with tenofovir/emtricitabine.

Recommended. Efavirenz is used once daily, preferably without food at bedtime. Central nervous system adverse effects include sleep disturbance, abnormal dreams, and, less commonly, depressed mood. Efavirenz can cause a rash, which usually but not always resolves despite continued treatment.

Alternatives. Nevirapine is now available in a 400-mg once-daily formulation. Nevirapine requires a 2-week lead-in of 200 mg once daily. Rash is more common and usually more severe than with efavirenz. Severe hepatotoxicity is occasionally seen with initial use. Both severe rash and hepatotoxicity are more common with baseline CD4 cell counts above 250/µL in women and 400/µL in men.

Rilpivirine is administered once daily. In 2 studies, rilpivirine was noninferior to efavirenz, although rates of virologic failure were higher with rilpivirine while rates of adverse events were higher with efavirenz. Virologic failure was more common in patients with baseline HIV-1 RNA above 100,000 copies/mL, and rilpivirine should be avoided in this population. Rilpivirine has substantial food interactions and should be taken with at least a 400-kcal meal. Concomitant use of rilpivirine and proton-pump inhibitors is contraindicated.

Protease Inhibitors

Protease inhibitors are used in combination with 2 NRTIs as part of initial ART. The bioavailability of PIs requires coadministration with a drug such as ritonavir that augments or “boosts” levels of the PI through inhibition of the CYP34A enzyme. Another drug with this property, cobicistat, is being developed. As a class, PIs are associated with mild to moderate nausea, diarrhea, and dyslipidemia. All PIs may be associated with cardiac conduction abnormalities, particularly PR interval prolongation. A baseline electrocardiogram and avoidance of other agents causing prolonged PR or QT intervals should be considered.

Recommended. Ritonavir-boosted atazanavir is used in initial therapy once daily. It blocks bilirubin conjugation, resulting in a nearly universal elevation in unconjugated (indirect) bilirubin. Usually modest, this can cause visible jaundice in some individuals but does not represent hepatotoxicity. Atazanavir requires gastric acidity for absorption and should be taken with meals and with avoidance of proton-pump inhibitors; if used, proton-pump inhibitors should be taken distant from the time of atazanavir/r administration. Unboosted atazanavir has reduced potency and is not recommended. Atazanavir may be associated with nephrolithiasis and in 1 study was associated with renal dysfunction. Atazanavir is the only PI/r shown to be noninferior to efavirenz-based therapy in a large randomized trial.

Daranavir must be boosted to be active. Ritonavir-boosted darunavir is used once daily in initial regimens and should be taken with a meal to improve bioavailability. Darunavir contains sulfia and may produce hypersensitivity reactions, especially in those with sulfia allergy.

Alternatives. Lopinavir is available only as an FDC with ritonavir. Fewer individuals randomized to lopinavir/r in combination with tenofovir/emtricitabine maintained HIV-1 RNA below 50 copies/mL at 48 and 96 weeks vs those randomized to darunavir/r or atazanavir/r. Ritonavir-boosted lopinavir causes more frequent gastrointestinal adverse effects than other PIs. It can be used once daily and does not require administration with food.

Fosamprenavir or saquinavir boosted with ritonavir may be used once daily, taken with a meal, in initial therapy. Fosamprenavir contains a sulfia moiety and may cause rash. In 1 randomized trial, once-daily saquinavir/r was noninferior to atazanavir/r and had comparably mild adverse effects.

Integrase Strand Transfer Inhibitors

The newest drug class of potent antiretroviral drugs used with a dual NRTI backbone, the InSTIs are well tolerated. Similar to NNRTIs, current InSTIs have a low genetic resistance barrier.

Recommended. Raltegravir should be used twice daily, as once-daily dosing diminishes efficacy. Raltegravir does not require concomitant food consumption.

Alternative. A once-daily coformulation of tenofovir, emtricitabine, el-
vitegravir, and cobicistat is pending regulatory approval in the United States for treatment-naïve patients. 78 Elvitegravir is an investigational INSTI pending regulatory approval in the United States for treatment-experienced patients. 79 It requires boosting to achieve sufficient potency. Cobicistat is an investigational pharmacokinetic booster pending regulatory approval in the United States that can cause substantial drug-drug interactions. Cobicistat causes an immediate and reversible small increase in serum creatinine and eGFR without actually affecting measured creatinine clearance because it competes with excretion of creatinine by the kidney. 80 When substantial or progressive increase in serum creatinine occurs, evaluation of kidney function and adjustment of the regimen should be considered.

