Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Downloaded from http://aidsinfo.nih.gov/guidelines on 3/17/2013

What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient (Last updated February 12, 2013; last reviewed February 12, 2013)

Panel's Recommendations

- The Panel recommends the following as preferred regimens (listed in order of FDA approval) for antiretroviral (ARV)-naive patients:
  - efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC) **(AI)**
  - ritonavir-boosted atazanavir + tenofovir disoproxil fumarate/emtricitabine (ATV/r + TDF/FTC) **(AI)**
  - ritonavir-boosted darunavir + tenofovir disoproxil fumarate/emtricitabine (DRV/r + TDF/FTC) **(AI)**
  - raltegravir + tenofovir disoproxil fumarate/emtricitabine (RAL + TDF/FTC) **(AI)**
- Panel-recommended alternative and other regimens can be found in Table 5a and Table 5b.
- Selection of a regimen should be individualized on the basis of virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and comorbid conditions.
- Based on individual patient characteristics and needs, in some instances, an alternative or other regimen may be a preferred regimen for a specific patient.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

More than 20 approved antiretroviral (ARV) drugs in 6 mechanistic classes are available to design combination regimens. These 6 classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), CCR5 antagonists, and integrase strand transfer inhibitors (INSTIs).

An initial ARV regimen generally consists of two NRTIs in combination with an NNRTI, a PI (preferably boosted with ritonavir [RTV]), an INSTI, or a CCR5 antagonist (namely maraviroc [MVC]). In clinical trials, NNRTI-, PI-, INSTI-, or CCR5 antagonist-based regimens have all resulted in HIV RNA decreases and CD4 cell increases in a large majority of patients.[1-7]

Data Used for Making Recommendations

The Panel's recommendations are primarily based on clinical trial data published in peer-reviewed journals and data prepared by manufacturers for Food and Drug Administration (FDA) review. In select cases, the Panel considers data presented in abstract format at major scientific meetings. The first criterion for selection of evidence on which to base recommendations is published information from a randomized, prospective clinical trial with an adequate sample size that demonstrates that an ARV regimen has shown durable viral suppression and immunologic enhancement (as evidenced by increase in CD4 count). Few of these trials include clinical endpoints, such as development of AIDS-defining illness or death. Thus, assessment of regimen efficacy and potency is primarily based on surrogate marker endpoints (HIV RNA and CD4 responses).

The Panel reviewed data from randomized clinical trials and other reports to arrive at "preferred," "alternative," or "other" ratings for each regimen noted in Tables 5a and 5b. "Preferred regimens" are those regimens studied in randomized controlled trials and shown to have optimal and durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use. "Alternative regimens" are those regimens that are effective but have potential disadvantages when compared with preferred regimens. In certain situations and based on individual patient characteristics and needs, a regimen listed as an alternative may actually be the preferred regimen for a specific patient. Some regimens are classified as "other regimens" because of reduced virologic activity, lack of efficacy data from large clinical trials, or other factors (such as greater

toxicities, pill burden, drug interaction potential, or need for additional testing before use) when compared with preferred or alternative regimens.

Considerations When Selecting a First Antiretroviral Regimen for Antiretroviral Therapy-Naive Patients

Factors to Consider When Selecting an Initial Regimen

Regimen selection should be individualized on the basis of several factors, including the following:

- the patient's comorbid conditions (e.g., cardiovascular disease [CVD], chemical dependency, liver or renal disease, psychiatric illnesses, or tuberculosis [TB]);
- potential adverse drug effects;
- known or potential drug interactions with other medications;
- pregnancy or pregnancy potential;
- results of genotypic drug-resistance testing;
- pre-treatment HIV viral load;
- gender and pretreatment CD4 count if considering nevirapine (NVP);
- HLA-B*5701 testing if considering abacavir (ABC);
- coreceptor tropism assay if considering MVC;
- patient preferences (when possible) and adherence potential; and
- convenience (e.g., factors such as pill burden, dosing frequency, availability of fixed dose combination products, and food and fluid requirements).

Potential advantages and disadvantages of the components recommended as initial therapy for ARV-naive patients are listed in Table 6 to guide prescribers in choosing the optimal regimen for an individual patient. Table 7 provides a list of agents or components not recommended for initial treatment. Appendix B, Tables 1–6 list characteristics of individual ARV agents, such as formulations, dosing recommendations, pharmacokinetics (PKs), and common adverse effects. Appendix B, Table 7 provides clinicians with ARV dosing recommendations for patients who have renal or hepatic insufficiency.

Choosing Between Preferred Initial Regimens

Each of the four preferred initial regimens listed in Table 5a has shown potent virologic efficacy as measured by the proportion of subjects achieving and maintaining viral suppression in comparative clinical trials. Given the comparable efficacy of the preferred regimens, selection of an optimal regimen for a specific patient will depend on other factors, including characteristics of the regimen (e.g., adverse event profile, barrier to resistance, dosing frequency, pill burden, food restrictions, the availability of fixed-dose combination formulations, the potential for drug-drug interactions), the patient's pre-treatment resistance testing results, and whether the patient is a woman who may become pregnant. A complete description of the advantages and disadvantages of the preferred and alternative options for therapy are listed in Table 6.

Currently, all of the preferred initial regimens include the NRTI combination of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), which is available as a fixed-dose combination tablet. In two comparative clinical trials, this NRTI combination was more effective than the alternative NRTI pair, abacavir/lamivudine (ABC/3TC),[8, 9] but in a third study, the NRTI combinations showed comparable efficacy.[10] TDF may cause kidney injury in some patients, particularly in those who have pre-existing renal disease or are receiving concomitant nephrotoxic drugs. In addition, TDF induces a greater decline in bone mineral density than other ARV drugs.[11]

Of the four preferred regimens, efavirenz (EFV) in combination with TDF/FTC has been studied in the greatest number of clinical trials.[6, 12-15] This regimen is available in a single tablet, once-daily formulation, and is generally well tolerated. Disadvantages of the regimen include central nervous system (CNS) side effects that resolve over time in some (but not all) patients, a higher incidence of rash (including severe skin reactions) than with other preferred regimens, and dyslipidemia. Owing to concerns related to potential teratogenicity emerging from animal studies and some human case reports, ARV regimens that do not include EFV should be strongly considered in women who wish to conceive or are sexually active and not using effective contraception, assuming these alternative regimens are not thought to compromise the woman's health.

Initial treatment with ritonavir (RTV) boosted PI-containing regimens is unique from the resistance perspective, as virologic failure rarely selects for PI-resistance and NRTI resistance is uncommon. As a result, some clinicians consider these the initial regimens of choice for patients at higher risk for virologic failure due to suboptimal adherence, inconsistent follow-up, or other factors. A disadvantage of RTV-boosted PI-based regimens is the large number of drug-drug interactions, in particular with medications metabolized through the cytochrome p450 pathway. As a result, RTV-boosted PI-based regimens may be difficult to use in patients who are taking many other medications.

RTV-boosted atazanavir (ATV/r) is as effective as EFV, but causes less rash and has a more favorable lipid profile.[13] ATV induces reversible indirect hyperbilirubinemia, which may result in visible jaundice or scleral icterus in a small proportion of patients; ATV has also been associated with nephrolithiasis and cholelithiasis. Optimal absorption of ATV depends on presence of food and low gastric pH; if acid-reducing agents are needed, co-administration should be done according to the dosing guidelines shown in Table 15a. RTV-boosted darunavir (DRV/r) shares many of the characteristics of boosted ATV, but does not cause hyperbilirubinemia and can be given with acid-reducing agents. There are no fully-powered clinical trials that compare the virologic efficacy of DRV/r and ATV/r. One small study found that these boosted-PIs had comparable effects on lipids.[16] Both ATV/r and DRV/r can be given once daily.

Raltegravir (RAL) plus TDF/FTC demonstrated comparable antiviral efficacy to EFV/TDF/FTC, with fewer drug-related adverse effects and a more favorable lipid profile.[6] RAL has fewer drug-drug interactions than both boosted-PI and EFV-based regimens, and is therefore easier to add to a patient's complex medication regimen. Rare but severe side effects (e.g., rhabdomyolysis, severe skin, systemic hypersensitivity reactions) have been reported with RAL. RAL plus TDF/FTC is the only preferred regimen that requires twice-daily dosing.

There are clinical scenarios in which options for initial therapy should be chosen from the list of alternative and other regimens rather than from the preferred list. Tables 5a and 5b provide a list of alternative and other regimens that may be prescribed for select patients. Table 6 lists the advantages and disadvantages of the individual ARV components of the regimens.

Acute symptomatic HIV infection may be diagnosed while an individual is receiving TDF/FTC for pre-exposure prophylaxis (PrEP) (see Acute and Recent [Early] HIV Infection). As with all newly diagnosed cases of HIV-infection, genotype testing should be performed. In most cases, HIV infection in this setting is secondary to suboptimal adherence[17] to the prescribed daily TDF/FTC regimen, hence resistance in the setting of PrEP failure in clinical trials has been uncommon. Pending genotype testing results, a regimen consisting of a boosted PI (ATV/r or DRV/r) plus TDF/FTC **(AIII)** can be initiated. ARV drugs should be modified as needed based on the results of baseline resistance testing.

Table 5a. Preferred and Alternative Antiretroviral Regimens for Antiretroviral Therapy-Naive Patients

A combination antiretroviral therapy (ART) regimen generally consists of two NRTIs plus one active drug from one of the following classes: NNRTI, PI (generally boosted with RTV), INSTI, or a CCR5 antagonist. Selection of a regimen should be individualized on the basis of virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, and the patient's resistance testing results and comorbid conditions. Refer to Table 6 for a list of advantages and disadvantages of the individual ARV agents listed below and to Appendix B, Tables 1–6 for dosing information. The regimens in each category are listed in alphabetical order. For more detailed recommendations on ARV use in HIV-infected pregnant women, refer to the latest perinatal guidelines available at http://aidsinfo.nih.gov/guidelines.

Preferred Regimens

Regimens with optimal and durable efficacy, favorable tolerability and toxicity profile, and ease of use.

The preferred regimens for non-pregnant patients are arranged by chronological order of FDA approval of components other than nucleosides and, thus, by duration of clinical experience.

NNRTI-Based Regimen	Comments
• EFV/TDF/FTC[a] **(AI)**	• **EFV** is teratogenic in non-human primates. A regimen that does not include EFV should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception.
PI-Based Regimens *(in alphabetical order)*	
• ATV/r + TDF/FTC[a] **(AI)**	
• DRV/r (once daily) + TDF/FTC[a] **(AI)**	• **TDF** should be used with caution in patients with renal insufficiency.
INSTI-Based Regimen	
• RAL + TDF/FTC[a] **(AI)**	• **ATV/r should not be used** in patients who require >20 mg omeprazole equivalent per day. Refer to Table 15a for dosing recommendations regarding interactions between ATV/r and acid-lowering agents.

Alternative Regimens

Regimens that are effective and tolerable, but have potential disadvantages when compared with preferred regimens. An alternative regimen may be the preferred regimen for some patients.

