

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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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/ μ L 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 iteration¹ 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/ μ L.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.⁶

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 (A1a).

ART is recommended regardless of CD4 cell count (A1a-B111). 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 $\leq 500/\mu\text{L}$: A1a

For CD4 cell counts of $>500/\mu\text{L}$: B111

Ratings for specific conditions with CD4 cell counts of $>500/\mu\text{L}$:

Pregnancy: A1a

Chronic hepatitis B virus co-infection: A1a

HIV-associated nephropathy: A1a

ART is recommended and should be offered to persons during the acute phase of primary HIV infection, regardless of symptoms (B111).

ART should be started as soon as possible, preferably within the first 2 weeks of diagnosis, in patients with opportunistic infections (A1a) and other opportunistic diseases and AIDS-defining illnesses (including all lymphomas and human papillomavirus-related cancers) (A1a-B111).

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 (B111).

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 $<50/\mu\text{L}$, and by 8 to 12 weeks for those with higher CD4 cell counts (A1a). 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 (B111).

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 (A1a).

CD4 cell count should be monitored at least every 3 months after initiation of therapy, especially among patients with cell counts of $<200/\mu\text{L}$, to determine the need for initiation or discontinuation of primary opportunistic infection prophylaxis (B111).

Once HIV-1 RNA level is suppressed for 1 year and CD4 cell count is stable at $\geq 350/\mu\text{L}$, viral load and CD4 cell count can be monitored at intervals of ≤ 6 months in patients with dependable adherence (C111).

Once viral load is demonstrated to be suppressed consistently for more than 2 years and CD4 cell counts are persistently $>500/\mu\text{L}$, monitoring CD4 cell counts is optional unless virologic failure occurs or there are intercurrent immunosuppressive treatments or conditions (C111).

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 (B111).

HIV-1 RNA level >200 copies/mL should prompt evaluation of factors leading to failure and consideration of switching ART (A11a).

Baseline genotypic testing for resistance should be performed in all treatment-naïve patients (A11a) and in cases of confirmed virologic failure (A1a).

Therapeutic drug monitoring is not recommended in routine care; however, selected patients might benefit from this intervention (B111).

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 (C111).

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 (A11a).

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 (A1a).

Monotherapy with a boosted protease inhibitor is not recommended when other options are available (A1a).

Maintenance of virologic suppression is paramount when switching the regimen to improve tolerability, reduce toxicity, and improve convenience (A1a).

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 (nucleoside reverse transcriptase inhibitors, unboosted protease inhibitors, or integrase strand transfer inhibitors) (A1a).

^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 $50/\mu\text{L}$ and severe cryptococcal meningitis with white blood cell counts of less than $5/\mu\text{L}$ 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 | Ala | Dolutegravir is dosed once daily. Associated with modest increases in creatinine level due to inhibition of creatinine secretion. |
| | Dolutegravir ^b plus abacavir ^c /lamivudine | Ala | 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 | Ala | 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. |
| Nonnucleoside reverse transcriptase inhibitor plus 2 nucleoside reverse transcriptase inhibitors | Raltegravir ^b plus tenofovir/emtricitabine | Ala | Raltegravir is taken twice daily. |
| | Efavirenz ^d /tenofovir/emtricitabine | Ala | 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 | Ala | Efavirenz central nervous symptoms may persist beyond 2-4 weeks but is no longer contraindicated for use in pregnant women. |
| Ritonavir-boosted protease inhibitor plus 2 nucleoside reverse transcriptase inhibitors | Rilpivirine ^f /tenofovir/emtricitabine | Ala | Once-daily fixed-dose combination. Rilpivirine-based therapy is not recommended in patients with baseline HIV-1 RNA levels > 100 000 copies/mL. |
| | Atazanavir ^{g,h} plus tenofovir/emtricitabine | Ala | Atazanavir is associated with nephrolithiasis, cholelithiasis, and chronic kidney injury. |
| | Atazanavir ^{g,h} plus abacavir ^c /lamivudine ^e | Ala | Atazanavir is associated with nephrolithiasis, cholelithiasis, and chronic kidney injury. |
| | Darunavir ^g plus tenofovir/emtricitabine | Ala | 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 (Ca²⁺, 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-naïve 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 | Bla | 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 | Bla | 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 | Ala | 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 | Bla | 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 | BIIb | Comparative clinical data from a subset of patients from a single, randomized study. |
| Nucleoside reverse transcriptase inhibitors limiting or sparing ^h | Lopinavir ^g fixed-dose combination with 2 nucleoside reverse transcriptase inhibitors | Bla | Main advantage is fixed-dose combination. May have increased cardiovascular risk and be less tolerable than recommended options. |
| | Darunavir ^{e-g} plus raltegravir | BIIb | 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 | Bla | 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 | Bla | 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 (Ca²⁺, 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 guidelines⁴⁷ has been adopted. Ideally, definitive studies to determine the optimal regimen for the majority of ART-naïve patients would simplify treatment strategies. However, such studies would be costly and are unlikely to be conducted. Wider availability of effective generic drugs¹⁴ 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 cholelithiasis⁷⁰ 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 trial⁷³ 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 formulations 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/ μ L, 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-naïve 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 rifampin 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 rifampin can be safely administered with efavirenz, suggesting that the 3-month regimen of weekly isoniazid and rifampin 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 m²), 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 favor-

able 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 success¹⁰⁷ 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/ μ L had a 97% probability of maintaining durable CD4 cell counts of greater than 200/ μ L for 4 years.¹⁰⁹ Other data¹¹⁰ 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 toxicity¹²⁶ 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 al¹³⁰ 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 (Aa-BIII).

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

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 (Aa).

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

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

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 a nucleoside reverse transcriptase inhibitor-sparing alternative regimen only to be used in certain circumstances (Bib).

Ritonavir-boosted lopinavir plus lamivudine has been added as a 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 (Aa).

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 (Aa).

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

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 (Aa).

