# Recommendations for Use of Antiretroviral Regimens in HIV-infected Treatment-naïve Veterans
# March 2013

**VHA Pharmacy Benefits Management Services, the Medical Advisory Panel, VISN Pharmacist Executives, Public Health Strategic Healthcare Group, and the HIV Treatment Advisory Group**

*The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician, however, must make the ultimate judgment regarding the propriety of any course of treatment in light of individual patient situations.*

**Background**

Updated Department of Health and Human Service (DHHS) guidelines for the use of antiretroviral agents in HIV-1 infected individuals recommend four Preferred Regimens for consideration in treatment-naïve HIV-infected individuals. Preferred regimens are those with optimal durable efficacy, more favorable tolerability and toxicity profiles, and ease of use. The guideline also includes Panel recommended Alternative Regimens; these regimens are also effective and tolerable but have *potential* disadvantages when compared to Preferred Regimens.

Selection of a regimen, (Preferred or Alternative), should still be individualized based on virologic efficacy, toxicity, pill burden, dosing frequency, drug-interaction potential, resistance profile and sequencing, comorbid conditions, pre-treatment viral load and CD4+ cell count, and cost. This may be particularly true for HIV-infected Veterans who, given their older age and higher rates of co-morbidities, represent a unique population not often represented in clinical trials.

It is important to note that most HIV infected Veterans are antiretroviral treatment experienced. In 2008, 80% of HIV-infected Veterans received prescriptions for antiretroviral medications but only 5.7% of HIV-infected Veterans filled their first VHA outpatient prescription for an antiretroviral medication. The DHHS guidelines do not specifically address antiretroviral management in treatment experienced individuals beyond performing drug resistance testing and using at least two fully active agents, if available.

**Preferred Regimens as recommended by DHHS guidelines**

*(listed by class) strength of evidence = A1*

| | |
|---|---|
| NNRTI-based Regimen: | Efavirenz/tenofovir/emtricitabine[a] every day (co-formulated as a single tablet) |
| Protease Inhibitor-based Regimens: | Atazanavir/ritonavir + tenofovir/emtricitabine[a] every day<br>Darunavir/ritonavir + tenofovir/emtricitabine[a] every day |
| Integrase strand transfer inhibitor-based Regimen: | Raltegravir twice daily + tenofovir/emtricitabine[a] every day |

**Preferred Regimen for Pregnant Women (A1)**

Lopinavir/ritonavir twice daily + zidovudine/lamivudine[a] every day

**Alternative Regimens as recommended by DHHS guidelines***

*On the basis of individual patient characteristics and needs, a regimen listed as an alternative regimen may actually be the preferred regimen in certain situations. *(listed by class then in alphabetical order); strength of evidence = B1*

| | |
|---|---|
| NNRTI-based Regimens: | Efavirenz + abacavir[b]/lamivudine[a] every day<br>Rilpivirine[c]/tenofovir/emtricitabine[a] every day (co-formulated as a single tablet) in patient with HIV-1 RNA ≤100,000 copies/mL<br>Rilpivirine[c] + abacavir[b]/lamivudine[a] every day in patient with HIV-1 RNA ≤100,000 copies/mL |
| PI-based Regimens: | Atazanavir/ritonavir + abacavir[b]/lamivudine[a]<br>Darunavir/ritonavir + abacavir[b]/ lamivudine[a]<br>Fosamprenavir/ritonavir twice daily or every day + either abacavir[b]/lamivudine[a] or tenofovir/emtricitabine[a]<br>Lopinavir/ritonavir twice daily or every day + either abacavir[b]/lamivudine[a] or tenofovir/emtricitabine[a] |

| | |
|---|---|
| Integrase strand transfer inhibitor-based Regimen: | Elvitegravir 150mg/cobicistat 150mg/tenofovir 300mg/emtricitabine 200mg every day in patients with CrCl >70 mL/min<br>Raltegravir twice daily + abacavir[b]/lamivudine[a] every day |

[a]Lamivudine may substitute for emtricitabine or vice versa
[b] Avoid abacavir in patients testing positive for HLA-B*5701; use with caution in patients with high risk of cardiovascular disease or pre-treatment HIV-RNA > 100,000 copies/mL
[c] More rilpivirine treated subjects with HIV-1 RNA >100,000 copies/mL at the start of therapy experienced virologic failure compared to subjects with HIV-1 RNA <100,000 copies/mL at the start of therapy. Regardless of HIV-1 RNA at the start of therapy, more rilpivirine treated subjects with CD4+ cell count less than 200 cells/mm$^3$ at the start of therapy experienced virologic failure compared to subjects with CD4+ cell count greater than or equal to 200 cells/mm$^3$ Observed virologic failure rate in rilpivirine treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz and more subjects treated with rilpivirine developed lamivudine/emtricitabine associated resistance compared to efavirenz.