NNRTI-Based Regimens *(in alphabetical order)*	Comments
• EFV + ABC/3TC[a] **(BI)**	• **RPV is not recommended** in patients with pretreatment HIV RNA >100,000 copies/mL.
• RPV/TDF/FTC[a] **(BI)**	• Higher rate of virologic failures reported in patients with pre-ART CD4 count <200 cells/mm^3 who are treated with RPV + 2NRTI
• RPV + ABC/3TC[a] **(BIII)**	• Use of PPIs with **RPV** is contraindicated.
PI-Based Regimens *(in alphabetical order)*	
• ATV/r + ABC/3TC[a] **(BI)**	• **ABC should not be used** in patients who test positive for HLA-B*5701.
• DRV/r + ABC/3TC[a] **(BII)**	• Use **ABC** with caution in patients with known high risk of CVD or with pretreatment HIV RNA >100,000 copies/mL (see text).
• FPV/r (once or twice daily) + ABC/3TC[a] or TDF/FTC[a] **(BI)**	
• LPV/r (once or twice daily) + ABC/3TC[a] or TDF/FTC[a] **(BI)**	• **Once-daily LPV/r is not recommended** for use in pregnant women.
INSTI-Based Regimen	
• EVG/COBI/TDF/FTC[a] **(BI)**	• **EVG/COBI/TDF/FTC** should not be started in patients with an estimated CrCl <70 ml/min, and should be changed to an alternative regimen if the patient's CrCl falls below 50 mL/min
• RAL + ABC/3TC[a] **(BIII)**	• **COBI** is a potent CYP 3A inhibitor. It can increase the concentration of other drugs metabolized by this pathway. Refer to Tables 15d and 16c for drug interaction information for concomitantly administered drugs.
	• **EVG/COBI/TDF/FTC** should not be used with other ARV drugs or with nephrotoxic drugs.

[a] 3TC may substitute for FTC or vice versa. The following combinations in the recommended list above are available as coformulated fixed-dose combinations: ABC/3TC, EFV/TDF/FTC, EVG/COBI/TDF/FTC, LPV/r, RPV/TDF/FTC, TDF/FTC, and ZDV/3TC.

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, ARV = antiretroviral, ATV/r = atazanavir/ritonavir, COBI = cobicistat, CrCl = creatinine clearance, CVD = cardiovascular disease, DRV/r = darunavir/ritonavir, EFV = efavirenz, EVG = elvitegravir, FDA = Food and Drug Administration, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, INSTI = integrase strand transfer inhibitor, LPV/r = lopinavir/ritonavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, PPI = proton pump inhibitor, RAL = raltegravir, RPV = rilpivirine, RTV = ritonavir, TDF = tenofovir disoproxil fumarate, ZDV = zidovudine

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Table 5b. Other Antiretroviral Regimens for Antiretroviral Therapy-Naive Patients

Regimens that may be selected for some patients but are less satisfactory than preferred or alternative regimens listed in Table 5a.	

NNRTI-Based Regimen
• EFV + ZDV/3TC[a]
• NVP + (ABC/3TC[a] or TDF/FTC[a] or ZDV/3TC[a])
• RPV + ZDV/3TC[a]
PI-Based Regimens
• (ATV or ATV/r or DRV/r or FPV/r or LPV/r or SQV/r) + ZDV/3TC[a]
• ATV + ABC/3TC[a]
• SQV/r + (ABC/3TC[a] or TDF/FTC[a])
INSTI-Based Regimen
• RAL + ZDV/3TC[a]
CCR5 Antagonist-Based Regimens
• MVC + (ABC/3TC or TDF/FTC or ZDV/3TC[a])
	Comments
	• **NVP** should not be used in patients with moderate to severe hepatic impairment (Child-Pugh B or C).[b]
	• **NVP** should not be used in women with pre-ART CD4 count >250 cells/mm^3 or in men with pre-ART CD4 count >400 cells/mm^3.
	• Use **NVP** and **ABC** together with caution; both can cause HSRs within the first few weeks after initiation of therapy.
	• **ZDV** can cause bone marrow suppression, myopathy, lipoatrophy, and rarely lactic acidosis with hepatic steatosis.
	• **ATV/r** is generally preferred over **unboosted ATV**.
	• Perform tropism testing before initiation of therapy with **MVC**. **MVC** may be considered in patients who have only CCR5-tropic virus.
	• **SQV/r** was associated with PR and QT prolongation in a healthy volunteer study. Baseline ECG is recommended before initiation of **SQV/r**.
	• **SQV/r** is not recommended in patients with:
	  • pretreatment QT interval >450 msec
	  • refractory hypokalemia or hypomagnesemia
	  • concomitant therapy with other drugs that prolong QT interval
	  • complete AV block without implanted pacemaker,
	  • risk of complete AV block

[a] 3TC may be substituted with FTC or vice versa.

[b] Refer to Appendix B, Table 7 for the criteria for Child-Pugh classification.

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, ATV = atazanavir, ATV/r = atazanavir/ritonavir, AV = atrioventricular, DRV/r = darunavir/ritonavir, ECG = electrocardiogram, EFV = efavirenz, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, HSR = hypersensitivity reaction, INSTI = integrase strand transfer inhibitor, LPV/r = lopinavir/ritonavir, msec = millisecond, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL = raltegravir, RPV = rilpivirine, RTV = ritonavir, SQV/r = saquinavir/ritonavir, TDF = tenofovir disoproxil fumarate, ZDV = zidovudine

The discussions below focus on the rationale for the Panel's recommendations, which are based on the efficacy, safety, and other characteristics of different agents within the individual drug classes.

Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens

Summary: Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens

Five NNRTIs (delavirdine [DLV], EFV, etravirine [ETR], NVP, and rilpivirine [RPV]) are currently FDA approved.

NNRTI-based regimens have demonstrated virologic potency and durability. The major disadvantages of currently available NNRTIs involve the prevalence of NNRTI-resistant viral strains in ART-naive patients[18-21] and the NNRTIs' low genetic barrier for the development of resistance. Resistance testing should be performed to guide therapy selection for ART-naive patients (see Drug-Resistance Testing). High level resistance to all NNRTIs (except ETR) may occur with a single mutation; cross resistance is common. ETR has *in vitro* activity against some viruses with mutations that confer resistance to DLV, EFV, and NVP.[22] In RPV-treated patients, the presence of RPV-resistant mutations at virologic failure is common and may confer cross resistance to other NNRTIs including ETR.[14, 23]

The Panel recommends that EFV, RPV, or NVP may be used as part of an initial regimen. EFV is preferred on the basis of its potency (as discussed below). RPV may be used as an alternative NNRTI option in patients with pre-treatment HIV RNA < 100,000 copies/mL; NVP may be another NNRTI option in women with pretreatment CD4 counts ≤250 cells/mm^3 or in men with pretreatment CD4 counts ≤400 cells/mm^3 (see discussions below).

Compared with the other NNRTIs, DLV has the highest dosing frequency (three times daily), the least supportive clinical trial data, and the least antiviral activity. Therefore, DLV is **not recommended** as part of an initial regimen **(BIII)**. ETR at a dose of 200 mg twice daily is approved for use in treatment-experienced patients with virologic failure.[24] In a small, randomized, double-blinded, placebo-controlled trial, ETR 400 mg once daily was compared with EFV 600 mg once daily (both in combination with two NRTIs) in treatment-naive subjects (79 and 78 subjects in the ETR and EFV arms, respectively). Virologic responses were comparable at 48 weeks.[25] However, pending results from larger clinical trials, the panel cannot recommend ETR as initial therapy at this time.

Following is a more detailed discussion of individual NNRTI-based regimens for initial therapy.

Preferred Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens

Efavirenz (EFV). Large randomized, controlled trials and cohort studies of ART-naive patients have demonstrated potent viral suppression in patients treated with EFV plus two NRTIs; a substantial proportion of these patients had HIV RNA <50 copies/mL at up to 7 years of follow-up.[1, 2, 26] Studies that compared EFV-based regimens with other regimens demonstrated that the combination of EFV with two NRTIs was superior or non-inferior virologically to ritonavir-boosted lopinavir (LPV/r),[4] NVP-,[27, 28] RPV-,[14] ATV-,[5] elvitegravir (EVG)-,[15] RAL-,[6] and MVC-based[7] regimens.

EFV can cause CNS adverse effects, such as abnormal dreams, dizziness, headache, and depression, which usually resolve over a few weeks in some (but not all) patients. In animal reproductive studies, EFV at drug exposure levels similar to those achieved in humans caused major congenital anomalies in the CNS of nonhuman primates.[29] In humans, several cases of neural tube defects in newborns of mothers exposed to EFV during the first trimester of pregnancy have been reported.[30, 31] Although emerging information about the use of EFV in pregnancy is reassuring,[32, 33] data remain insufficient to rule out a potential 2 to 3 fold increase in neural tube birth defects with first-trimester exposure to EFV. Therefore, alternative ARV regimens that do not include EFV should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception, assuming these alternative regimens are acceptable to the provider and are not thought to compromise the woman's health. Because the risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy (before pregnancy is usually recognized), and because unnecessary ARV changes during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission, EFV can be continued in pregnant women receiving an EFV-based regimen who present for antenatal care in the first trimester, provided the regimen produces virologic suppression.[34]

In studies using EFV and dual-NRTI combinations (ABC, didanosine [ddI], stavudine [d4T], TDF, or zidovudine [ZDV] together with FTC or 3TC), the regimens show durable virologic activity, although responses vary depending on the dual-NRTI combination chosen (see Dual-Nucleoside Reverse Transcriptase Inhibitor Options). EFV is formulated both as a single-drug tablet and in a fixed-dose combination tablet of EFV/TDF/FTC that allows for once daily dosing. EFV/TDF/FTC is currently a preferred initial treatment regimen **(AI)**.

Alternative Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens

Rilpivirine (RPV). In two large, multinational, randomized, double-blind clinical trials, RPV (25 mg once daily) was compared with EFV (600 mg once daily), each agent in combination with two NRTIs. In a pooled

analysis of the 2 studies, 76% of RPV-treated subjects and 77% of EFV-treated subjects had plasma HIV RNA <50 copies/mL at 96 weeks.[23] Although RPV demonstrated non-inferiority to EFV overall, in participants with higher pretreatment HIV RNA (>100,000 copies/mL), virologic failure occurred more frequently in those randomized to receive RPV. Moreover, more subjects with pre-treatment CD4 count <200 cells/mm^3, regardless of baseline HIV RNA, experienced virologic failure than those with pre-ART CD4 count ≥200 cells/mm^3. Subjects with virologic failure on RPV were also more likely to have genotypic resistance to other NNRTIs (i.e., EFV, ETR, and NVP) and to have TDF- and/or 3TC/FTC-associated genotypic resistance.

Drug discontinuations because of adverse effects were more common with EFV than with RPV. The frequency of depressive disorders and discontinuations due to depressive disorders were similar between the two arms, whereas dizziness, abnormal dreams, rash, and hyperlipidemia were more frequent with EFV than with RPV.

At higher than the approved dose of 25 mg, RPV (75 mg once daily or 300 mg once daily) may prolong the QTc interval. As a result, RPV should be used cautiously when co-administered with a drug that has a known risk of torsades de pointes. Although RPV has shown no teratogenicity in animal studies, data on PKs and safety of RPV in pregnant HIV-infected women are insufficient at this time.

RPV is formulated both as an individual tablet and in a fixed-dose combination tablet of RPV/TDF/FTC. The latter allows for one-tablet once-daily dosing. RPV must be administered with a meal. Because the oral bioavailability of RPV may be significantly reduced in the presence of acid-lowering agents, RPV should be used with caution with antacids and H2-receptor antagonists. RPV use with proton pump inhibitors (PPIs) is contraindicated. Table 15b provides guidance on the timing of RPV administration when the agent is used with antacids or H2 receptor antagonists.