^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-naïve patients.^{145,146} Dolutegravir has better activity than raltegravir in ART-experienced, INSTI-naïve patients, and is dosed once daily.¹⁴⁷ Dolutegravir should be dosed twice daily in patients who experienced treatment failure with a raltegravir-

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-naïve 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/emtricitabine¹⁵⁸⁻¹⁶⁰ 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/ μ L 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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REFERENCES

- Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society–USA panel. *JAMA*. 2012;308(4):387-402.
- Cohen MS, Chen YQ, McCauley M, et al; HPTN 052 Study Team. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365(6):493-505.
- Tanser F, Bärnighausen T, Grapsa E, Zaidi J, Newell ML. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. *Science*. 2013;339(6122):966-971.
- Rodger A, Bruun T, Cambiano V, et al. HIV transmission risk through condomless sex if HIV+ partner on suppressive ART: PARTNER study [Abstract 153LB]. *Top Antivir Med*. 2014;22(e-1):24-25.
- Rodger AJ, Lodwick R, Schechter M, et al; INSIGHT SMART, ESPRIT Study Groups. Mortality in well controlled HIV in the continuous antiretroviral therapy arms of the SMART and ESPRIT trials compared with the general population. *AIDS*. 2013;27(6):973-979.
- Sáez-Cirión A, Bacchus C, Hocqueloux L, et al; ANRS VISCONTI Study Group. Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study. *PLoS Pathog*. 2013;9(3):e1003211.
- Persaud D, Gay H, Ziemniak C, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. *N Engl J Med*. 2013;369(19):1828-1835.
- Canadian Task Force on the Periodic Health Examination. The Periodic Health Examination. *Can Med Assoc J*. 1979;121(9):1193-1254.
- Wada N, Jacobson LP, Cohen M, French A, Phair J, Muñoz A. Cause-specific mortality among HIV-infected individuals, by CD4(+) cell count at HAART initiation, compared with HIV-uninfected individuals. *AIDS*. 2014;28(2):257-265.
- Mcroft A, Furrer HJ, Miro JM, et al; Opportunistic Infections Working Group on behalf of the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study in EuroCOORD. The incidence of AIDS-defining illnesses at a current CD4 count \geq 200 cells/ μ L in the post-combination antiretroviral therapy era. *Clin Infect Dis*. 2013;57(7):1038-1047.
- Cheung C, Ding E, Zhu J, et al. Expansion of ART and progressive declines in all-cause mortality in British Columbia, Canada [Poster 559]. *Top Antivir Med*. 2014;22(e-1):271-272.
- Grinsztajn B, Hosseinipour MC, Ribaudo HJ, et al; HPTN 052-ACTG Study Team. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. *Lancet Infect Dis*. 2014;14(4):281-290.
- Koenig SP, Bang H, Severe P, et al. Cost-effectiveness of early versus standard antiretroviral therapy in HIV-infected adults in Haiti. *PLoS Med*. 2011;8(9):e1001095.
- Walensky RP, Sax PE, Nakamura YM, et al. Economic savings versus health losses: the cost-effectiveness of generic antiretroviral therapy in the United States. *Ann Intern Med*. 2013;158(2):84-92.
- Kovari H, Sabin CA, Ledergerber B, et al. Antiretroviral drug-related liver mortality among HIV-positive persons in the absence of hepatitis B or C virus coinfection: the data collection on adverse events of anti-HIV drugs study. *Clin Infect Dis*. 2013;56(6):870-879.
- World Health Organization (WHO). March 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. http://apps.who.int/iris/bitstream/10665/104264/1/9789241506830_eng.pdf. Accessed April 3, 2014.
- Chun TW, Shawn Justement J, Murray D, et al. Effect of antiretroviral therapy on HIV reservoirs in elite controllers. *J Infect Dis*. 2013;208(9):1443-1447.
- Hatano H, Yukl SA, Ferre AL, et al. Prospective antiretroviral treatment of asymptomatic, HIV-1 infected controllers. *PLoS Pathog*. 2013;9(10):e1003691.
- Boufassa F, Lechenadec J, Meyer L, et al; ANRS CO18 HIV Controllers Cohort; Cascade Collaboration in Eurocoord; SCOPE Cohort; International HIV Controllers Study. Blunted response to combination antiretroviral therapy in HIV elite controllers: an international HIV controller collaboration. *PLoS One*. 2014;9(1):e85516.
- Wyl Vv, Gianella S, Fischer M, et al; Swiss HIV Cohort Study-SHCS. Early antiretroviral therapy during primary HIV-1 infection results in a transient reduction of the viral setpoint upon treatment interruption. *PLoS One*. 2011;6(11):e27463.
- Hocqueloux L, Avettand-Fènoël V, Jacquot S, et al; AC32 (Coordinated Action on HIV Reservoirs) of the Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS). Long-term antiretroviral therapy initiated during primary HIV-1 infection is key to achieving both low HIV reservoirs and normal T cell counts. *J Antimicrob Chemother*. 2013;68(5):1169-1178.
- Grijzen ML, Steingrover R, Wit FWNM, et al; Primo-SHM Study Group. No treatment versus 24 or 60 weeks of antiretroviral treatment during primary HIV infection: the randomized Primo-SHM trial. *PLoS Med*. 2012;9(3):e1001196.
- Le T, Wright EJ, Smith DM, et al. Enhanced CD4+ T-cell recovery with earlier HIV-1 antiretroviral therapy. *N Engl J Med*. 2013;368(3):218-230.
- Chen J, Han X, An M, et al. Immunological and virological benefits resulted from short-course treatment during primary HIV infection: a meta-analysis. *PLoS One*. 2013;8(12):e82461.
- Vinikoor MJ, Cope A, Gay CL, et al. Antiretroviral therapy initiated during acute HIV infection fails to prevent persistent T-cell activation. *J Acquir Immune Defic Syndr*. 2013;62(5):505-508.
- Archin NM, Vaidya NK, Kuruc JD, et al. Immediate antiviral therapy appears to restrict resting CD4+ cell HIV-1 infection without accelerating the decay of latent infection. *Proc Natl Acad Sci U S A*. 2012;109(24):9523-9528.
- Rieder P, Joos B, von Wyl V, et al; Swiss HIV Cohort Study. HIV-1 transmission after cessation of early antiretroviral therapy among men having sex with men. *AIDS*. 2010;24(8):1177-1183.