Attachment Inhibitors

Drugs that block CCR5 have durable antiretroviral activity only if the individual is infected with HIV that uses CCR5 exclusively and not CXCR4. The use of these drugs thus requires receptor tropism screening. The phenotypic assay that measures tropism is expensive and time-consuming, but genotypic tropism testing is faster, cheaper, and may facilitate the use of such drugs. 81 Maraviroc is the only currently approved CCR5 attachment inhibitor. It is used twice daily and has no food restrictions.

Special Considerations

Pregnancy. The choice of ART in pregnant women should take into consideration the same benefits and risks as in all HIV-infected adults as well as any specific considerations associated with the pregnancy. The Antiretroviral Pregnancy Registry of more than 15,000 HIV exposures (January 1989–July 2011) notes no increase in rates of congenital birth defects with exposure to ART, including efavirenz, even in the first trimester. 82

Comorbid Diseases. Preexisting risks or existence of particular comorbidities influence the choices among otherwise equally effective recommended initial regimens. Comorbidities may be exacerbated by the potential toxicity of individual ART drugs and may be subject to drug-drug interactions with treatments needed for such conditions. 51

Cardiovascular, Renal, and Bone Diseases. Abacavir, lopinavir/r, and fosamprenavir/r each have been associated with an increased risk of cardiovascular disease (CVD) in some 59,60 but not all 62,63 studies. Such associations have not been found for tenofovir, efavirenz, nevirapine, or atazanavir/r. 60,63 Data on CVD risks are not yet available for darunavir/r, raltegravir, rilpivirine, or elvitegravir. In persons at high risk of CVD, avoiding abacavir, lopinavir/r, and fosamprenavir/r might be considered. In patients with reduced renal function, prolonged use of tenofovir is associated with cumulative nephrotoxicity 56,74 and should be avoided. Prolonged use of atazanavir/r and lopinavir/r is also associated with cumulative loss of renal function. 55,74

Compared with uninfected individuals, persons with HIV infection are at increased risk of osteoporotic fragility fractures. In addition to traditional factors associated with bone loss, use of tenofovir and lopinavir/r are independent risk factors for fractures in some but not all recent studies. 59,84 Although all initial ART regimens are associated with a reduction in bone mineral density during the first year of treatment, the effect is more pronounced with tenofovir-containing regimens. 59,85 Notably, in postmenopausal women, both HIV infection and tenofovir use are independently associated with higher rates of bone loss. 86 Given their increased risk of fragility fractures, it may be prudent to consider avoiding tenofovir as part of initial therapy in postmenopausal women.

Opportunistic Infections. Drug interactions and tolerability are key considerations in the context of acute opportunistic infections. Drug interactions with triazole antifungal drugs and those associated with rifamycins are among the most important. The recommended initial ART regimen in the setting of rifampin-based TB therapy is efavirenz plus NRTIs. Data are conflicting about the effect of rifampin coadministration on efavirenz concentrations. Early studies reported a 26% reduction in efavirenz exposure, 87 but more recent studies in patients with HIV and TB coinfection have not shown a clinically significant effect of rifampin on efavirenz exposure. 31,34,88,89 Although the prescribing information for efavirenz indicates the dosage should be increased to 800 mg/d for patients weighing more than 50 kg who are being treated with rifampin, the current FDC with 600 mg of efavirenz is associated with good HIV and TB outcomes regardless of weight. 33,34,88,90 If efavirenz cannot be used, rifabutin-based TB therapy with a PI/r plus NRTIs is recommended. Rifabutin reportedly has little effect on atazanavir/r 91 or lopinavir/r 92 results in only modest increases in darunavir 93 and has no clinically meaningful effect on raltegravir. 94 However, serum concentrations of rifabutin and its major metabolite are markedly increased by all PI/r/s, requiring dosage adjustment of rifabutin in this setting. Rifabutin, 150 mg every other day, resulted in increased rates of acquired rifamycin resistance when used with a PI/r regimen 95,96 and lower-than-expected concentrations of rifabutin. 92 Additional clinical trials are under way, but in the interim, rifabutin, 150 mg/d, is suggested when used with a PI/r regimen, and patients should be closely monitored. Raltegravir concentrations are decreased when coadministered with rifampin; if a raltegravir-based ART regimen is used, the raltegravir dosage should be increased to 800 mg twice daily or rifabutin should be substituted for rifampin, but none of these approaches has been evaluated in patients with HIV and TB coinfection. The recent recommendation for use of a 3-month, once-weekly regimen of isoniazid with rifapentine for treatment of latent TB infection is not recommended for HIV-infected patients receiving ART. 97