In patients with high pretreatment viral load (HIV RNA >100,000 copies/mL) or low CD4 cell count (<200 cells/mm^3), RPV has less virologic activity and a higher rate of resistance at virologic failure than EFV. The panel recommends RPV/TDF/FTC as an alternative regimen for initial therapy, which should only be used in patients with pre-treatment HIV RNA < 100,000 copies/mL **(BI)**. RPV should not be used in patients with plasma HIV RNA >100,000 copies/mL.

Other Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens

Nevirapine (NVP). The 2NN trial compared NVP with EFV, both given d4T and 3TC, in ART-naive patients. In this trial, 65% of participants in the twice-daily NVP arm and 70% in the EFV arm achieved virologic suppression (defined as HIV RNA <50 copies/mL) at 48 weeks. This difference did not reach criteria necessary to demonstrate non-inferiority of NVP.[27] Two deaths were attributed to NVP use: one from fulminant hepatitis and one from staphylococcal sepsis as a complication of Stevens-Johnson syndrome (SJS).

In the ARTEN trial, ART-naive participants were randomized to NVP 200 mg twice daily or 400 mg once daily, or to RTV-boosted ATV (ATV/r), all in combination with TDF/FTC. The proportion of participants in each arm who achieved the primary endpoint of having at least two consecutive plasma HIV RNA levels <50 copies/mL before Week 48 was similar (66.8% of NVP participants vs. 65.3% of ATV/r participants). However, more participants in the NVP arms than in the ATV/r arm discontinued study drugs before Week 48 because of adverse events (13.6% on NVP vs. 2.6% on ATV/r) or lack of efficacy (8.4% on NVP vs. 1.6% on ATV/r). NNRTI- and/or NRTI-resistance mutations were selected in 29 of 44 (65.9%) participants who experienced virologic failure while on NVP, whereas resistance mutations were not detected in any of the 28 participants who had virologic failure on ATV/r.[35]

Serious hepatic events have been observed when NVP was initiated in ART-naive patients. These events generally occur within the first few weeks of treatment. In addition to experiencing elevated serum

transaminases, approximately half of the patients also develop skin rash, with or without fever or flu-like symptoms. Some events, particularly those with rash and other systemic symptoms, have progressed to liver failure. Retrospective analysis of reported events suggests that women with higher CD4 counts appear to be at highest risk for serious hepatic events.[36, 37] A 12-fold higher incidence of symptomatic hepatic events was seen in women with CD4 counts >250 cells/mm^3 at the time of NVP initiation than in women with CD4 counts ≤250 cells/mm^3 at NVP initiation (11.0% vs. 0.9%, respectively). The risk was also greater in men with pre-treatment CD4 counts >400 cells/mm^3 than in with men with pre-treatment CD4 counts ≤400 cells/mm^3 (6.3% vs. 1.2%, respectively). Most of these patients had no identifiable underlying hepatic abnormalities. In some cases, hepatic injuries continued to progress despite discontinuation of NVP.[37, 38] In contrast, other studies have not shown an association between baseline CD4 counts and severe NVP hepatotoxicity.[39, 40] Symptomatic hepatic events have not been reported in mothers or infants given single-dose NVP to prevent perinatal HIV infection.

On the basis of the safety and efficacy data discussed above, the Panel classifies NVP-based combinations in the Other NNRTI-Based Regimens category as initial therapy in women with pretreatment CD4 counts ≤250 cells/mm^3 or in men with pretreatment CD4 counts ≤400 cells/mm^3 **(C)**. Patients whose CD4 count increases to levels above these thresholds as a result of NVP-containing therapy can safely continue therapy without an increased risk of adverse hepatic events.[41]

NVP should be initiated at a dosage of 200 mg once daily for a 14-day lead-in period before being increased to the maintenance dosage of 400 mg per day (as an extended-release 400 mg tablet once daily or 200 mg immediate-release tablet twice daily). The lead-in period has been observed to decrease the incidence of rash. Some experts recommend monitoring serum transaminases at baseline, at 2 weeks, again 2 weeks after dose escalation, and then monthly for the first 18 weeks. Clinical and laboratory parameters should be assessed at each patient visit.

Protease Inhibitor-Based Regimens

Summary: Protease Inhibitor-Based Regimens

PI-based regimens (particularly with RTV-boosting) have demonstrated virologic potency and durability in treatment-naive subjects. In contrast to NNRTI- and INSTI-based regimens, few or no PI mutations are detected in patients who developed virologic failure on their first PI-based regimen.[35, 42] Each PI has its own virologic potency, adverse effect profile, and pharmacokinetic (PK) properties. The characteristics, advantages, and disadvantages of each PI are listed in Table 6 and Appendix B, Table 3. When selecting a boosted PI-based regimen for an ART-naive patient, clinicians should consider factors such as dosing frequency, food requirements, pill burden, daily RTV dose, drug interaction potential, toxicity profile of the individual PI, and baseline lipid profile and pregnancy status of the patient. See the *Perinatal Guidelines* for specific recommendations in pregnancy.[34]

A number of metabolic abnormalities, including dyslipidemia and insulin resistance, have been associated with PI use. The currently available PIs differ in their propensity to cause these metabolic complications, which also depends on the dose of RTV used as a PK boosting agent. Two large observational cohort studies suggest that LPV/r, indinavir (IDV), fosamprenavir (FPV), or RTV-boosted FPV (FPV/r) may be associated with increased rates of myocardial infarction (MI) or stroke.[43, 44] This association was not seen with ATV.[45] These studies had too few patients receiving DRV/r to be included in the analysis.

RTV-boosted saquinavir (SQV/r) can prolong the PR and QT intervals on electrocardiogram (ECG). The degree of QT prolongation seen with SQV/r is greater than that seen with some other boosted PIs. Therefore, SQV/r should be used with caution in patients with underlying heart conditions such as heart rate or rhythm problems, or who use concomitant drugs that may increase the risk of developing these ECG abnormalities.[46] SQV/r is rarely used for initial therapy for this reason, and because, when compared with other PI-based

regimens, the regimen has a higher pill burden and no clear advantages.

The potent inhibitory effect of RTV on the cytochrome P (CYP) 450 3A isoenzyme allows the addition of low-dose RTV to other PIs as a PK enhancer to increase drug exposure and prolong the plasma half-life of the active PI. The drawbacks associated with this strategy are the potential for increased risk of hyperlipidemia and a greater potential of drug-drug interactions from the addition of RTV. RTV boosting is recommended in all PI-based regimens whenever possible; when boosting is not possible and a PI-based regimen is desired, only ATV should be used. In patients without pre-existing PI resistance, once-daily boosted PI regimens that use only 100 mg of RTV per day are preferred. These regimens tend to cause fewer gastrointestinal (GI) side effects and less metabolic toxicity than regimens that use RTV at a dose of 200 mg per day.

The Panel uses the following criteria to distinguish between preferred, alternative, and other PIs for use in ART-naive patients:

- Demonstrated superior or non-inferior virologic efficacy when compared with at least one other PI-based regimen, based on, at least, published 48-week data
- RTV-boosted PI using no more than 100 mg of RTV per day
- Once-daily dosing
- Low pill count
- Good tolerability.

Using these criteria, the Panel recommends once-daily ATV/r and DRV/r as preferred PIs.

Preferred Protease Inhibitor-Based Regimens

In alphabetical order, by active PI component

Ritonavir-Boosted Atazanavir (ATV/r). In a clinical trial, ATV/r enhanced ATV concentrations and improved virologic activity more than unboosted ATV.[47] The CASTLE study compared once-daily ATV/r with twice-daily LPV/r, each in combination with TDF/FTC, in 883 ARV-naive participants. In this open-label, noninferiority study, the two regimens showed similar virologic and CD4 responses at 48 weeks[48] and at 96 weeks.[49] More hyperbilirubinemia and less GI toxicity were seen in the ATV/r arm than in the LPV/r arm. This study supports the designation of ATV/r + TDF/FTC as a preferred PI-based regimen **(AI)**.

The main adverse effect associated with ATV/r is indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. Nephrolithiasis[50-52] and cholelithiasis[53] also have been reported in patients who received ATV. ATV/r requires acidic gastric pH for dissolution. Thus, concomitant use of drugs that raise gastric pH (e.g., antacids, H2 antagonists, and particularly PPIs), may impair absorption of ATV. Table 15a provides recommendations for use of ATV/r with these agents.

Ritonavir-Boosted Darunavir (DRV/r). The ARTEMIS study compared DRV/r (800/100 mg once daily) with LPV/r (once or twice daily), both in combination with TDF/FTC, in a randomized, open-label, non-inferiority trial. The study enrolled 689 ART-naive participants. DRV/r was non-inferior to LPV/r at 48 weeks[54], and superior at week 192.[55] In participants with baseline HIV RNA levels >100,000 copies/mL, virologic response rates were lower in the LPV/r arm than in the DRV/r arm. Grades 2 to 4 adverse events, primarily diarrhea, were seen more frequently in LPV/r recipients than in DRV/r recipients. At virologic failure, no major PI mutations were detected in participants randomized to either arm.[42, 55] Based on these data, the Panel recommends DRV/r + TDF/FTC as a preferred PI-based regimen **(AI)**. No randomized controlled trial to evaluate the efficacy of DRV/r with other 2-NRTI combinations exists. A small

retrospective study suggested that DRV/r plus ABC/3TC may be effective in treatment-naive patients for up to 48 weeks.[56] Based on this preliminary information, the Panel recommends this combination as an alternative PI-based regimen **(BIII)**.

Alternative Protease Inhibitor-Based Regimens

In alphabetical order, by active PI component

Ritonavir-Boosted Fosamprenavir (FPV/r, once or twice daily). FPV/r is an alternative PI. The KLEAN trial compared twice-daily FPV/r with LPV/r, each in combination with ABC and 3TC, in ART-naive patients. At Weeks 48 and 144, similar percentages of subjects achieved viral loads <400 copies/mL.[57, 58] The frequency and severity of adverse events did not differ between the regimens. Twice-daily FPV/r was non-inferior to twice-daily LPV/r. Based on the preference for once-daily regimens with no more than 100 mg/day of RTV, twice-daily FPV is considered an alternative choice.

A comparative trial of once-daily FPV/r (1400/100 mg) and once-daily ATV/r, both in combination with TDF/FTC, was conducted in 106 ARV-naive participants.[59] The regimens showed similar virologic and CD4 benefits. The study's small sample size precludes the assessment of superior or non-inferior virologic efficacy required for a preferred PI. Collectively, FPV/r regimens, with once- or twice-daily dosing, are recommended as alternative PI-based regimens.