28. Jarvis JN, Bicanic T, Loyse A, et al. Determinants of mortality in a combined cohort of 501 patients with HIV-associated cryptococcal meningitis: implications for improving outcomes. *Clin Infect Dis*. 2014;58(5):736-745.
29. Bisson GP, Molefi M, Bellamy S, et al. Early versus delayed antiretroviral therapy and cerebrospinal fluid fungal clearance in adults with HIV and cryptococcal meningitis. *Clin Infect Dis*. 2013;56(8):1165-1173.
30. Njei B, Kongnyuy EJ, Kumar S, Okwen MP, Sankar MJ, Mbuagbaw L. Optimal timing for antiretroviral therapy initiation in patients with HIV infection and concurrent cryptococcal meningitis. *Cochrane Database Syst Rev*. 2013;2:CD009012.
31. Boulware DR, Meya DB, Muzoora C, et al; for the COAT Trial Team. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med*. 2014;370(26):2487-2498.
32. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50(3):291-322.
33. Freedberg KA, Losina E, Weinstein MC, et al. The cost effectiveness of combination antiretroviral therapy for HIV disease. *N Engl J Med*. 2001;344(11):824-831.
34. Schackman BR, Freedberg KA, Weinstein MC, et al. Cost-effectiveness implications of the timing of antiretroviral therapy in HIV-infected adults. *Arch Intern Med*. 2002;162(21):2478-2486.
35. Mauskopf J, Kitahata M, Kauf T, Richter A, Tolson J. HIV antiretroviral treatment: early versus later. *J Acquir Immune Defic Syndr*. 2005;39(5):562-569.
36. Chen RY, Accortt NA, Westfall AO, et al. Distribution of health care expenditures for HIV-infected patients. *Clin Infect Dis*. 2006;42(7):1003-1010.
37. Walmsley SL, Antela A, Clumeck N, et al; SINGLE Investigators. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med*. 2013;369(19):1807-1818.
38. Raffi F, Rachlis A, Stellbrink HJ, et al; SPRING-2 Study Group. Once-daily dolutegravir versus raltegravir in antiretroviral-naïve adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. *Lancet*. 2013;381(9868):735-743.
39. Raffi F, Jaeger H, Quiros-Roldan E, et al; extended SPRING-2 Study Group. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naïve adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. *Lancet Infect Dis*. 2013;13(11):927-935.
40. Wohl DA, Cohen C, Gallant JE, et al; GS-US-236-0102 Study Team. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF versus single-tablet regimen efavirenz/emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. *J Acquir Immune Defic Syndr*. 2014;65(3):e118-e120.
41. Clumeck N, Molina JM, Henry K, et al; GS-236-0103 Study Team. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF versus ritonavir-boosted atazanavir plus emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. *J Acquir Immune Defic Syndr*. 2014;65(3):e121-e124.
42. Sax PE, DeJesus E, Mills A, et al; GS-US-236-0102 study team. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. *Lancet*. 2012;379(9835):2439-2448.
43. DeJesus E, Rockstroh JK, Henry K, et al; GS-236-0103 Study Team. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet*. 2012;379(9835):2429-2438.
44. Landovitz RJ, Ribaudo HJ, Ofotokun I, et al. Efficacy and tolerability of atazanavir, raltegravir, or darunavir with FTC/tenofovir: ACTG 5257 [Abstract 85]. *Top Antivir Med*. 2014;22(e-1):42-43.
45. Clotet B, Feinberg J, van Lunzen J, et al; on behalf of the ING114915 Study Team. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naïve adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. *Lancet*. 2014.
46. Elzi L, Erb S, Furrer H, et al; Swiss HIV Cohort Study. Choice of initial combination antiretroviral therapy in individuals with HIV infection: determinants and outcomes. *Arch Intern Med*. 2012;172(17):1313-1321.
47. World Health Organization. The strategic use of antiretrovirals to help end the HIV epidemic. http://www.who.int/hiv/pub/arv/strategic_use/en/. Accessed March 24, 2014.
48. Feinberg J, Clotet B, Khuong MA, et al. Once-daily dolutegravir is superior to darunavir/ritonavir in antiretroviral naïve adults: 48 week results from FLAMINGO (ING114915). Presented at: 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 10-13, 2013; Denver, CO. Abstract H-1464a.
49. Zolopa A, Sax PE, DeJesus E, et al; GS-US-236-0102 Study Team. A randomized double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: analysis of week 96 results. *J Acquir Immune Defic Syndr*. 2013;63(1):96-100.
50. Cohen C, Wohl D, Arribas JR, et al. Week 48 results from a randomized clinical trial of rilpivirine/emtricitabine/tenofovir disoproxil fumarate vs efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naïve HIV-1-infected adults. *AIDS*. 2014;28(7):989-997.
51. Cohen CJ, Molina JM, Cassetti I, et al; ECHO, THRIVE study groups. Week 96 efficacy and safety of rilpivirine in treatment-naïve, HIV-1 patients in two phase III randomized trials. *AIDS*. 2013;27(6):939-950.
52. Cahn P, Andrade-Villanueva J, Arribas JR, et al; on behalf of the GARDEL Study Group. Dual therapy with lopinavir and ritonavir plus lamivudine versus triple therapy with lopinavir and ritonavir plus two nucleoside reverse transcriptase inhibitors in antiretroviral-therapy-naïve adults with HIV-1 infection: 48 week results of the randomised, open label, non-inferiority GARDEL trial. *Lancet Infect Dis*. 2014;14(7):572-580.
53. Raffi F, Babiker AG, Richert L, et al. First-line RAL + DRV/r is non-inferior to TDF/FTC + DRV/r: the NEAT001/ANRS143 randomised trial [Abstract 84LB]. *Top Antivir Med*. 2014;22(e-1):41-42.
54. D:A:D Study Group; Sabin CA, Worm SW, Weber R, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet*. 2008;371(9622):1417-1426.
55. Strategies for Management of Anti-Retroviral Therapy/INSIGHT; DAD Study Groups. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS*. 2008;22(14):F17-F24.
56. Bedimo RJ, Westfall AO, Drechsler H, Vidiella G, Tebas P. Abacavir use and risk of acute myocardial infarction and cerebrovascular events in the highly active antiretroviral therapy era. *Clin Infect Dis*. 2011;53(1):84-91.
57. Ding X, Andraca-Carrera E, Cooper C, et al. No association of abacavir use with myocardial infarction: findings of an FDA meta-analysis. *J Acquir Immune Defic Syndr*. 2012;61(4):441-447.
58. Sabin C, Reiss P, Ryom L, et al. Is there continued evidence for an association between abacavir and myocardial infarction risk? [Abstract 747LB]. *Top Antivir Med*. 2014;22(e-1):382-383.
59. Sax PE, Tierney C, Collier AC, et al; AIDS Clinical Trials Group Study A5202 Team. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *N Engl J Med*. 2009;361(23):2230-2240.
60. Eron Jr J, Rockstroh J, Pozniak A, et al. Abstracts of the Eleventh International Congress on Drug Therapy in HIV Infection 11-15 November 2012, Glasgow, UK. *J Int AIDS Soc*. 2012;15(suppl 4):3-179.
61. Ryom L, Mocroft A, Kirk O, et al; D:A:D Study Group. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. *J Infect Dis*. 2013;207(9):1359-1369.
62. Rockstroh JK, DeJesus E, Lennox JL, et al; STARTMRK Investigators. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naïve HIV-1-infected patients: final 5-year results from STARTMRK. *J Acquir Immune Defic Syndr*. 2013;63(1):77-85.
63. Walmsley S, Berenguer J, Khuong-Josses MA, et al. Dolutegravir regimen statistically superior to tenofovir/emtricitabine/efavirenz: 96-wk data [Abstract 543]. *Top Antivir Med*. 2014;22(e-1):261-262.
64. German P, Liu HC, Szwarcberg J, et al. Effect of cobicistat on glomerular filtration rate in subjects with normal and impaired renal function. *J Acquir Immune Defic Syndr*. 2012;61(1):32-40.
65. Mollan KR, Smurzynski M, Eron JJ, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal

- ideation or attempted or completed suicide: an analysis of trial data. *Ann Intern Med.* 2014;161(1):1-10.
66. Napoli A, Coumbis J, Wood J, Soitkar A, Seekins D. Disproportionality analysis of antiretrovirals with suicidality using FDA AERS data [Abstract 761]. *Top Antivir Med.* 2014;22(e-1):419.
67. Rimsky L, Vingerhoets J, Van Eygen V, et al. Genotypic and phenotypic characterization of HIV-1 isolates obtained from patients on rilpivirine therapy experiencing virologic failure in the phase 3 ECHO and THRIVE studies: 48-week analysis. *J Acquir Immune Defic Syndr.* 2012;59(1):39-46.
68. ENCORE1 Study Group. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial [published correction appears in *Lancet.* 2014;383(9927):1464]. *Lancet.* 2014;383(9927):1474-1482.
69. Soliman EZ, Lundgren JD, Roediger MP, et al; INSIGHT SMART Study Group. Boosted protease inhibitors and the electrocardiographic measures of QT and PR durations. *AIDS.* 2011;25(3):367-377.
70. Rakotondravelo S, Poinssignon Y, Borsa-Lebas F, et al. Complicated atazanavir-associated cholelithiasis: a report of 14 cases. *Clin Infect Dis.* 2012;55(9):1270-1272.
71. Hamada Y, Nishijima T, Watanabe K, et al. High incidence of renal stones among HIV-infected patients on ritonavir-boosted atazanavir than in those receiving other protease inhibitor-containing antiretroviral therapy. *Clin Infect Dis.* 2012;55(9):1262-1269.
72. Mocroft A, Kirk O, Reiss P, et al. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. *AIDS.* 2010;24(11):1667-1678.
73. Daar ES, Tierney C, Fischl MA, et al; AIDS Clinical Trials Group A5202 Team. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. *Ann Intern Med.* 2011;154(7):445-456.
74. Monforte Ad, Reiss P, Ryom L, et al. Atazanavir is not associated with an increased risk of cardio- or cerebrovascular disease events. *AIDS.* 2013;27(3):407-415.
75. Gallant JE, Koenig E, Andrade-Villanueva J, et al. Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV type 1-infected patients: week 48 results. *J Infect Dis.* 2013;208(1):32-39.
76. Reynes J, Trinh R, Pulido F, et al. Lopinavir/ritonavir combined with raltegravir or tenofovir/emtricitabine in antiretroviral-naive subjects: 96-week results of the PROGRESS study. *AIDS Res Hum Retroviruses.* 2013;29(2):256-265.
77. National Institutes of Health. Comparative trial of maraviroc versus emtricitabine/tenofovir both with darunavir/ritonavir in antiretroviral-naive patients infected with Ccr5 tropic HIV 1 (MODERN). <http://clinicaltrials.gov/ct2/show/NCT01345630?term=maraviroc+once-daily+AND+darunavir+AND+enhanced+AND+ritonavir&rank=1>. Accessed March 26, 2014.
78. Antiretroviral Pregnancy Registry; Wilmington North Carolina Registry Coordinating Center. The antiretroviral pregnancy registry: interim report: 1 January 1989 through 31 January 2013. http://www.apregistry.com/forms/interim_report.pdf. Accessed January 6, 2014.
79. Zorrilla CD, Wright R, Osiyemi OO, et al. Total and unbound darunavir pharmacokinetics in pregnant women infected with HIV-1: results of a study of darunavir/ritonavir 600/100 mg administered twice daily. *HIV Med.* 2014;15(1):50-56.
80. Fayet-Mello A, Buclin T, Guignard N, et al; Swiss HIV Cohort Study; Mother & Child HIV Cohort Study. Free and total plasma levels of lopinavir during pregnancy, at delivery and postpartum: implications for dosage adjustments in pregnant women. *Antivir Ther.* 2013;18(2):171-182.
81. Siberry GK, Jacobson DL, Kalkwarf H, et al. Lower newborn bone mineral content associated with maternal use of tenofovir disoproxil fumarate. *Top Antivir Med.* 2014;22(e-1):34.
82. Cohan D, Natureeba P, Plenty A, et al. Efficacy and safety of LPV/r versus EFV in HIV+ pregnant and breast-feeding Ugandan women. *Top Antivir Med.* 2014;22(e-1):34-35.
83. Ofotokun I, Ribaud H, Na L, et al. Darunavir or atazanavir vs raltegravir lipid changes are unlinked to ritonavir exposure: ACTG 5257 [Abstract 746]. *Top Antivir Med.* 2014;22(e-1):381-382.
84. Morlat P, Vivot A, Vandenhende MA, et al; Groupe D'epidemiologie Clinique du Sida en Aquitaine (GeCSa). Role of traditional risk factors and antiretroviral drugs in the incidence of chronic kidney disease, ANRS CO3 Aquitaine cohort, France, 2004-2012. *PLoS One.* 2013;8(6):e66223.
85. Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir) [package insert]. Foster City, CA: Gilead Sciences Inc; 2012.
86. McComsey GA, Kitch D, Daar ES, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: AIDS Clinical Trials Group A5224s, a substudy of ACTG A5202. *J Infect Dis.* 2011;203(12):1791-1801.
87. Brown T, Moser C, Currier J, et al. Bone density changes after antiretroviral initiation with protease inhibitors or raltegravir [Abstract 779LB]. *Top Antivir Med.* 2014;22(e-1):401.
88. Overton ET, Chan ES, Brown TT, et al. High-dose vitamin D and calcium attenuates bone loss with ART initiation: results from ACTG A5280 [Abstract 133]. *Top Antivir Med.* 2014;22(e-1):66-67.
89. Luetkemeyer AF, Rosenkranz SL, Lu D, et al; Adult AIDS Clinical Trials Group A5221 Study Team. Relationship between weight, efavirenz exposure, and virologic suppression in HIV-infected patients on rifampin-based tuberculosis treatment in the AIDS Clinical Trials Group A5221 STRIDE Study. *Clin Infect Dis.* 2013;57(4):586-593.
90. Blanc FX, Sok T, Laureillard D, et al; CAMELIA (ANRS 1295-CIPRA KH001) Study Team. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med.* 2011;365(16):1471-1481.
91. Havlir DV, Kendall MA, Ive P, et al; AIDS Clinical Trials Group Study A5221. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med.* 2011;365(16):1482-1491.
92. Abdool Karim S, Naidoo K, Padayatchi N, et al. Optimal timing of ART during TB therapy: findings of the SAPIT trial. Presented at: 18th Conference on Retroviruses and Opportunistic Infections; February 27-March 2, 2011; Boston, MA.
93. Friedland G, Khoo S, Jack C, Lalloo U. Administration of efavirenz (600 mg/day) with rifampicin results in highly variable levels but excellent clinical outcomes in patients treated for tuberculosis and HIV. *J Antimicrob Chemother.* 2006;58(6):1299-1302.
94. Boule A, Van Cutsem G, Cohen K, et al. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA.* 2008;300(5):530-539.
95. Naiker S, Conolly C, Weisner L, et al. Pharmacokinetic evaluation of different rifabutin dosing strategies in African TB patients on lopinavir/ritonavir-based ART. Presented at: 18th Conference on Retroviruses and Opportunistic Infections; February 27-March 2, 2011; Boston, MA.
96. Boulanger C, Hollender E, Farrell K, et al. Pharmacokinetic evaluation of rifabutin in combination with lopinavir-ritonavir in patients with HIV infection and active tuberculosis. *Clin Infect Dis.* 2009;49(9):1305-1311.
97. Jenny-Avital ER, Joseph K. Rifamycin-resistant *Mycobacterium tuberculosis* in the highly active antiretroviral therapy era: a report of 3 relapses with acquired rifampin resistance following alternate-day rifabutin and boosted protease inhibitor therapy. *Clin Infect Dis.* 2009;48(10):1471-1474.
98. Grinsztejn B, De Castro N, Arnold V, et al; ANRS 12 180 Reflate TB study group. Raltegravir for the treatment of patients co-infected with HIV and tuberculosis (ANRS 12 180 Reflate TB): a multicentre, phase 2, non-comparative, open-label, randomised trial. *Lancet Infect Dis.* 2014;14(6):459-467.
99. Dooley KE, Sayre P, Borland J, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. *J Acquir Immune Defic Syndr.* 2013;62(1):21-27.
100. Centers for Disease Control and Prevention (CDC). Recommendations for use of an isoniazid-rifampentine regimen with direct observation to treat latent *Mycobacterium tuberculosis* infection. *MMWR Morb Mortal Wkly Rep.* 2011;60(48):1650-1653.
101. Sterling T, Benson C, Scott N, et al. Three months of weekly rifampentine + INH for *M. tuberculosis* infection in HIV-infected persons [Abstract 817]. *Top Antivir Med.* 2014;22(e-1):425.
102. Podany AT, Bao Y, Chaisson RE, et al. Efavirenz pharmacokinetics in HIV+ persons receiving rifampentine and isoniazid for TB prevention [Abstract 105]. *Top Antivir Med.* 2014;22(e-1):54-55.
103. Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. *N Engl J Med.* 2009;360(23):2397-2405.
104. Karageorgopoulos DE, El-Sherif O, Bhagani S, Khoo SH. Drug interactions between antiretrovirals and new or emerging direct-acting antivirals in HIV/hepatitis C virus coinfection. *Curr Opin Infect Dis.* 2014;27(1):36-45.