Cirrhosis. In persons with cirrhosis but without encephalopathy, coagula-
Box 2. Recommendations for Initial Treatment in the Setting of Specific Conditions, With Strength of Recommendations and Quality of Evidence

In patients with or at high risk of cardiovascular disease, avoiding use of abacavir, ritonavir-boosted lopinavir, or ritonavir-boosted fosamprenavir might be considered (BIIa).

In patients with reduced renal function, tenofovir should be avoided, or if treatment for hepatitis B virus (HBV) coinfection is needed, dosing should be adjusted according to the prescribing information (AIIa).

Given the increased risk of fragility fractures, it may be prudent to avoid tenofovir as part of initial therapy in postmenopausal women (BIIa).

The recommended initial ART regimen in the setting of rifampin-based tuberculosis treatment is efavirenz plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) (AIII).

The recent recommendation for use of a 3-month, once-weekly regimen of isoniazid with rifapentine for treatment of latent TB infection is not recommended for human immunodeficiency virus (HIV)-infected patients receiving ART (BIIa).

The ART regimen for HIV- and HBV-coinfected persons should include tenofovir and emtricitabine (or lamivudine) as the NRTI background (AIII).

*Ratings of the strength of the recommendations and quality of evidence are described in the eBox.

Background. If renal insufficiency occurs in HBV- and HIV-coinfected persons, a reduced dose of tenofovir, but not of the other components in the regimen, can be used. Entecavir has been used safely in coinfected patients but has impaired activity against lamivudine-resistant HBV and can select for M184V in HIV reverse transcriptase. In persons without lamivudine-resistant HBV, entecavir is an alternative to tenofovir if used with a fully suppressive antiretroviral regimen. Treatment of coinfected patients with regimens containing lamivudine or emtricitabine as the only antivirals with activity against HBV provides suboptimal efficacy and usually results in NRTI-resistant HBV. Interferon alfa is approved for treatment of chronic HBV infection but has not been rigorously tested in HIV-coinfected persons. Hepatitis C Virus. Peginterferon alfa and ribavirin have been routinely used in HIV- and HCV-coinfected persons. Ribavirin cannot be used with didanosine and has overlapping toxicity with zidovudine. It is not clear whether peginterferon alfa plus ribavirin is less effective when used with abacavir than with tenofovir. The addition of the HCV PIs telaprevir or boceprevir to peginterferon alfa and ribavirin improves treatment responses for genotype 1 chronic HCV infection. Likewise, preliminary phase 2 data in HIV-/HCV-coinfected persons showed superior responses in those randomized to peginterferon alfa, ribavirin, and boceprevir or telaprevir compared with peginterferon alfa, ribavirin, and placebo. As phase 3 studies are ongoing and US Food and Drug Administration (FDA) approval is pending for coinfected patients, the superior responses suggest either telaprevir or boceprevir should be added to peginterferon alfa/ribavirin when treating genotype 1 chronic HCV infection.

Drug-drug interactions between telaprevir or boceprevir and antiretroviral drugs may alter the optimal choice of ART when their use is anticipated. Data from clinical trials continue to evolve but are currently insufficient to guide firm recommendations about recommended regimens. Available data suggest that tenofovir, emtricitabine, raltegravir, and etravirine may be safely used with boceprevir, and these drugs and rilpivirine, atazanavir/r, and efavirenz (with increased telaprevir dose) may be used with telaprevir. However, HIV and HCV RNA levels should be carefully monitored when coadministering these drugs, and evolving data on drug-drug interactions should be considered.

Malignancy. Concomitant use of anticancer drugs and ART is associated with overlapping toxicities and the potential for substantial drug interactions due to elimination using CYP450 routes of metabolism. Raltegravir-based regimens may be considered in this setting because of their favorable drug interaction profile. Recommendations for initial regimen in the above specific circumstances are summarized in Box 2.

MONITORING

Suppression of plasma HIV-1 RNA to less than 50 copies/mL by 24 weeks should occur with effective therapy, regardless of prior treatment experience. No recent work has defined the optimal frequency of monitoring in resource-rich economies, despite the perception that such research could lead to substantial cost savings. Therefore, previous recommendations for frequency of CD4 cell count and HIV-1 RNA monitoring have not changed.