Ritonavir-Boosted Lopinavir (LPV/r, coformulated). LPV/r is the only available coformulated boosted PI. It can be given once or twice daily. However, because LPV/r must be boosted with 200 mg/day of RTV and is associated with higher rates of GI side effects and hyperlipidemia than other PIs boosted with 100 mg of RTV, LPV/r is recommended as an alternative PI for ART-naive patients. A 7-year follow-up study of LPV/r and 2 NRTIs showed sustained virologic suppression in patients who were maintained on the originally assigned regimen.[60] Results of clinical trials that compared LPV/r with ATV/r, DRV/r, FPV/r, or SQV/r are discussed in the related sections of this document. The ACTG 5142 study showed that, when compared with EFV plus 2 NRTIs, the regimen of twice-daily LPV/r plus 2 NRTIs had decreased virologic efficacy. However, the CD4 response was greater with LPV/r, and there was less drug resistance associated with virologic failure.[4]

In addition to diarrhea, major adverse effects of LPV/r include insulin resistance and hyperlipidemia, especially hypertriglyceridemia; these required pharmacologic management in some patients. In the D:A:D and French observational cohorts, cumulative use of LPV/r was associated with a slightly increased risk of MI.[43, 44] Once-daily LPV/r should not be used in patients who have HIV mutations associated with PI resistance, because higher LPV trough levels may be required to suppress resistant virus. Once-daily dosing should not be used in pregnant women, especially during the third trimester, when LPV levels are expected to decline. For more detailed information regarding ART drug choices and related issues in pregnancy, see the *Perinatal Guidelines*.[34]

Other Protease Inhibitor-Based Regimens

Atazanavir (ATV). In a clinical trial, ATV concentrations were enhanced with the addition of RTV 100 mg when compared to once-daily unboosted ATV, as a result, better virologic activity was seen with ATV/r.[47] Nevertheless, unboosted ATV may be selected for some patients because it has fewer GI adverse effects including less hyperbilirubinemia and less impact on lipid profiles than ATV/r. Three studies compared unboosted ATV-based combination regimens with either NFV- or EFV-based regimens. These studies established that ATV 400 mg once daily and both comparator treatments had similar virologic efficacy in ARV-naive patients after 48 weeks of therapy.[5, 47, 61, 62] In a multinational randomized trial comparing three initial treatment strategies, unboosted ATV + ddI + FTC was inferior to both EFV + TDF/FTC and EFV + ZDV/3TC.[63]

Unboosted ATV may be used as initial therapy when a once-daily regimen without RTV is desired and in patients with underlying risk factors that indicate that hyperlipidemia may be particularly undesirable **(C)**. However, in these situations, other NNRTI- and INSTI-based regimens should generally be used instead of unboosted ATV. When ATV is co-administered with TDF or EFV, it should be boosted with RTV because ATV concentrations are reduced in the presence of these drugs. ATV requires acidic gastric pH for dissolution. Thus, concomitant use of drugs that raise gastric pH (such as antacids, H2 antagonists, and PPIs) may significantly impair ATV absorption. PPIs should not be used in patients who are taking unboosted ATV. H2 antagonists and antacids should be used with caution and with careful dose separation (see Tables 14 and 15a).

Ritonavir-Boosted Saquinavir (SQV/r). The GEMINI study compared SQV/r (1000/100 mg twice daily) and LPV/r, both given twice daily, in combination with TDF/FTC given once daily, in 337 ART-naive participants who were monitored over 48 weeks. Levels of viral suppression and increases in CD4 counts were similar in both arms of the study.[64] Triglyceride (TG) levels were higher in the LPV/r arm than in the SQV/r arm. The SQV/r regimen has a higher pill burden and requires twice-daily dosing and 200 mg of RTV. In a healthy volunteer study, SQV/r use at the recommended dose was associated with increases in both QT and PR intervals. The degree of QT prolongation with SQV/r was greater than that seen with some other boosted PIs used at their recommended doses. Rare cases of torsades de pointes and complete heart block have been reported in post-marketing surveillance. Based on these findings, an ECG before initiation of SQV/r is recommended. SQV/r is not recommended for patients with any of the following conditions: documented congenital or acquired QT prolongation, pretreatment QT interval of >450 milliseconds (msec), refractory hypokalemia or hypomagnesemia, complete atrioventricular (AV) block without implanted pacemakers, at risk of complete AV block, or receiving other drugs that prolong QT interval.[46] On the basis of these restrictions, and because several other preferred or alternative PI options are available, the Panel recommends that, although SQV/r may be acceptable, it should be used with caution in select ARV-naive patients **(C)**.

Integrase Strand Transfer Inhibitor (INSTI)-Based Regimens

Preferred Integrase Strand Transfer Inhibitor-Based Regimen

Raltegravir (RAL). RAL is an INSTI that is approved for use in ART-naive patients on the basis of results of STARTMRK, a Phase III study that compared RAL (400 mg twice daily) and EFV (600 mg once daily), each in combination with TDF/FTC, in ART-naive subjects. This multinational, double-blind, placebo-controlled study enrolled 563 subjects with plasma viral loads >5,000 copies/mL. At Week 48, similar percentages of subjects in both groups achieved viral loads <50 copies/mL (86.1% and 81.9% for RAL and EFV, respectively, P <0.001 for non-inferiority). CD4 counts rose by 189 cells/mm^3 in the RAL group and 163 cells/mm^3 in the EFV group. The frequency of serious adverse events was similar in both groups.[6] At 156 weeks, virologic and immunologic responses remained similar in both groups with no new safety concerns identified.[65] On the basis of these data, the Panel recommends RAL + TDF/FTC as a preferred regimen in ART-naive patients **(AI)**. In a small single-arm pilot study of 35 subjects who received a regimen of RAL + ABC/3TC, 91% of subjects had viral loads <50 copies/mL at Week 48.[66] On the basis of these preliminary data, RAL + ABC/3TC may be used as an alternative INSTI-based regimen **(BIII)**. RAL use has been associated with creatine kinase elevations. Myositis and rhabdomyolysis have been reported. Rare cases of severe skin reactions and systemic hypersensitivity reactions (HSRs) in patients who received RAL have been reported during post-marketing surveillance.[67]

Comparisons of RAL-based regimens and boosted PI-based regimens in ART-naive subjects have not been reported. RAL must be administered twice daily—a potential disadvantage when comparing RAL-based treatment with some other regimens. RAL, like EFV, has a lower genetic barrier to resistance than RTV-boosted PIs. In the STARTMRK comparative trial, resistance mutations were observed with approximately the same frequency in RAL- and EFV-treated participants.

Alternative Integrase Strand Transfer Inhibitor-Based Regimen

Elvitegravir (EVG). EVG is an INSTI available as a fixed-dose combination product with cobicistat (COBI), TDF, and FTC (EVG/COBI/TDF/FTC), and is approved as a single-tablet, once-daily regimen for ART-naive patients. EVG is metabolized primarily by CYP3A enzymes; as a result, CYP3A inducers or inhibitors may alter EVG concentrations. COBI is a specific, potent CYP3A inhibitor with no activity against HIV. It acts as a PK enhancer of EVG, which allows for once daily dosing of the combination product.[68] EVG/COBI/TDF/FTC is not recommended for patients with pre-treatment estimated creatinine clearance less than 70 mL/min.[69] For more information on PK enhancement with RTV or COBI, see Drug-Drug Interactions—Pharmacokinetic Enhancing.

In two Phase 3 randomized clinical studies, the safety and efficacy of this combination regimen in ART-naive HIV-infected subjects was compared to that of two currently recommended first-line regimens. Co-formulated EVG/COBI/TDF/FTC was non-inferior to co-formulated EFV/TDF/FTC: 87.6% of the EVG/COBI/TDF/FTC-treated subjects versus 84.1% of the EFV/TDF/FTC-treated subjects achieved virologic suppression <50 copies/mL at 48 weeks (difference 3.5%, 95% CI -1.6, 8.8).[15] Similarly, EVG/COBI/TDF/FTC was non-inferior to ATV/r plus co-formulated TDF/FTC: 89.5% versus 86.8% of subjects achieved virologic suppression <50 copies/mL at 48 weeks, respectively (difference 3%, 95% CI -1.9, 7.8).[70] Rates of virologic failure were low and comparable across study arms, with non-inferior results for treatment arms maintained at 96 weeks.[71, 72] At virologic failure, INSTI-associated mutations were detected in some EVG/COBI/TDF/FTC-treated patients who failed therapy.[15, 70] These mutations conferred varying degrees of cross-resistance to RAL. The most common adverse events reported with EVG/COBI/TDF/FTC were diarrhea, nausea, and headache.

COBI inhibits active tubular secretion of creatinine, resulting in increases in serum creatinine and a reduction in estimated creatinine clearance (CrCl) without reducing glomerular function.[73] Although the overall incidence of study drug discontinuation due to adverse events was lower in the EVG/COBI/TDF/FTC arms (3.7%) than in either comparator arm (5.1% each), more subjects in the EVG/COBI/TDF/FTC arms (8 subjects) discontinued study drugs because of renal adverse events than in the comparator arms (one in the ATV/r + TDF/FTC arm). Four of the eight subjects in the EVG/COBI/TDF/FTC arms who discontinued study drug had evidence of proximal tubular dysfunction; after drug discontinuation, abnormal lab values in these four patients improved but did not completely resolve. CrCl, urine glucose and urine protein should be assessed before starting therapy and monitored during therapy. Consideration should be given to periodic monitoring of serum phosphorus in patients at risk for renal impairment. Although COBI may cause modest increases in serum creatinine and modest declines in CrCl, patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg/dL from baseline should be closely monitored and evaluated for evidence of tubulopathy. Proteinuria, normoglycemic glycosuria, and increased fractional excretion of phosphorous may represent the first signs of tubulopathy and precede any decline in renal function. Patients on EVG/COBI/TDF/FTC should be switched to an alternative ARV regimen if estimated CrCl decreases to less than 50 mL/min. Concomitant use of nephrotoxic drugs should be avoided.

In summary, EVG/COBI/FTC/TDF has rates of virologic suppression comparable to two currently preferred regimens. As a co-formulated tablet, it can be given as one tablet, once daily. Limitations of this combination include a possible increased risk of proximal renal tubulopathy in addition to inhibition of active tubular secretion of creatinine, significant drug-drug interactions, limited data in patients with advanced HIV disease and in women, and food requirement. On the basis of these factors, the Panel recommends EVG/COBI/FTC/TDF as an alternative regimen in ART-naive patients **(BI)**.

CCR5 Antagonist-Based Regimens

Maraviroc (MVC). The MERIT study compared the CCR5 antagonist MVC with EFV, both in combination with ZDV/3TC, in a randomized, double-blind trial in ART-naive participants.[7] Only participants who had

CCR5-tropic virus and no evidence of resistance to any drugs used in the study were enrolled (n = 721). At 48 weeks, HIV RNA level <50 copies/mL was observed in 65.3% of MVC recipients and 69.3% of EFV recipients. The HIV RNA <50 copies/mL results did not meet the criteria set by the investigators to demonstrate noninferiority for MVC in this study. CD4 count increased by an average of 170 cells/mm^3 in the MVC arm and by 144 cells/mm^3 in the EFV arm. Through 48 weeks, compared with participants receiving EFV, more participants discontinued MVC because of lack of efficacy (11.9% vs. 4.2%), whereas fewer participants discontinued MVC because of toxicity (4.2% vs. 13.6%). Follow-up results at 96 weeks demonstrated durable responses for both ARVs.[74] In a post-hoc reanalysis using a more sensitive viral tropism assay, 15% of patients with dual/mixed tropic virus at screening virus were excluded from analysis. Their retrospective exclusion resulted in similar virologic suppression in both arms. Because MVC requires twice-daily dosing and requires a tropism assay before use, and experience with regimens other than ZDV/3TC is limited, the Panel recommends MVC + ZDV/3TC as another option for use in ART-naive patients **(CI)**. Although ZDV/3TC was used as the NRTI backbone in the MERIT trial, pending further data, many clinicians favor the combination of MVC with TDF/FTC or ABC/3TC **(CIII)**.

Dual-Nucleoside Reverse Transcriptase Inhibitor Options as Part of Initial Combination Therapy

Summary: Dual-Nucleoside Reverse Transcriptase Inhibitor Components

Dual NRTIs are commonly used in combination with an NNRTI, a PI (usually boosted with RTV), an INSTI, or a CCR5 antagonist. Most dual-NRTI combinations used in clinical practice consist of a primary NRTI plus 3TC or FTC. Both 3TC and FTC have few adverse effects but may select for the M184V resistance mutation, which confers high-level resistance to both drugs; a modest decrease in susceptibility to ddI and ABC; and improved susceptibility to ZDV, d4T, and TDF.[75]

All NRTIs except ddI can be taken with or without food. Adherence may be additionally improved with once-daily dosing (available for all NRTIs except d4T and ZDV) and with fixed-dosage combinations, such as ABC/3TC, TDF/FTC (with or without EFV, RPV, or EVG/COBI), or ZDV/3TC.