- 105.** AASLD; IDSA IAS-USA. Recommendations for testing, managing, and treating hepatitis C. <http://hcvguidelines.org/>. Accessed May 20, 2014.
- 106.** Liverpool HIV and Hepatitis Pharmacology Group. Drug interaction chart. <http://www.hiv-druginteractions.org/>. Accessed March 25, 2014.
- 107.** Sax PE. Editorial commentary: can we break the habit of routine CD4 monitoring in HIV care? *Clin Infect Dis*. 2013;56(9):1344-1346.
- 108.** Bonner K, Mezocho A, Roberts T, Ford N, Cohn J. Viral load monitoring as a tool to reinforce adherence: a systematic review. *J Acquir Immune Defic Syndr*. 2013;64(1):74-78.
- 109.** Gale HB, Gitterman SR, Hoffman HJ, et al. Is frequent CD4+ T-lymphocyte count monitoring necessary for persons with counts >=300 cells/μL and HIV-1 suppression? *Clin Infect Dis*. 2013;56(9):1340-1343.
- 110.** Whitlock GG, Ahmed N, Benn P, Edwards S, Waters L. Stop routine CD4 monitoring in HIV-infected patients with fully suppressed virus and CD4 >=350 cells/ml. *Clin Infect Dis*. 2013;57(2):327-328.
- 111.** Hyle EP, Sax PE, Walensky RP. Potential savings by reduced CD4 monitoring in stable patients with HIV receiving antiretroviral therapy. *JAMA Intern Med*. 2013;173(18):1746-1748.
- 112.** Swenson LC, Cobb B, Geretti AM, et al; International Viral Load Assay Collaboration. Comparative performances of HIV-1 RNA load assays at low viral load levels: results of an international collaboration. *J Clin Microbiol*. 2014;52(2):517-523.
- 113.** Ruelle J, Debaisieux L, Vancutsem E, et al. HIV-1 low-level viraemia assessed with 3 commercial real-time PCR assays show high variability. *BMC Infect Dis*. 2012;12:100.
- 114.** Li JZ, Gallien S, Ribaud H, Heisey A, Bangsberg DR, Kuritzkes DR. Incomplete adherence to antiretroviral therapy is associated with higher levels of residual HIV-1 viremia. *AIDS*. 2014;28(2):181-186.
- 115.** Pugliese P, Delpierre C, Cuzin L, et al; Dat AIDS Study Group. An undetectable polymerase chain reaction signal in routine HIV plasma viral load monitoring is associated with better virological outcomes in patients receiving highly active antiretroviral therapy. *HIV Med*. 2013;14(8):509-515.
- 116.** Maggiolo F, Callegaro A, Cologni G, et al. Ultrasensitive assessment of residual low-level HIV viremia in HAART-treated patients and risk of virological failure. *J Acquir Immune Defic Syndr*. 2012;60(5):473-482.
- 117.** Charpentier C, Landman R, Laouénan C, et al. Persistent low-level HIV-1 RNA between 20 and 50 copies/mL in antiretroviral-treated patients: associated factors and virological outcome. *J Antimicrob Chemother*. 2012;67(9):2231-2235.
- 118.** Laprise C, de Pokomandy A, Baril JG, Dufresne S, Trottier H. Virologic failure following persistent low-level viremia in a cohort of HIV-positive patients: results from 12 years of observation. *Clin Infect Dis*. 2013;57(10):1489-1496.
- 119.** Vandenhende MA, Ingle S, May M, et al. Impact of low-level viremia on clinical and virological outcomes in treated HIV infected patients [Abstract 1014]. *Top Antivir Med*. 2014;22(e-1):535-536.
- 120.** Li JZ, Gallien S, Do TD, et al. Prevalence and significance of HIV-1 drug resistance mutations among patients on antiretroviral therapy with detectable low-level viremia. *Antimicrob Agents Chemother*. 2012;56(11):5998-6000.
- 121.** Swenson LC, Min JE, Woods CK, et al. HIV drug resistance detected during low-level viraemia is associated with subsequent virologic failure. *AIDS*. 2014.
- 122.** Delaugerre C, Gallien S, Flandre P, et al. Impact of low-level-viremia on HIV-1 drug-resistance evolution among antiretroviral treated-patients. *PLoS One*. 2012;7(5):e36673.
- 123.** Gonzalez-Serna A, Min JE, Woods C, et al. Performance of HIV-1 drug resistance testing at low-level viremia and its ability to predict future virologic outcomes and viral evolution in treatment-naïve individuals. *Clin Infect Dis*. 2014;58(8):1165-1173.
- 124.** Hirsch MS, Günthard HF, Schapiro JM, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA panel. *Clin Infect Dis*. 2008;47(2):266-285.
- 125.** Wittkop L, Günthard HF, de Wolf F, et al; EuroCoord-CHAIN study group. Effect of transmitted drug resistance on virological and immunological response to initial combination antiretroviral therapy for HIV (EuroCoord-CHAIN joint project): a European multicohort study. *Lancet Infect Dis*. 2011;11(5):363-371.
- 126.** Schoenenberger JA, Aragones AM, Cano SM, et al. The advantages of therapeutic drug monitoring in patients receiving antiretroviral treatment and experiencing medication-related problems. *Ther Drug Monit*. 2013;35(1):71-77.
- 127.** Colbers A, Greupink R, Burger D. Pharmacological considerations on the use of antiretrovirals in pregnancy. *Curr Opin Infect Dis*. 2013;26(6):575-588.
- 128.** Rakhmanina N, Phelps BR. Pharmacotherapy of pediatric HIV infection. *Pediatr Clin North Am*. 2012;59(5):1093-1115.
- 129.** Charania MR, Marshall KJ, Lyles CM, et al; HIV/AIDS Prevention Research Synthesis (PRS) Team. Identification of evidence-based interventions for promoting HIV medication adherence: findings from a systematic review of US-based studies, 1996-2011. *AIDS Behav*. 2014;18(4):646-660.
- 130.** Taiwo B, Yanik EL, Napravnik S, et al; CFAR Network of Integrated Clinical Systems (CNICS) Cohort Study. Evidence for risk stratification when monitoring for toxicities following initiation of combination antiretroviral therapy. *AIDS*. 2013;27(10):1593-1602.
- 131.** Buscher A, Mugavero M, Westfall AO, et al. The association of clinical follow-up intervals in HIV-infected persons with viral suppression on subsequent viral suppression. *AIDS Patient Care STDS*. 2013;27(8):459-466.
- 132.** Miller V, Nwokike J, Stergachis A. Pharmacovigilance and global HIV/AIDS. *Curr Opin HIV AIDS*. 2012;7(4):299-304.
- 133.** Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV medicine association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;58(1):e1-e34.
- 134.** Kulkarni R, Abram ME, Rhee MS, et al. Week 144 resistance analyses of the phase 3 EVG/COBI/FTC/TDF studies. *Top Antivir Med*. 2014;22(e1):288.
- 135.** Hill A, McBride A, Sawyer AW, Clumeck N, Gupta RK. Resistance at virological failure using boosted protease inhibitors versus nonnucleoside reverse transcriptase inhibitors as first-line antiretroviral therapy—implications for sustained efficacy of ART in resource-limited settings. *J Infect Dis*. 2013;207(suppl 2):S78-S84.
- 136.** Scherrer AU, Böni J, Yerly S, et al; Swiss HIV Cohort Study (SHCS). Long-lasting protection of activity of nucleoside reverse transcriptase inhibitors and protease inhibitors (PIs) by boosted PI containing regimens. *PLoS One*. 2012;7(11):e50307.
- 137.** Ajose O, Mookerjee S, Mills EJ, Boule A, Ford N. Treatment outcomes of patients on second-line antiretroviral therapy in resource-limited settings: a systematic review and meta-analysis. *AIDS*. 2012;26(8):929-938.
- 138.** Boyd MA, Kumarasamy N, Moore CL, et al; SECOND-LINE Study Group. Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study. *Lancet*. 2013;381(9883):2091-2099.
- 139.** Paton N, Kityo C, Hoppe A, et al. A pragmatic randomised controlled strategy trial of three second-line treatment options for use in public health rollout programme settings: the Europe-Africa Research Network for Evaluation of Second-line Therapy (EARNEST) Trial. Presented at: 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention; Kuala Lumpur, Malaysia; June 30-July 3, 2013. Abstract WELBBO2.
- 140.** Sension M, Cahn P, Domingo P, et al. Subgroup analysis of virological response rates with once- and twice-daily darunavir/ritonavir in treatment-experienced patients without darunavir resistance-associated mutations in the ODIN trial. *HIV Med*. 2013;14(7):437-444.
- 141.** Hicks CB, Cahn P, Cooper DA, et al; RESIST investigator group. Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multi-drug resistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two randomised open-label trials. *Lancet*. 2006;368(9534):466-475.
- 142.** Trottier B, Di Perri G, Madrugá JV, et al. Impact of the background regimen on virologic response to etravirine: pooled 48-week analysis of DUET-1 and -2. *HIV Clin Trials*. 2010;11(4):175-185.
- 143.** Katlama C, Haubrich R, Lalezari J, et al; DUET-1, DUET-2 study groups. Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: pooled 48 week analysis of two randomized, controlled trials. *AIDS*. 2009;23(17):2289-2300.
- 144.** Vingerhoets J, Tambuyzer L, Azijn H, et al. Resistance profile of etravirine: combined analysis of baseline genotypic and phenotypic data from the