Recently introduced third-generation HIV-1 RNA assays show a lower limit of quantification of 40 or 20 copies/mL and can report qualitative RNA detection below these cutoffs. In addition, many patients receiving stable suppressive treatment show residual viremia of 1 to 10 copies/mL using research-based assays. The source, significance, and optimal management of detectable viremia of less than 50 copies/mL during treatment are poorly defined. Recent studies indicate that detectable HIV-1 RNA below the 50 copies/mL threshold predicted rebound; however, the lower the viral load, the less likely it is to result in con-
firmed rebound. Evolution of viral resistance can occur in the setting of low-level viremia. In 2 clinical trials and a cohort analysis, new resistance mutations were detected in 37% and 65%, respectively, of participants who developed persistent low-level viremia. There is lack of consensus on management of patients with HIV-1 RNA levels between 50 and 200 copies/mL. The AIDS Clinical Trials Group definition of virologic failure (confirmed detectable HIV-1 RNA >200 copies/mL after virologic suppression) is commonly used. However, the optimal management of these patients has not been determined.

There is limited evidence that ART modifications have an appreciable impact for patients with residual HIV-1 RNA levels between 1 and 10 copies/mL. In practice, it is recommended that a detectable HIV-1 RNA level during therapy should be confirmed in a subsequent sample, usually drawn within 2 to 4 weeks, prior to making management decisions. However, the optimal interval before repeating the HIV-1 RNA test after low-level viremia occurs has not been determined, and guidance about management strategies awaits further evidence.

Published data suggest that the prevalence of transmitted drug resistance has remained stable worldwide and averages 11% in Europe and 15% in North America. The presence of transmitted drug resistance may be underestimated if a resistance test is not performed early in infection. Although some mutations may persist in the long term (such as resistance mutations to NNRTIs), others (such as M184V) that confer impaired fitness are quickly replaced by wild-type HIV variants. Patients with resistance mutations detected prior to initiation of ART have a 3- to 5-fold greater risk of virologic failure if a drug to which the virus is resistant is included in the regimen, underscoring the importance of pretherapy resistance testing. For confirmed virologic failure, resistance testing is essential and should, when possible, be performed while the patient is still receiving the failing regimen.

Therapeutic drug monitoring is not recommended for general care. However, it may be useful in pregnant women, children, and patients with renal or liver impairment to minimize overexposure and adverse effects. Therapeutic drug monitoring also may serve to assess adherence or to evaluate virologic failure in the absence of resistance. Therapeutic drug monitoring may be useful if HCV PIs (telaprevir or boceprevir) must be used with ART for which the drug interactions are either not clarified or are known to cause substantially increased or decreased exposure of 1 of the drugs. Awareness of the potential for drug interactions with these agents is important.

Increasing attention has been focused on determinants, measurements, and interventions to improve entry into and retention in care and monitoring of ART adherence. Recent recommendations have covered these issues. National initiatives have generated quality-of-care indicators, including in the area of follow-up of patients receiving treatment. An important quality-of-care factor is management by physicians experienced in HIV medicine. Recommendations for monitoring are summarized in Box 3.

TREATMENT-EXPERIENCED PATIENTS

New regimens for ART-experienced patients should include the most active drugs available based on genotypic analysis, treatment and adverse effect history, and availability of additional classes of drugs.

Initial Virologic Failure

Management of virologic failure of an initial regimen is usually straightforward, and a new regimen with 3 active drugs can generally be constructed. The regimen should be changed promptly on confirmation of virologic failure.

Initial NNRTI-Based Regimens. Delaying a treatment change allows the accumulation of additional NNRTI resistance mutations that may limit future treatment options with etravirine and rilpivirine. Generating a new regimen with 3 active agents is attainable using a PI/r and active NRTIs. If choice is limi-
vitelgravir. The entry inhibitor enfuviride also was used successfully in salvage regimens but is poorly tolerated because of injection site reactions. Maraviroc was used effectively in those with CCR5-tropic HIV in combination with other active or partially active drugs in salvage regimens. In patients with MDR HIV and no treatment option with a regimen containing 2 active drugs, continuation of some NRTIs, such as lamivudine or emtricitabine and/or tenofovir, might be considered for continuation in a regimen, even if resistance is present, because residual activity of these compounds has been demonstrated in this setting. Expert advice should be sought in the setting of MDR virus.