The Panel's recommendations on specific dual-NRTI options are made on the basis of virologic potency and durability, short- and long-term toxicities, the propensity to select for resistance mutations, and dosing convenience.

Preferred Dual-Nucleoside Reverse Transcriptase Inhibitors

Tenofovir/Emtricitabine (TDF/FTC, co-formulated). TDF is a nucleotide analog with potent activity against both HIV and hepatitis B virus (HBV) and a long intracellular half-life that allows for once-daily dosing. The fixed-dose combinations of TDF/FTC, EFV/TDF/FTC, RPV/TDF/FTC, and EVG/COBI/TDF/FTC are administered as one tablet, once daily and are designed to improve adherence.

TDF, when used with either 3TC or FTC as part of an EFV-based regimen in ART-naive patients, demonstrated potent virologic suppression[26] and was superior to ZDV/3TC in virologic efficacy up to 144 weeks.[76] In the 934 study, more participants in the ZDV/3TC arm than in the TDF/FTC arm developed loss of limb fat (as assessed by dual-energy x-ray absorptiometry [DXA]) and anemia at 96 and 144 weeks.[76] Emergence of the M184V mutation was less frequent with TDF/FTC than with ZDV/3TC, and by 144 weeks of therapy no participant had developed the K65R mutation. TDF + FTC or 3TC has also been studied in combination with RPV, several boosted PIs, EVG/COBI, and RAL in randomized clinical trials; all trials demonstrate good virologic benefit.[6, 15, 48, 54, 59, 70, 77]

TDF/FTC was compared with ABC/3TC in the ACTG 5202 study[8] and the HEAT trial.[10] In the ACTG 5202 trial, inferior virologic responses were observed in participants randomized to ABC/3TC who had a pre-

treatment HIV RNA >100,000 copies/mL. This was not observed in the HEAT trial or in other trials (see the ABC/3TC section below for more detailed discussion).

Renal impairment, manifested by increases in serum creatinine, proteinuria, glycosuria, hypophosphatemia, proximal renal tubulopathy, and acute tubular necrosis, has been associated with TDF use.[78, 79] Risk factors may include advanced HIV disease, longer treatment history, and pre-existing renal impairment.[80] In the HEAT trial, 15% of subjects receiving TDF/FTC versus 10% of those receiving ABC/3TC progressed to a more advanced stage of chronic kidney disease (CKD) on treatment.[10] Renal function, urinalysis, and electrolytes should be monitored in patients who are on TDF. In patients who have some degree of pre-existing renal insufficiency (CrCl <50 mL/min), TDF dosage adjustment is required (see Appendix B, Table 7 for dosage recommendations). However, in this setting, the use of alternative NRTIs (for example, ABC) may be preferred over dose-adjusted TDF because available dosage adjustment guidelines for renal dysfunction are based on PK studies only and not on safety and efficacy data.

Concomitant use of boosted PIs and COBI can increase TDF concentrations, and studies have suggested a greater risk of renal dysfunction when TDF is used in PI- and COBI-based regimens.[69, 78, 81-84] TDF has been used in combination with PIs without significant renal toxicity in several clinical trials that involved patients who had CrCl >50 mL/min to 60 mL/min.[49, 85] Furthermore, in two randomized studies comparing TDF/FTC with ABC/3TC, participants receiving TDF/FTC experienced a significantly greater decline in bone mineral density than ABC/3TC-treated participants.[11, 86]

TDF plus FTC is the preferred NRTI combination, especially in HIV/HBV-coinfected patients because these drugs have activity against both viruses. The use of a single HBV-active NRTI (e.g., 3TC or FTC) can lead to HBV resistance and is not recommended (see HIV/Hepatitis B Co-infection).

Alternative Dual Nucleoside Reverse Transcriptase Inhibitors

Abacavir/Lamivudine (ABC/3TC, co-formulated) for patients who test negative for HLA-B*5701. In a comparative trial of ABC/3TC and ZDV/3TC (both given twice daily and combined with EFV), participants in both arms achieved similar virologic responses. CD4 T-cell increase at 48 weeks was greater in the ABC-treated participants than in the ZDV-treated participants.[87] The ACTG 5202 study, a randomized controlled trial in more than 1,800 participants, evaluated the efficacy and safety of ABC/3TC and TDF/FTC when used in combination with either EFV or RTV-boosted ATV. Treatment randomization was stratified on the basis of a screening HIV RNA of <100,000 copies/mL or ≥100,000 copies/mL. HLA-B*5701 testing was not required before study entry, which may have influenced the results of the trial with respect to some of the safety and tolerability endpoints. A Data Safety Monitoring Board recommended early termination of the ≥100,000 copies/mL stratification group because of a significantly shorter time to study-defined virologic failure in the ABC/3TC arm than in the TDF/FTC arm.[8] This difference in time to virologic failure between arms was observed regardless of whether the third active drug was EFV or ATV/r. There was no difference between ABC/3TC and TDF/FTC in time to virologic failure for participants who had plasma HIV RNA <100,000 copies/mL at screening.[88]

In the HEAT study, 688 participants received ABC/3TC or TDF/FTC in combination with once-daily LPV/r. A subgroup analysis according to baseline HIV RNA <100,000 copies/mL or ≥100,000 copies/mL yielded similar percentages of participants with HIV RNA <50 copies/mL at 96 weeks in the two regimens (63% vs. 58% in those with HIV RNA <100,000 copies/mL and 56% vs. 58% in those with ≥100,000 copies/mL).[10] The ASSERT study compared open label ABC/3TC with TDF/FTC in 385 HLA-B*5701-negative, ART-naive patients; all study subjects also received EFV. At 48 weeks, the proportion of participants with HIV RNA <50 copies/mL was lower among ABC/3TC-treated subjects (59%) than among TDF/FTC subjects (71%) (difference 11.6%, 95% confidence interval [CI], 2.2–21.1).[9]

Clinically suspected HSRs have been observed in 5% to 8% of patients who start ABC. The risk of this

reaction is highly associated with the presence of the HLA-B*5701 allele (see HLA-B*5701 Screening).[89, 90] HLA-B*5701 testing should precede use of ABC. ABC should not be given to patients who test positive for HLA-B*5701 and, on the basis of test results, ABC hypersensitivity should be noted on the patient's allergy list. Patients who test HLA-B*5701 negative are less likely to experience an HSR, but they should be counseled about the symptoms of the reaction. Patients who discontinue ABC for suspected HSR should never be rechallenged, regardless of HLA-B*5701 status.

An association between ABC use and MI was first reported in the D:A:D study. This large, multinational observational study group found that recent (within 6 months) or current use of ABC, but not TDF, was associated with an increased risk of MI, particularly in participants with pre-existing cardiac risk factors.[43, 91] Since the report of this study, multiple studies have explored this association. Some studies have found an association;[92-95] others have found a weak association or no association.[44, 96-99] Several studies have also been conducted to evaluate potential mechanistic pathways that may underlie the association between ABC use and an increased risk of MI, including endothelial dysfunction, increased platelet reactivity, leukocyte adhesion, inflammation, and hypercoagulability.[100-107] However, to date, no consensus on the association between ABC use and MI risk or the mechanism for such an association has been reached.

The fixed-dose combination of ABC/3TC allows for once-daily dosing. Pending additional data, ABC/3TC should be used with caution in individuals who have plasma HIV RNA levels ≥100,000 copies/mL and in persons at high risk of CVD. However, the combination of ABC/3TC remains an alternative dual-NRTI option for some ART-naive patients **(BI)**.

Other Dual Nucleoside Reverse Transcriptase Inhibitors

Zidovudine/Lamivudine (ZDV/3TC, coformulated). The dual-NRTI combination of ZDV/3TC has extensive durability, safety, and tolerability experience.[3, 5, 108-112] In a multinational, randomized trial comparing three initial treatment strategies, EFV/ZDV/3TC and EFV/TDF/FTC showed similar virologic efficacy; both regimens were superior to ATV/ddI/FTC.[63]

A fixed-dose combination of ZDV/3TC is available for one-tablet, twice-daily dosing. Selection of the 3TC-associated M184V mutation has been associated with increased susceptibility to ZDV. In a comparative trial of ABC/3TC and ZDV/3TC (both given twice daily and combined with EFV), the CD4 count increase was greater in the ABC/3TC-treated patients than in the ZDV/3TC-treated patients,[87] even though virologic responses were similar in both arms.

Bone marrow suppression, manifested by macrocytic anemia and/or neutropenia, is seen in some patients. ZDV also is associated with GI toxicity, fatigue, and possibly mitochondrial toxicity, including lactic acidosis/hepatic steatosis and lipoatrophy. Because ZDV/3TC has greater toxicity than TDF/FTC or ABC/3TC and requires twice-daily dosing, the Panel classifies ZDV/3TC in the Other Dual-NRTI category, rather than as a preferred or alternative, dual-NRTI option **(CI)**.

ZDV/3TC remains as a preferred NRTI option in pregnant women because the two drugs have the most PK, safety, and efficacy data for both mother and newborn of any other ARVs. For more detailed information regarding ARV drug choices and related issues in pregnancy, see the *Perinatal Guidelines*.[34]

Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Hepatitis B Virus (HBV). Three of the currently approved NRTIs—FTC, 3TC, and TDF—have activity against HBV. Most HIV/HBV-coinfected patients should use coformulated TDF/FTC (or TDF + 3TC) as their NRTI backbone to provide additional activity against HBV and to avoid selection of HBV mutation that confers resistance to 3TC and FTC. Importantly, patients who have HIV/HBV coinfection may be at risk of acute exacerbation of hepatitis after initiation or discontinuation of TDF, 3TC, or FTC.[113-115] Thus, these patients should be monitored closely for clinical or chemical hepatitis if these drugs are initiated or discontinued (see HIV/Hepatitis B Coinfection and Initiating Antiretroviral Therapy).

Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 1 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
NNRTIs (in alphabetical order)		**NNRTI Class Advantages:** • Long half-lives	**NNRTI Class Disadvantages:** • Greater risk of resistance at the time of treatment failure than with PIs • Potential for cross resistance • Skin rash • Potential for CYP450 drug interactions (see Tables 14, 15b, and 16b) • Transmitted resistance more common than with PIs.
	EFV	• Virologic responses non-inferior or superior to most comparators to date • Once-daily dosing • Coformulated with TDF/FTC	• Neuropsychiatric side effects • Teratogenic in nonhuman primates. Several cases of neural tube defect in infants born to women who were exposed to EFV in the first trimester of pregnancy have been reported. • Dyslipidemia
	NVP	• No food requirement • Fewer lipid effects than EFV • Once-daily dosing with extended-release tablet formulation	• Higher incidence of rash, including rare but serious HSRs (SJS or TEN), than with other NNRTIs • Higher incidence of hepatotoxicity, including serious and even fatal cases of hepatic necrosis, than with other NNRTIs • Contraindicated in patients with moderate or severe (Child-Pugh B or C) hepatic impairment • ART-naive patients with high pre-treatment CD4 counts (>250 cells/mm^3 for females, >400 cells/mm^3 for males) are at higher risk of symptomatic hepatic events. NVP is not recommended in these patients unless the benefit clearly outweighs the risk. • Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials

	RPV	• Once-daily dosing
		• Co-formulated with TDF/FTC
		• Smaller pill size than co-formulated TDF/FTC/EFV or TDF/FTC/EVG/COBI
		• Compared with EFV:
		  • Fewer discontinuations for CNS adverse effects
		  • Fewer lipid effects
		  • Fewer rashes
		  • Smaller pill size
			• Not recommended for use in patients with pre-ART HIV RNA >100,000 copies/mL because the rate of virologic failures is higher in these patients
			• Higher rate of virologic failures observed in patients with pre-ART CD4 count < 200 cells/mm^3
			• More NNRTI-, TDF-, and 3TC-associated mutations at virological failure than with regimen containing EFV + two NRTIs
			• Meal requirement
			• Absorption depends on lower gastric pH (see Table 15a for detailed information regarding interactions with H2 antagonists and antacids).
			• Contraindicated with PPIs
			• RPV-associated depression reported
			• Use RPV with caution when co-administered with a drug having a known risk of torsades de pointes.

Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 2 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
PIs (in alphabetical order)		**PI Class Advantages:** • Higher genetic barrier to resistance than NNRTIs and RAL • PI resistance at the time of treatment failure uncommon with RTV-boosted PIs	**PI Class Disadvantages:** • Metabolic complications such as dyslipidemia, insulin resistance, and hepatotoxicity • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions—more pronounced with RTV-based regimens (see Tables 14 and 15a)
	ATV (unboosted)	• Fewer adverse effects on lipids than other PIs • Once-daily dosing • Low pill burden • Good GI tolerability • Signature mutation (I50L) not associated with broad PI cross resistance	• Indirect hyperbilirubinemia sometimes leading to jaundice or scleral icterus • PR interval prolongation, which is generally inconsequential unless ATV is combined with another drug that has a similar effect. • Unboosted ATV should not be co-administered with TDF, EFV, or NVP (see ATV/r). • Nephrolithiasis, cholelithiasis • Skin rash • Food requirement • Absorption depends on food and low gastric pH (see Table 15a for detailed information regarding interactions with H2 antagonists, antacids, and PPIs)
	ATV/r	• RTV boosting: higher trough ATV concentration and greater antiviral effect • Once-daily dosing • Low pill burden	• More adverse effects on lipids than unboosted ATV • More hyperbilirubinemia and jaundice than unboosted ATV • Food requirement • Absorption depends on food and low gastric pH (see Table 15a for interactions with H2 antagonists, antacids, and PPIs) • RTV boosting required with TDF and EFV. With EFV, use ATV 400 mg and RTV 100 mg, once daily (PI-naive patients only). • Should not be co-administered with NVP. • Nephrolithiasis, cholelithiasis
	DRV/r	• Once-daily dosing • Potent virologic efficacy	• Skin rash • Food requirement
	FPV/r	• Twice-daily dosing resulted in efficacy comparable to LPV/r • Once-daily dosing possible with RTV 100 mg or 200 mg daily • No food effect	• Skin rash • Hyperlipidemia • Once-daily dosing results in lower APV concentrations than with twice-daily dosing • For FPV/r 1400/200 mg: requires 200 mg of RTV • Fewer data on FPV/r 1400/100 mg dose than on DRV/r and ATV/r
	LPV/r	• Co-formulated • No food requirement • Greater CD4 count increase than with EFV-based regimens	• Requires 200 mg per day of RTV • Lower drug exposure in pregnant women—may need dose increase in third trimester • Once-daily dosing not recommended in pregnant women • Once-daily dosing results in lower trough concentration than twice-daily dosing • Possible higher risk of MI associated with cumulative use of LPV/r • PR and QT interval prolongation have been reported. Use with caution in patients at risk of cardiac conduction abnormalities or receiving other drugs with similar effect.

Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 3 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages

PIs (in alphabetical order)	**SQV/r**	• Similar efficacy but less hyperlipidemia than with LPV/r	• Highest pill burden (6 pills per day) of available PI regimens
			• Requires 200 mg of RTV
			• Food requirement
			• PR and/or QT interval prolongations in a healthy volunteer study
			• Pretreatment ECG recommended
			• SQV/r is not recommended for patients with any of the following conditions:
			  • congenital or acquired QT prolongation
			  • pretreatment ECG >450 msec
			  • on concomitant therapy with other drugs that prolong QT interval
			  • complete AV block without implanted pacemakers
			  • risk of complete AV block

INSTIs (in alphabetical order)	**EVG**	• Co-formulation with COBI/TDF/FTC • Once daily dosing • Non-inferior to EFV/TDF/FTC and ATV/r + TDF/FTC	• COBI is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates • COBI inhibits active tubular secretion of creatinine and can decrease CrCL without affecting renal glomerular function • Has potential for new onset or worsening of renal impairment • Only recommended for patients with baseline CrCl >70 mL/min; therapy should be discontinued if CrCl decreased to <50mL/min • Lower genetic barrier to resistance than with boosted PI-based regimens • Food requirement
	RAL	• Virologic response noninferior to EFV; superior at 4–5 years • Fewer drug-related adverse events and lipid changes than with EFV • No food effect • Fewer drug-drug interactions than with EVG/COBI/TDF/FTC-, PI-, NNRTI-, or MVC-based regimens	• Twice-daily dosing • Lower genetic barrier to resistance than with boosted PI-based regimens • Increase in creatine kinase, myopathy, and rhabdomyolysis have been reported • Rare cases of severe hypersensitivity reactions (including SJS and TEN) have been reported.
CCR5 Antagonist	**MVC**	• Virologic response noninferior to EFV in post hoc analysis of MERIT study (see text) • Fewer adverse effects than EFV	• Requires viral tropism testing before initiation of therapy, which results in additional cost and possible delay in initiation of therapy • In the MERIT study, more MVC-treated than EFV-treated patients discontinued therapy due to lack of efficacy • Less long-term experience in ART-naive patients than with boosted PI- or NNRTI-based regimens • Limited experience with dual-NRTIs other than ZDV/3TC • Twice-daily dosing • CYP3A4 substrate; dosing depends on presence or absence of concomitant CYP3A4 inducer(s) or inhibitor(s)

Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 4 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
Dual-NRTI pairs (in alphabetical order)	**ABC/3TC**	• Virologic response non-inferior to ZDV/3TC • Better CD4 count responses than with ZDV/3TC • Once-daily dosing • Coformulation • No food effect • No cumulative TAM-mediated resistance	• Potential for ABC HSR in patients with HLA-B*5701 • Inferior virologic responses in patients with baseline HIV RNA >100,000 copies/mL when compared with TDF/FTC in ACTG 5202 study; but not in the HEAT study. • Some observational cohort studies show increased potential for cardiovascular events, especially in patients with cardiovascular risk factors
	TDF/FTC	• Better virologic responses than with ABC/3TC in patients with baseline viral load >100,000 copies/mL in ACTG 5202 study; however, this was not seen in the HEAT study. • Active against HBV; recommended dual-NRTI for HIV/HBV co-infection • Once-daily dosing • No food effect • Co-formulated (TDF/FTC, EFV/TDF/FTC, EVG/COBI/TDF/FTC, and RPV/TDF/FTC) • No cumulative TAM-mediated resistance	• Potential for renal impairment, including proximal tubulopathy and acute or chronic renal insufficiency • Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials • Potential for decrease in BMD
	ZDV/3TC	• Co-formulated (ZDV/3TC and ZDV/3TC/ABC) • No food effect (although better tolerated with food) • Preferred dual NRTI in pregnant women	• Bone marrow suppression, especially anemia and neutropenia • GI intolerance, headache • Mitochondrial toxicity, including lipoatrophy, lactic acidosis, hepatic steatosis • Compared with TDF/FTC, inferior in combination with EFV • Less CD4 increase compared with ABC/3TC • Twice-daily dosing

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, APV = amprenavir, ART = antiretroviral therapy, ARV = antiretroviral, ATV = atazanavir, ATV/r = atazanavir/ritonavir, AV = atrioventricular, BMD = bone mineral density, CNS = central nervous system, COBI = cobicistat, CrCl = creatinine clearance, CYP = cytochrome P, d4T = stavudine, ddI = didanosine, DRV/r = darunavir/ritonavir, ECG = electrocardiogram, EFV = efavirenz, EVG = elvitegravir, FPV = fosamprenavir, FPV/r = fosamprenavir/ ritonavir, FTC = emtricitabine, GI = gastrointestinal, HBV = hepatitis B virus, HSR = hypersensitivity reaction, INSTI = integrase strand transfer inhibitor, LPV/r = lopinavir/ritonavir, MI = myocardial infarction, msec = milliseconds, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, PPI = proton pump inhibitor, RAL = raltegravir, RPV = rilpivirine, RTV = ritonavir, SJS = Stevens-Johnson syndrome, SQV/r = saquinavir/ritonavir, TAM = thymidine analogue mutation, TDF = tenofovir disoproxil fumarate, TEN = toxic epidermal necrosis, ZDV = zidovudine

Table 7. Antiretroviral Components or Regimens Not Recommended as Initial Therapy

ARV drugs or components (in alphabetical order)	**Reasons for NOT recommending as initial therapy**
ABC/3TC/ZDV (co-formulated) as triple-NRTI combination regimen **(BI)**	• Inferior virologic efficacy
ABC + 3TC + ZDV + TDF as quadruple-NRTI combination regimen **(BI)**	• Inferior virologic efficacy
DRV (unboosted)	• Use without RTV has not been studied
DLV **(BIII)**	• Inferior virologic efficacy • Inconvenient (three times daily) dosing
ddI + 3TC (or FTC) **(BIII)**	• Inferior virologic efficacy • Limited clinical trial experience in ART-naive patients • ddI toxicity
ddI + TDF **(BII)**	• High rate of early virologic failure • Rapid selection of resistance mutations • Potential for immunologic nonresponse/CD4 T-cell decline • Increased ddI drug exposure and toxicities
EVG/COBI/TDF/FTC + other ARV drugs **(BIII)**	• Potential for drug-drug interactions, especially with NNRTI, PI, and MVC; appropriate dosages of EVG/COBI/TDF/FTC and other ARV drugs have not been established
T20 **(BIII)**	• No clinical trial experience in ART-naive patients • Requires twice-daily subcutaneous injections
ETR **(BIII)**	• Insufficient data in ART-naive patients
FPV (unboosted) **(BIII)**	• Less potent than RTV-boosted FPV • Virologic failure with unboosted FPV-based regimen may result in selection of mutations that confer resistance to DRV
IDV (unboosted) **(BIII)**	• Inconvenient dosing (three times daily with meal restrictions) • Fluid requirement • IDV toxicities
IDV (RTV-boosted) **(BIII)**	• IDV toxicities • Fluid requirement
NFV **(BI)**	• Inferior virologic efficacy • Diarrhea
RTV as sole PI **(BIII)**	• High pill burden • GI intolerance • Metabolic toxicity
SQV (unboosted) **(BI)**	• Inadequate bioavailability • Inferior virologic efficacy
d4T + 3TC **(BI)**	• Significant toxicities including lipoatrophy; peripheral neuropathy; and hyperlactatemia, including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis
TPV (RTV-boosted) **(BI)**	• Inferior virologic efficacy

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, ARV = antiretroviral, COBI = cobicistat, d4T = stavudine, ddI = didanosine, DLV = delavirdine, DRV = darunavir, ETR = etravirine, EVG = elvitegravir, FPV = fosamprenavir, FTC = emtricitabine, GI = gastrointestinal, IDV = indinavir, MVC = maraviroc, NFV = nelfinavir, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, RTV = ritonavir, SQV = sacquinavir, T20 = enfuvirtide, TDF = tenofovir disoproxil fumarate, TPV = tipranavir, ZDV = zidovudine

References

1. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Three- vs four-drug antiretroviral regimens for the initial treatment of HIV-1 infection: a randomized controlled trial. *JAMA*. 2006;296(7):769-781. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16905783.
2. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA*. 2004;292(2):191-201. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15249568.
3. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med*. 1999;341(25):1865-1873. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10601505.
4. Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med*. 2008;358(20):2095-2106. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18480202.
5. Squires K, Lazzarin A, Gatell JM, et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. *J Acquir Immune Defic Syndr*. 2004;36(5):1011-1019. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15247553.
6. Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet*. 2009;374(9692):796-806. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19647866.
7. Cooper DA, Heera J, Goodrich J, et al. Maraviroc versus efavirenz, both in combination with zidovudine-lamivudine, for the treatment of antiretroviral-naive subjects with CCR5-tropic HIV-1 infection. *J Infect Dis*. 2010;201(6):803-813. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20151839.
8. Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *N Engl J Med*. 2009;361(23):2230-2240. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19952143.
9. Post FA, Moyle GJ, Stellbrink HJ, et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. *J Acquir Immune Defic Syndr*. 2010;55(1):49-57. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20431394.
10. Smith KY, Patel P, Fine D, et al. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. *AIDS*. 2009;23(12):1547-1556. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19542866.
11. 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. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21606537.
12. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med*. 2006;354(3):251-260. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16421366.
13. Daar ES, Tierney C, Fischl MA, et al. 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. Available at http://www.ncbi.nlm.nih.gov/pubmed/21320923.