randomized, controlled phase III clinical studies. *AIDS*. 2010;24(4):503-514.

- 145.** Zolopa AR, Berger DS, Lampiris H, et al. Activity of elvitegravir, a once-daily integrase inhibitor, against resistant HIV type 1: results of a phase 2, randomized, controlled, dose-ranging clinical trial. *J Infect Dis*. 2010;201(6):814-822.
- 146.** Molina JM, Lamarca A, Andrade-Villanueva J, et al; Study 145 Team. Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study. *Lancet Infect Dis*. 2012;12(1):27-35.
- 147.** Cahn P, Pozniak AL, Mingrone H, et al; Extended SAILING Study Team. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naïve adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. *Lancet*. 2013;382(9893):700-708.
- 148.** Eron JJ, Clotet B, Durant J, et al; VIKING Study Group. Safety and efficacy of dolutegravir in treatment-experienced subjects with raltegravir-resistant HIV type 1 infection: 24-week results of the VIKING Study. *J Infect Dis*. 2013;207(5):740-748.
- 149.** Castagna A, Maggiolo F, Penco G, et al; for the VIKING-3 Study Group. Dolutegravir in antiretroviral-experienced patients with raltegravir-and/or elvitegravir-resistant HIV-1: 24-week results of the phase III VIKING-3 study [published ahead of print February 23, 2014]. *J Infect Dis*. doi:10.1093/infdis/jiu051.
- 150.** Hardy WD, Gulick RM, Mayer H, et al. Two-year safety and virologic efficacy of maraviroc in treatment-experienced patients with CCR5-tropic HIV-1 infection: 96-week combined analysis of MOTIVATE 1 and 2. *J Acquir Immune Defic Syndr*. 2010;55(5):558-564.
- 151.** Tashima K, Smeaton L, Andrade A, et al. Omitting NRTI from ARV regimens is not inferior to adding NRTI in treatment-experienced HIV+ subjects failing a protease inhibitor regimen: the ACTG OPTIONS study. Presented at: 20th Conference on Retroviruses and Opportunistic Infections; March 3-6, 2013; Atlanta, GA.
- 152.** Wohl DA, Bhatti L, Small CB, et al. Simplification to abacavir/lamivudine + atazanavir maintains viral suppression and improves bone and renal biomarkers in ASSURE, a randomized, open label, non-inferiority trial. *PLoS One*. 2014;9(5):e96187.
- 153.** Masiá M, Martínez E, Padilla S, Gatell JM, Gutiérrez F. Endothelial function in HIV-infected patients switching from a boosted protease inhibitor-based regimen to raltegravir: a substudy

of the SPIRAL study. *J Antimicrob Chemother*. 2013;68(2):409-413.