Dolutegravir, an InSTI currently in development, appears to have good activity against raltegravir- and elvitegravir-resistant virus, but reduced susceptibility has been reported for virus with the Q148 or G140 signature mutations. It is administered once daily in the absence of integrase mutations and twice daily when integrase mutations are present. It does not require boosting. An expanded access program for dolutegravir provides access to drugs for patients with documented resistance to raltegravir and elvitegravir and who are unable to construct a viable new background regimen with commercially available medications (http://www.dolutegravir-eap.com/).

Treatment interruption is not recommended outside of clinical trials, apart from very short interruptions due to surgery, severe illness, or serious drug toxicity. Studies have shown either no benefit or inferior clinical and virologic outcomes. For planned short treatment interruptions, the different half-lives of the individual components of ART regimens may require a staggered cessation of treatment. Immune Failure

There is no consensus definition of immunologic failure, which encompasses patients who are unable to achieve adequately protective CD4 cell count increases despite durable virologic suppression with ART. Higher risk of morbidity (due to AIDS and serious non-AIDS events) and mortality are reported in those with poor immunologic recovery despite virologic suppression. A number of strategies to improve CD4 cell count responses have been evaluated with no consistent benefit, including switching of NRTIs or class of drugs and treatment intensification. Currently, there is no immune-based therapy that has shown a clinical benefit.

Switching for Toxicity or Improved Tolerability and Adherence

Switching regimens to reduce toxicity, improve adherence and tolerability, and avoid drug interactions in virologically suppressed patients can be done by switching 1 or more agents in the regimen. Switches of single agents for acute or chronic toxicity are possible in patients with virologic suppression, as long as regimen potency is maintained. Although switching from enfuvirtide to raltegravir in virologically suppressed patients with MDR was not associated with virologic rebound, switching a PI/r to raltegravir has shown conflicting results, primarily associated with the activity of the background regimen.

In virologically suppressed patients with efavirenz intolerance or toxicity, substitution with nevirapine or rilpivirine is possible. There was no increased risk of nevirapine-induced hepatotoxicity or rash at high CD4 cell count at the time of the switch from efavirenz to nevirapine. The rilpivirine switch can be accomplished with a rilpivirine/tenofovir/emtricitabine FDC. Changing efavirenz to a PI/r or InSTI is another approach. There are fewer supporting data for switching to a maraviroc-based regimen in virologically suppressed individuals. Some virologically suppressed patients may require switching of regimen components owing to anticipated drug interactions such as with chemotherapy, treatment for TB, or need for proton-pump inhibitors or HCV PI therapy. If dose modification and therapeutic drug monitoring are
not possible (see “Monitoring” section), then switching the antiretroviral drug anticipated to cause the problem is appropriate.

Preemptive or reactive changes for short- and long-term toxic effects such as metabolic abnormalities\textsuperscript{136} and prevention or management of lipodystrophy, cardiovascular risk,\textsuperscript{137} and renal impairment have been used successfully with maintenance of virologic suppression.\textsuperscript{5}

Regimens that avoid NRTIs are currently being investigated and may be considered in circumstances where recommended or alternate regimens are contraindicated. Selection of components should be guided by resistance testing.

**Simplification**

A number of strategies have been explored for regimen simplification in virologically suppressed patients. Reduction in pill burden using FDCs or decreasing regimen dosing frequency to improve or maintain adherence has been used successfully, and a meta-analysis has confirmed better adherence for once-daily vs twice-daily regimens.\textsuperscript{138} Not all dose frequency reductions effectively maintain virologic suppression in treatment-experienced patients; raltegravir once-daily dosing was inferior to twice-daily dosing in a study of simplification from PI/r based regimens.\textsuperscript{139} Once-daily dosing of darunavir/r is effective in treatment-experienced patients with either no prior exposure to PIs or no darunavir-associated resistance mutations.\textsuperscript{160}

The induction/maintenance strategy of initiating therapy with 2 NRTIs and a PI/r until virologic suppression is achieved, with subsequent continuation of PI/r monotherapy alone, has been evaluated for lopinavir/r and darunavir/r. A darunavir/r monotherapy maintenance strategy reported good efficacy, but concern about poor central nervous system penetration persists, with reports of discordant plasma and cerebrospinal fluid viral loads.\textsuperscript{7,141} This also was observed in a randomized trial of lopinavir/r mono-therapy maintenance.\textsuperscript{142} At this point, there are insufficient data to support PI/r monotherapy owing to higher rates of virologic failure than for combination therapy.\textsuperscript{143} Recommendations for treatment-experienced patients are summarized in Box 4. Selected new recommendations since the last report\textsuperscript{7} are summarized in Box 5.