14. Cohen CJ, Molina JM, Cahn P, et al. Efficacy and safety of rilpivirine (TMC278) versus efavirenz at 48 weeks in treatment-naive HIV-1-infected patients: pooled results from the phase 3 double-blind randomized ECHO and THRIVE Trials. *J Acquir Immune Defic Syndr*. 2012;60(1):33-42. Available at http://www.ncbi.nlm.nih.gov/pubmed/22343174.

15. Sax PE, DeJesus E, Mills A, et al. 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. Available at http://www.ncbi.nlm.nih.gov/pubmed/22748591.

16. Aberg JA, Tebas P, Overton ET, et al. Metabolic effects of darunavir/ritonavir versus atazanavir/ritonavir in treatment-naive, HIV type 1-infected subjects over 48 weeks. *AIDS Res Hum Retroviruses*. 2012;28(10):1184-1195. Available at http://www.ncbi.nlm.nih.gov/pubmed/22352336.

17. Anderson PL, Glidden DV, Liu A, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. *Sci Transl Med*. 2012;4(151):151ra125. Available at http://www.ncbi.nlm.nih.gov/pubmed/22972843.

18. Kim D, Wheeler W, Ziebell R, et al. Prevalence of transmitted antiretroviral drug resistance among newly-diagnosed HIV-1-infected persons, US, 2007. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections. 2010. San Francisco, CA.

19. Novak RM, Chen L, MacArthur RD, et al. Prevalence of antiretroviral drug resistance mutations in chronically HIV-infected, treatment-naive patients: implications for routine resistance screening before initiation of antiretroviral therapy. *Clin Infect Dis*. 2005;40(3):468-474. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15668873.

20. Wensing AM, van de Vijver DA, Angarano G, et al. Prevalence of drug-resistant HIV-1 variants in untreated individuals in Europe: implications for clinical management. *J Infect Dis*. 2005;192(6):958-966. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16107947.

21. Weinstock HS, Zaidi I, Heneine W, et al. The epidemiology of antiretroviral drug resistance among drug-naive HIV-1-infected persons in 10 US cities. *J Infect Dis*. 2004;189(12):2174-2180. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15181563.

22. Andries K, Azijn H, Thielemans T, et al. TMC125, a novel next-generation nonnucleoside reverse transcriptase inhibitor active against nonnucleoside reverse transcriptase inhibitor-resistant human immunodeficiency virus type 1. *Antimicrob Agents Chemother*. 2004;48(12):4680-4686. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15561844.

23. Food and Drug Administration. Edurant (package insert). 2012. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202022s002lbl.pdf. Accessed December 28, 2012.

24. Food and Drug Administration. Intelence (package insert). 2011. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022187s008lbl.pdf. Accessed January 18, 2013.

25. Gazzard B, Duvivier C, Zagler C, et al. Phase 2 double-blind, randomised trial of etravirine versus efavirenz in treatment-naive patients: 48 week results. *AIDS*. 2011. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21881478.

26. Cassetti I, Madruga JV, Etzel A, et al. The safety and efficacy of tenofovir DF (TDF) in combination with lamivudine (3TC) and efavirenz (EFV) in antiretroviral-naive patients through seven years. Paper presented at:17th International AIDS Conference. 2008. Mexico City, Mexico.

27. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet*. 2004;363(9417):1253-1263. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15094269.

28. Nunez M, Soriano V, Martin-Carbonero L, et al. SENC (Spanish efavirenz vs. nevirapine comparison) trial: a randomized, open-label study in HIV-infected naive individuals. *HIV Clin Trials*. 2002;3(3):186-194. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12032877.

29. Food and Drug Administration. Sustiva (package insert). 2009. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020972s033,021360s021lbl.pdf. Accessed January 18, 2013.

30. Fundaro C, Genovese O, Rendeli C, Tamburrini E, Salvaggio E. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS*. 2002;16(2):299-300. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11807320.

31. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989 through 31 January 2012. Available at http://www.apregistry.com/forms/interim_report.pdf. Accessed December 28, 2012.

32. World Health Organization. Technical update on treatment optimization: Use of efavirenz during pregnancy: A public health perspective. Available at http://www.who.int/hiv/pub/treatment2/efavirenz/en/. Accessed June 25, 2012.

33. Ford N, Calmy A, Mofenson L. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS*. 2011;25(18):2301-2304. Available at http://www.ncbi.nlm.nih.gov/pubmed/21918421.

34. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.

35. Soriano V, Arasteh K, Migrone H, et al. Nevirapine versus atazanavir/ritonavir, each combined with tenofovir disoproxil fumarate/emtricitabine, in antiretroviral-naive HIV-1 patients: the ARTEN Trial. *Antivir Ther*. 2011;16(3):339-348. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21555816.

36. Sanne I, Mommeja-Marin H, Hinkle J, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. *J Infect Dis*. 2005;191(6):825-829. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15717255.

37. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr*. 2004;35(5):538-539. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15021321.

38. Boehringer Ingelheim. Dear Health Care Professional Letter: Clarification of risk factors for severe, life-threatening and fatal hepatotoxicity with VIRAMUNE® (nevirapine). February 2004. Available at http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM166534.pdf.

39. Peters P, Stringer J, McConnell MS, et al. Nevirapine-associated hepatotoxicity was not predicted by CD4 count ≥250 cells/muL among women in Zambia, Thailand and Kenya. *HIV Med*. 2010. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20659176.

40. Coffie PA, Tonwe-Gold B, Tanon AK, et al. Incidence and risk factors of severe adverse events with nevirapine-based antiretroviral therapy in HIV-infected women. MTCT-Plus program, Abidjan, Cote d'Ivoire. *BMC Infect Dis*. 2010;10:188. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20576111.

41. Kesselring AM, Wit FW, Sabin CA, et al. Risk factors for treatment-limiting toxicities in patients starting nevirapine-containing antiretroviral therapy. *AIDS*. 2009;23(13):1689-1699. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19487907.

42. Lathouwers E, De Meyer S, Dierynck I, et al. Virological characterization of patients failing darunavir/ritonavir or lopinavir/ritonavir treatment in the ARTEMIS study: 96-week analysis. *Antivir Ther*. 2011;16(1):99-108. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21311113.

43. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis*. 2010;201(3):318-330. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20039804.

44. Lang S, Mary-Krause M, Cotte L, et al. Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4. *Arch Intern Med*. 2010;170(14):1228-1238. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20660842.

45. 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. Available at http://www.ncbi.nlm.nih.gov/pubmed/23291539.

46. Food and Drug Administration (FDA). Invirase (package insert). 2010. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020628s033,021785s010lbl.pdf. Accessed January 18, 2013.

47. Malan DR, Krantz E, David N, Wirtz V, Hammond J, McGrath D. Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily highly active antiretroviral therapy regimens in antiretroviral-naive patients. *J Acquir Immune Defic Syndr*. 2008;47(2):161-7. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17971713.

48. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet*. 2008;372(9639):646-655. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18722869.

49. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. *J Acquir Immune Defic Syndr*. 2010;53(3):323-332. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20032785.

50. Chan-Tack KM, Truffa MM, Struble KA, Birnkrant DB. Atazanavir-associated nephrolithiasis: cases from the US Food and Drug Administration's Adverse Event Reporting System. *AIDS*. 2007;21(9):1215-1218. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17502736.

51. Rockwood N, Mandalia S, Bower M, Gazzard B, Nelson M. Ritonavir-boosted atazanavir exposure is associated with an increased rate of renal stones compared with efavirenz, ritonavir-boosted lopinavir and ritonavir-boosted darunavir. *AIDS*. 2011;25(13):1671-1673. Available at http://www.ncbi.nlm.nih.gov/pubmed/21716074.

52. 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. Available at http://www.ncbi.nlm.nih.gov/pubmed/22820542.

53. Rakotondravelo S, Poinsignon Y, Borsa-Lebas F, et al. Complicated atazanavir-associated cholelithiasis: a report of 14 cases. *Clin Infect Dis*. 2012;55(9):1270-1272. Available at http://www.ncbi.nlm.nih.gov/pubmed/22820540.

54. Ortiz R, Dejesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. *AIDS*. 2008;22(12):1389-1397. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18614861.

55. Orkin C, Dejesus E, Khanlou H, et al. Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naive patients in the ARTEMIS trial. *HIV Med*. 2013;14(1):49-59. Available at http://www.ncbi.nlm.nih.gov/pubmed/23088336.

56. Trottier B, Machouf N, Thomas R, et al. Abacavir/lamivudine fixed-dose combination with ritonavir-boosted darunavir: a safe and efficacious regimen for HIV therapy. *HIV Clin Trials*. 2012;13(6):335-342. Available at http://www.ncbi.nlm.nih.gov/pubmed/23195671.

57. Eron J, Jr., Yeni P, Gathe J, Jr., et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet*. 2006;368(9534):476-482. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16890834.

58. Pulido F, Estrada V, Baril JG, et al. Long-term efficacy and safety of fosamprenavir plus ritonavir versus lopinavir/ritonavir in combination with abacavir/lamivudine over 144 weeks. *HIV Clin Trials*. 2009;10(2):76-87. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19487177.

59. Smith KY, Weinberg WG, Dejesus E, et al. Fosamprenavir or atazanavir once daily boosted with ritonavir 100 mg, plus tenofovir/emtricitabine, for the initial treatment of HIV infection: 48-week results of ALERT. *AIDS Res Ther*. 2008;5:5. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18373851.

60. Murphy RL, da Silva BA, Hicks CB, et al. Seven-year efficacy of a lopinavir/ritonavir-based regimen in antiretroviral-naive HIV-1-infected patients. *HIV Clin Trials*. 2008;9(1):1-10. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18215977.

61. Murphy RL, Sanne I, Cahn P, et al. Dose-ranging, randomized, clinical trial of atazanavir with lamivudine and stavudine in antiretroviral-naive subjects: 48-week results. *AIDS*. 2003;17(18):2603-2614. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14685054.