- 154.** Curran A, Martinez E, Saumoy M, et al. Body composition changes after switching from protease inhibitors to raltegravir: SPIRAL-LIP substudy. *AIDS*. 2012;26(4):475-481.
- 155.** Martínez E, D'Albuquerque PM, Llibre JM, et al; SPIRAL Trial Group. Changes in cardiovascular biomarkers in HIV-infected patients switching from ritonavir-boosted protease inhibitors to raltegravir. *AIDS*. 2012;26(18):2315-2326.
- 156.** Eron JJ, Young B, Cooper DA, et al; SWITCHMRK 1 and 2 Investigators. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. *Lancet*. 2010;375(9712):396-407.
- 157.** Mills AM, Cohen C, Dejesus E, et al. Efficacy and safety 48 weeks after switching from efavirenz to rilpivirine using emtricitabine/tenofovir disoproxil fumarate-based single-tablet regimens. *HIV Clin Trials*. 2013;14(5):216-223.
- 158.** Mills A, Crofoot G, Ortiz R, et al. Switching from twice-daily raltegravir plus tenofovir disoproxil fumarate/emtricitabine to once-daily elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate in virologically suppressed, HIV-1-infected subjects: 48 weeks data. *HIV Clin Trials*. 2014;15(2):51-56.
- 159.** Arribas JR, Pialoux G, Di Perri G, et al. Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results of a randomised, open-label, phase 3b, non-inferiority trial. *Lancet Infect Dis*. 2014;14(7):581-589.
- 160.** Pozniak A, Markowitz M, Mills A, et al. Switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of non-nucleoside reverse transcriptase inhibitor with emtricitabine and tenofovir in virologically suppressed adults with HIV (STRATEGY-NNRTI): 48 week results of a randomised, open-label, phase 3b non-inferiority trial. *Lancet Infect Dis*. 2014;14(7):590-599.
- 161.** Palella FJ Jr, Fisher M, Tebas P, et al. Simplification to rilpivirine/emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial of HIV-1 RNA-suppressed participants. *AIDS*. 2014;28(3):335-344.
- 162.** Ghosn J, Slama L, Chermak A, et al; RADAR Study Group. Switching to darunavir/ritonavir

800/100 mg once-daily containing regimen maintains virological control in fully suppressed pre-treated patients infected with HIV-1. *J Med Virol*. 2013;85(1):8-15.

- 163.** Reina E, San Miguel R, Larrea N, Garcia P, Napal V. Potential for simplification of HIV treatment with boosted protease inhibitor monotherapy. *Int J Clin Pharm*. 2012;34(6):911-916.
- 164.** Guiguet M, Ghosn J, Duvivier C, et al; FHDH-ANRS CO4. Boosted protease inhibitor monotherapy as a maintenance strategy: an observational study. *AIDS*. 2012;26(18):2345-2350.
- 165.** Lambert-Niclot S, Flandre P, Valantin MA, et al. Factors associated with virological failure in HIV-1-infected patients receiving darunavir/ritonavir monotherapy. *J Infect Dis*. 2011;204(8):1211-1216.
- 166.** Mathis S, Khanlari B, Pulido F, et al. Effectiveness of protease inhibitor monotherapy versus combination antiretroviral maintenance therapy: a meta-analysis. *PLoS One*. 2011;6(7):e22003.
- 167.** Paton N, Stohr W, Arenas-Pinto A, Dunn D, et al; PIVOT Trial Group. Randomised controlled trial of a PI monotherapy switch strategy for long-term HIV management [Abstract 550LB]. *Top Antivir Med*. 2014;22(e-1):266-267.
- 168.** Gutmann C, Cusini A, Günthard HF, et al; Swiss HIV Cohort Study (SHCS). Randomized controlled study demonstrating failure of LPV/r monotherapy in HIV: the role of compartment and CD4-nadir. *AIDS*. 2010;24(15):2347-2354.
- 169.** UNAIDS. Epidemiology publications. <http://www.unaids.org/en/dataanalysis/knowyourepidemic/epidemiologypublications/>. Accessed March 25, 2014.
- 170.** Avila D, Althoff KN, Mugglin C, et al; IeDEA and ART Cohort Collaborations. Immunodeficiency at the start of combination antiretroviral therapy in low-, middle-, and high-income countries. *J Acquir Immune Defic Syndr*. 2014;65(1):e8-e16.
- 171.** Volz EM, Ionides E, Romero-Severson EO, Brandt MG, Mokotoff E, Koopman JS. HIV-1 transmission during early infection in men who have sex with men: a phylogenetic analysis. *PLoS Med*. 2013;10(12):e1001568.
- 172.** Brenner BG, Roger M, Stephens D, et al; Montreal PHI Cohort Study Group. Transmission clustering drives the onward spread of the HIV epidemic among men who have sex with men in Quebec. *J Infect Dis*. 2011;204(7):1115-1119.
- 173.** Drescher SM, von Wyl V, Yang WL, et al; Swiss HIV Cohort Study. Treatment-naïve individuals are the major source of transmitted HIV-1 drug resistance in men who have sex with men in the Swiss HIV Cohort Study. *Clin Infect Dis*. 2014;58(2):285-294.