**EMERGING ISSUES: PREEXPOSURE PROPHYLAXIS**

The field of HIV transmission prevention has dramatically changed since the last published guidelines.\textsuperscript{7} In addition to crucial modes including behavioral change, condoms for men and women, male circumcision, and access to safe injecting methods, strategies based on antiretroviral drugs have gained ground based on important clinical trials. ART can prevent mother-to-child transmission and has a role in postexposure prophylaxis. Antiretroviral-containing vaginal and anal gels and other formulations are also being studied, though no commercially available products are available. Recently, ART used as oral preexposure prophylaxis (PrEP) has been shown to be effective in 3 large trials using daily tenofovir/emtricitabine or tenofovir in gay and bisexual men and transgender women (iPrEx),\textsuperscript{3} heterosexual HIV-serodiscordant couples (Partners PrEP),\textsuperscript{4} and heterosexual men and women (TDF2).\textsuperscript{3} A PrEP trial in high-risk women (FEM-PrEP)\textsuperscript{144} and one with an oral daily tenofovir group (VOICE)\textsuperscript{145} failed to show benefit (although the tenofovir/emtricitabine treatment group of VOICE is continuing). The degree of efficacy of PrEP in these trials had an overall positive correlation with medication adherence, particularly as measured by drug levels. Pharmacokinetic and pharmacodynamic variability and the presence of vaginal or rectal inflammation also may affect outcome. Following publication of the iPrEX results, the Centers for Disease Control and Prevention issued interim guidance for management of HIV-seronegative men who have sex with men who elect to take tenofovir/emtricitabine for prophylaxis.

An update to this document is expected should the FDA approve the application for this expanded indication.\textsuperscript{146}

**Box 4. Recommendations for Management of Treatment-Experienced Patients, With Strength of Recommendations and Quality of Evidence\textsuperscript{a}**

In the setting of confirmed virologic failure, changing to a new regimen should occur promptly, with consideration of potential contributory factors to prevent further evolution of drug resistance (AIIa).

A new regimen should be constructed using resistance testing (both past and present), treatment history, and consideration of tolerability and adherence issues (AIIa).

Initial failed regimens should be changed to regimens including a minimum of 2 and ideally 3 fully active drugs (AIIa).

Management of multidrug resistance is complex and expert advice should be sought (BIII).

In virologically suppressed patients, switching single agents for toxicity or prevention of anticipated adverse reactions or drug interactions is generally safe and effective (AIIa).

Intensification of or switching therapy has not been successful in improving suboptimal CD4 cell count responses in the setting of durable virologic suppression and is not recommended (AIIa).

Treatment interruptions (outside of clinical trials) should be avoided because of increased risk of death, AIDS, and serious non-AIDS morbidity associated with untreated human immunodeficiency virus (HIV) infection (AIIa).

Ritonavir-boosted protease inhibitor monotherapy is associated with an increased risk of virologic failure and is not recommended when other options are available (AIIa).

**Box 5. Ratings of the strength of the recommendations and quality of evidence are described in the ebox.**

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Antiretroviral therapy (ART) is recommended and should be offered regardless of CD4 cell count (Ala–CI11 depending on CD4 cell count and existing conditions).

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

ART should be started as soon as possible, preferably within the first 2 weeks of diagnosis, in patients with opportunistic infections (other than cryptococcal and tuberculous meningitis), with attention to drug interactions and the potential for immune reconstitution inflammatory syndrome (Ala).

The optimal timing of ART initiation in patients with cryptococcal meningitis is less certain, but initiating ART early during cryptococcal treatment may be associated with higher mortality; therefore, ART initiation in patients with cryptococcal meningitis should be managed in consultation with experts (BIII).

ART is recommended in all HIV-infected persons with tuberculosis (TB) and should be started within 2 weeks of TB treatment when CD4 cell count is below 300/µL and by 8 to 12 weeks for those with higher CD4 cell counts (Ala). The optimal timing for patients with TB meningitis is less certain, but ART should be started within the first 2 to 8 weeks of TB treatment and managed in consultation with experts (BIII).