62. Sanne I, Piliero P, Squires K, Thiry A, Schnittman S. Results of a phase 2 clinical trial at 48 weeks (AI424-007): a dose-ranging, safety, and efficacy comparative trial of atazanavir at three doses in combination with didanosine and stavudine in antiretroviral-naive subjects. *J Acquir Immune Defic Syndr*. 2003;32(1):18-29. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12514410.

63. Campbell TB, Smeaton LM, Kumarasamy N, et al. Efficacy and safety of three antiretroviral regimens for initial treatment of HIV-1: a randomized clinical trial in diverse multinational settings. *PLoS Med*. 2012;9(8):e1001290. Available at http://www.ncbi.nlm.nih.gov/pubmed/22936892.

64. Walmsley S, Avihingsanon A, Slim J, et al. Gemini: a noninferiority study of saquinavir/ritonavir versus lopinavir/ritonavir as initial HIV-1 therapy in adults. *J Acquir Immune Defic Syndr*. 2009;50(4):367-374. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19214123.

65. Rockstroh JK, Lennox JL, Dejesus E, et al. Long-term Treatment With Raltegravir or Efavirenz Combined With Tenofovir/Emtricitabine for Treatment-Naive Human Immunodeficiency Virus-1-Infected Patients: 156-Week Results From STARTMRK. *Clin Infect Dis*. 2011;53(8):807-816. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21921224.

66. Young B, Vanig T, Dejesus E, et al. A pilot study of abacavir/lamivudine and raltegravir in antiretroviral-naive HIV-1-infected patients: 48-week results of the SHIELD trial. *HIV Clin Trials*. 2010;11(5):260-269. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21126956.

67. Food and Drug Administration. Isentress (package insert). 2011. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022145s018lbl.pdf. Accessed February 19, 2012.

68. Mathias AA, West S, Hui J, Kearney BP. Dose-response of ritonavir on hepatic CYP3A activity and elvitegravir oral exposure. *Clin Pharmacol Ther*. 2009;85(1):64-70. Available at http://www.ncbi.nlm.nih.gov/pubmed/18815591.

69. Food and Drug Administration. Stribild (package insert). 2012. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203100s000lbl.pdf. Accessed December 28, 2012.

70. DeJesus E, Rockstroh JK, Henry K, et al. 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. Available at http://www.ncbi.nlm.nih.gov/pubmed/22748590.

71. Rockstroh JK, Dejesus E, Henry K, et al. A randomized, double-blind comparison of co-formulated

elvitegravir/cobicistat/emtricitabine/tenofovir versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir DF for initial treatment of HIV-1 infection: analysis of week 96 results. *J Acquir Immune Defic Syndr*. 2013. Available at http://www.ncbi.nlm.nih.gov/pubmed/23337366.

72. Zolopa A, Gallant J, Cohen C, et al. Elvitegravir/cobicistat/emtricitabine/tenofovir DF (Quad) has durable efficacy and differentiated safety compared to efavirenz/emtricitabine/tenofovir DF at week 96 in treatment-naive HIV-1-infected patients. *Journal of the International AIDS Society*. 2012;15(6):18219. Available at http://www.ncbi.nlm.nih.gov/pubmed/23234891.
73. 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. Available at http://www.ncbi.nlm.nih.gov/pubmed/22732469.
74. Sierra-Madero J, Di Perri G, Wood R, et al. Efficacy and safety of maraviroc versus efavirenz, both with zidovudine/lamivudine: 96-week results from the MERIT study. *HIV Clin Trials*. 2010;11(3):125-132. Available at http://www.ncbi.nlm.nih.gov/pubmed/20736149.
75. Ait-Khaled M, Stone C, Amphlett G, et al. M184V is associated with a low incidence of thymidine analogue mutations and low phenotypic resistance to zidovudine and stavudine. *AIDS*. 2002;16(12):1686-1689. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12172093.
76. Arribas JR, Pozniak AL, Gallant JE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naive patients: 144-week analysis. *J Acquir Immune Defic Syndr*. 2008;47(1):74-78. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17971715.
77. Molina JM, Podsadecki TJ, Johnson MA, et al. A lopinavir/ritonavir-based once-daily regimen results in better compliance and is non-inferior to a twice-daily regimen through 96 weeks. *AIDS Res Hum Retroviruses*. 2007;23(12):1505-1514. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18160008.
78. Zimmermann AE, Pizzoferrato T, Bedford J, Morris A, Hoffman R, Braden G. Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. *Clin Infect Dis*. 2006;42(2):283-290. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16355343.
79. Karras A, Lafaurie M, Furco A, et al. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. *Clin Infect Dis*. 2003;36(8):1070-1073. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12684922.
80. Moore R, Keruly J, Gallant J. Tenofovir and renal dysfunction in clinical practice. Paper presented at: 14th Conference on Retrovirus and Opportunistic Infections. 2007. Los Angeles, CA.
81. Kearney BP, Mathias A, Mittan A, Sayre J, Ebrahimi R, Cheng AK. Pharmacokinetics and safety of tenofovir disoproxil fumarate on co-administration with lopinavir/ritonavir. *J Acquir Immune Defic Syndr*. 2006;43(3):278-283. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17079992.
82. Kiser JJ, Carten ML, Aquilante CL, et al. The effect of lopinavir/ritonavir on the renal clearance of tenofovir in HIV-infected patients. *Clin Pharmacol Ther*. 2008;83(2):265-272. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17597712.
83. Gallant JE, Moore RD. Renal function with use of a tenofovir-containing initial antiretroviral regimen. *AIDS*. 2009;23(15):1971-1975. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19696652.
84. Goicoechea M, Liu S, Best B, et al. Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. *J Infect Dis*. 2008;197(1):102-108. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18171292.
85. Mills AM, Nelson M, Jayaweera D, et al. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-

infected patients: 96-week analysis. *AIDS*. 2009;23(13):1679-1688. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19487905.

86. Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin Infect Dis*. 2010;51(8):963-972. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20828304.
87. DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. *Clin Infect Dis*. 2004;39(7):1038-1046. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15472858.
88. Sax PE, Tierney C, Collier AC, et al. Abacavir/Lamivudine Versus Tenofovir DF/Emtricitabine as Part of Combination Regimens for Initial Treatment of HIV: Final Results. *J Infect Dis*. 2011;204(8):1191-1201. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21917892.
89. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358(6):568-579. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18256392.
90. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis*. 2008;46(7):1111-1118. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18444831.
91. 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. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18387667.
92. Choi AI, Vittinghoff E, Deeks SG, Weekley CC, Li Y, Shlipak MG. Cardiovascular risks associated with abacavir and tenofovir exposure in HIV-infected persons. *AIDS*. 2011;25(10):1289-1298. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21516027.
93. Durand M, Sheehy O, Baril JG, Lelorier J, Tremblay CL. Association between HIV infection, antiretroviral therapy, and risk of acute myocardial infarction: a cohort and nested case-control study using Quebec's public health insurance database. *J Acquir Immune Defic Syndr*. 2011;57(3):245-253. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21499115.
94. Obel N, Farkas DK, Kronborg G, et al. Abacavir and risk of myocardial infarction in HIV-infected patients on highly active antiretroviral therapy: a population-based nationwide cohort study. *HIV Med*. 2010;11(2):130-136. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19682101.
95. The SMART/INSIGHT and the D:A:D Study Groups TSIatDADSG. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS*. 2008;22(14):F17-24. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18753925.
96. Ribaudo HJ, Benson CA, Zheng Y, et al. No risk of myocardial infarction associated with initial antiretroviral treatment containing abacavir: short and long-term results from ACTG A5001/ALLRT. *Clin Infect Dis*. 2011;52(7):929-940. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21427402.
97. 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. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21653308.
98. Brothers CH, Hernandez JE, Cutrell AG, et al. Risk of myocardial infarction and abacavir therapy: no increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. *J Acquir Immune Defic Syndr*. 2009;51(1):20-28. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19282778.

99. 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. Available at http://www.ncbi.nlm.nih.gov/pubmed/22932321.

100. Hsue PY, Hunt PW, Wu Y, et al. Association of abacavir and impaired endothelial function in treated and suppressed HIV-infected patients. *AIDS*. 2009;23(15):2021-2027. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19542863.

101. Satchell CS, O'Halloran JA, Cotter AG, et al. Increased Platelet Reactivity in HIV-1-Infected Patients Receiving Abacavir-Containing Antiretroviral Therapy. *J Infect Dis*. 2011;204(8):1202-1210. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21917893.

102. Kristoffersen US, Kofoed K, Kronborg G, Benfield T, Kjaer A, Lebech AM. Changes in biomarkers of cardiovascular risk after a switch to abacavir in HIV-1-infected individuals receiving combination antiretroviral therapy. *HIV Med*. 2009;10(10):627-633. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19891054.

103. De Pablo C, Orden S, Apostolova N, Blanquer A, Esplugues JV, Alvarez A. Abacavir and didanosine induce the interaction between human leukocytes and endothelial cells through Mac-1 upregulation. *AIDS*. 2010;24(9):1259-1266. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20453628.

104. Martinez E, Larrousse M, Podzamczer D, et al. Abacavir-based therapy does not affect biological mechanisms associated with cardiovascular dysfunction. *AIDS*. 2010;24(3):F1-9. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20009917.

105. Palella FJ, Jr., Gange SJ, Benning L, et al. Inflammatory biomarkers and abacavir use in the Women's Interagency HIV Study and the Multicenter AIDS Cohort Study. *AIDS*. 2010;24(11):1657-1665. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20588104.

106. Martin A, Amin J, Cooper DA, et al. Abacavir does not affect circulating levels of inflammatory or coagulopathic biomarkers in suppressed HIV: a randomized clinical trial. *AIDS*. 2010;24(17):2657-2663. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20827168.

107. Jong E, Meijers JC, van Gorp EC, Spek CA, Mulder JW. Markers of inflammation and coagulation indicate a prothrombotic state in HIV-infected patients with long-term use of antiretroviral therapy with or without abacavir. *AIDS Res Ther*. 2010;7:9. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20398387.

108. Podzamczer D, Ferrer E, Consiglio E, et al. A randomized clinical trial comparing nelfinavir or nevirapine associated to zidovudine/lamivudine in HIV-infected naive patients (the Combine Study). *Antivir Ther*. 2002;7(2):81-90. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12212928.

109. Vibhagool A, Cahn P, Schechter M, et al. Triple nucleoside treatment with abacavir plus the lamivudine/zidovudine combination tablet (COM) compared to indinavir/COM in antiretroviral therapy-naive adults: results of a 48-week open-label, equivalence trial (CNA3014). *Curr Med Res Opin*. 2004;20(7):1103-1114. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15265255.

110. Staszewski S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naive HIV-infected adults: A randomized equivalence trial. *JAMA*. 2001;285(9):1155-1163. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11231744.

111. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med*. 2004;350(18):1850-1861. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15115831.

112. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med*. 2003;349(24):2293-2303. Available at

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14668455.

113. Drake A, Mijch A, Sasadeusz J. Immune reconstitution hepatitis in HIV and hepatitis B coinfection, despite lamivudine therapy as part of HAART. *Clin Infect Dis*. 2004;39(1):129-132. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15206064.

114. Bessesen M, Ives D, Condreay L, Lawrence S, Sherman KE. Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance to or withdrawal of lamivudine. *Clin Infect Dis*.1999;28(5):1032-1035. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10452630.

115. Sellier P, Clevenbergh P, Mazeron MC, et al. Fatal interruption of a 3TC-containing regimen in a HIV-infected patient due to re-activation of chronic hepatitis B virus infection. *Scand J Infect Dis*. 2004;36(6-7):533-535. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15307596.