Abacavir/lamivudine (in patients with HIV-1 RNA levels <100 000 copies/mL) is now a recommended rather than alternative dual nucleoside reverse transcriptase inhibitor (NRTI) component of initial ART (Ala).

Rilpivirine has been added as an alternative NNRTI component of initial ART (Ala).

Coformulated elvitegravir/cobicistat/tenofovir/emtricitabine has been added as an initial regimen component, pending regulatory approval (BIIb). Elvitegravir is an investigational integrase strand transfer inhibitor and cobicistat is an investigational pharmacokinetic booster.

Given increased risk of fragility fractures in postmenopausal women, it may be prudent to consider avoiding tenofovir as part of initial therapy in this group (BIIa).

The recommended initial ART regimen in the setting of rifampin-based TB therapy is efavirenz plus 2 NRTIs (Ala).

The recent recommendation for use of a 3-month, once-weekly regimen of isoniazid with rifapentine for treatment of latent TB infection is not recommended for HIV-infected patients receiving ART (BIII).

Sustained elevation of plasma HIV-1 RNA between 50 and 200 copies/mL should prompt evaluation of factors leading to failure and consideration for switching of ART (BII).

Health care practitioners and health systems should initiate strategies to monitor and improve entry into and retention in care and ART adherence and to incorporate and analyze quality-of-care indicators (CIII).

Management of multidrug resistance is complex and expert advice should be sought (BII).

**CONCLUSIONS AND FUTURE DIRECTIONS**

When HIV is allowed to replicate uninhibited by ART, resultant immune activation and inflammation are associated not only with immune destruction and opportunistic infections but also increased rates of cardiovascular, renal, hepatic, and neurologic diseases; malignancies; and other serious non-AIDS diseases. Evidence from clinical trials, observational cohorts, and pathogenesis studies all point toward the health benefits of earlier ART. Potent and tolerable treatment regimens now make durable viral suppression possible for most persons throughout the course of HIV infection. Clinical trial and ecological data likewise underscore the role of treatment in the prevention of new HIV infections.

Although it is crucial to intensify efforts to find a cure for persons who are already infected and an effective vaccine for those who are not, many of the tools needed to control the HIV/AIDS pandemic are already at hand. Critical components of the toolkit to eradicate AIDS include expanded HIV testing, increased focus on engagement in HIV care, early and persistent access to ART, and attention to improving ART adherence. These must occur in the context of strategies to address social determinants of health, including the elimination of stigma and discrimination. Although preventing and treating HIV are cost-effective, current economic realities demand bold steps to ensure that ART and quality medical care are globally accessible for all persons with HIV and that advances in prevention also become broadly available as their efficacy is proven.

**Author Contributions:** Dr Thompson 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. Study concept and design: Thompson, Aberg, Hoy, Telenti, Benson, Cahn, Eron, Günthard, Hammer, Reiss, Richman, Rizzardi, Thomas, Jacobsen, Volberding. Acquisition of data: Thompson, Hoy, Telenti, Benson, Richman, Volberding. Analysis and interpretation of data: Thompson, Aberg, Hoy, Benson, Cahn, Eron, Günthard, Hammer, Reiss, Richman, Volberding. Drafting of the manuscript: Thompson, Aberg, Hoy, Telenti, Benson, Cahn, Richman, Thomas, Jacobsen, Volberding. Critical revision of the manuscript for important intellectual content: Thompson, Aberg, Hoy, Telenti, Benson, Cahn, Eron, Günthard, Hammer, Reiss, Richman, Volberding.

**Box 5. Summary of Selected New Recommendations and Those for Which Strength or Quality of Evidence Has Changed Substantially**

Antiretroviral therapy (ART) is recommended and should be offered regardless of CD4 cell count (Ala–CI11 depending on CD4 cell count and existing conditions).

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Management of multidrug resistance is complex and expert advice should be sought (BII).
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Antiretroviral Treatment of Adult HIV Infection


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**Author in the Room**

Join Drs Thompson and Volberding, authors of this article, on Wednesday, August 15, from 2 to 3 PM eastern time for “Author in the Room,” an interactive teleconference aimed at closing the gap between knowledge—what is published in this article—and action—how much of this knowledge can be put into your actual practice. This teleconference, facilitated by clinical experts, should help readers answer their questions and consider the implications of the article for their practice.

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