Specific issues for consideration regarding DHHS recommended Preferred or Alternative Regimens are included in the Evidence Summary section below.

**Evidence Summary**

- PI-based regimens are generally associated with more GI symptoms and lipid abnormalities whereas efavirenz-based regimens are associated with more rash and CNS adverse effects. Among PIs, atazanavir/rtv and to a lesser extent darunavir/rtv have shown less evidence for causing lipid abnormalities when compared with lopinavir/rtv.
- In patients with pre-existing PI resistance there is growing support for the use of once-daily boosted PI regimens that use only 100mg/day of ritonavir because they tend to cause fewer GI side effects and less metabolic toxicity than regimens that use 200mg of ritonavir per day.
- Drug resistance to most PIs requires multiple mutations and seldom develops after early virologic failure, particularly with ritonavir boosting. Resistance to efavirenz is conferred by a single mutation and develops rapidly after virologic failure. Raltegravir also has a lower genetic barrier to resistance than PI-based regimens. Resistance mutations were observed at approximately the same frequency between raltegravir and efavirenz in the comparative trial.
- Efavirenz in combination with dual-NRTIs was associated with a significantly better virologic response than lopinavir/ritonavir plus dual-NRTIs at 96 weeks, whereas the dual-NRTI with lopinavir/ritonavir regimen was associated with significantly better CD4 cell response and less drug resistance.
- Darunavir/rtv and atazanavir/rtv have both shown superiority over lopinavir/rtv in naïve patients with baseline HIV viral loads greater than 100,000 and/or who have fewer than 200 CD4$^+$ cells/µL. No significant differences between lopinavir/rtv and either darunavir/rtv or atazanavir/rtv have been observed in naïve patients with baseline HIV viral loads less than 100,000 and/or a CD4$^+$ cell count >200 cells/µL. When considering the use of protease inhibitors in treatment-naïve HIV-infected individuals the following guidelines are recommended:
  - Darunavir/rtv or atazanavir/rtv should be considered as preferred options in patients with HIV VL > 100,000 copies/mL *and/or* < 200 CD4$^+$ cells/µL.
    - Darunavir/rtv is preferred in patients receiving proton pump inhibitors (and proton pump inhibitor therapy needs to be continued)
  - Atazanavir/rtv or lopinavir/rtv can be considered as options in patients with VL < 100,000 copies/mL *and* >200 CD4+ cells/µL.
    - If co-morbidities make the use of these agents less desirable (i.e.GERD requiring use of PPIs for atazanavir or severe hypertriglyceridemia for lopinavir/ritonavir in the setting of atazanavir intolerance) then darunavir/rtv should be considered.
- Raltegravir in combination with tenofovir and emtricitabine has shown similar efficacy as efavirenz/tenofovir/emtricitabine up to 96 weeks.
- No head-to-head studies are available comparing atazanavir/rtv vs. darunavir/rtv or raltegravir vs. PI-based regimens
- Each of the preferred regimens has been associated with hepatotoxicity. These have generally occurred in patients with advanced HIV disease taking multiple medications, having co-morbidities including hepatitis B or C co-infection, and/or developing immune reconstitution syndrome. Monitor LFTs before and during therapy, especially in patients with pre-existing liver dysfunction.

**Table 1. Advantages and Disadvantages of Antiretroviral Classes for Preferred Regimen**

| | Advantages | Disadvantages |
|---|---|---|
| **NNRTI** | • Saves PIs and RAL for future use<br>• EFV/TDF/EFV (coformulated product) has lowest pill burden of Preferred Regimens | • Low genetic barrier to resistance<br>• Potential for cross resistance<br>• CYP450 drug interactions<br>• Neuropsychiatric side effects (EFV) |
| **Boosted PIs** | • Higher genetic barrier to resistance<br>• PI resistance uncommon with failure<br>• Fewer adverse effects on lipids than other PIs (ATV) | • Metabolic complications<br>• GI adverse effects<br>• CYP450 drug interactions |
| **INSTI** | • Fewer drug related adverse events<br>• Fewer drug interactions (RAL only) | • Less long-term experience in treatment-naïve patients<br>• Fewer comparative studies (i.e. vs PI-based regimens)<br>• BID dosing (RAL)<br>• Lower genetic barrier to resistance than boosted PI regimens<br>• No data with NRTIs other than TDF/FTC in treatment naïve patients |

INSTI: Integrase strand transfer inhibitor

**Table 2. Clinical Studies Comparing Recommended Regimens in HIV-infected Treatment Naïve Individuals**

<table>
<tr><th>Study</th><th>Regimen</th><th>Results</th></tr>
<tr><td>ARTEMIS</td><td>drv/rtv (800/100) QD (n=343) vs lop/rtv QD or BID (n=346) + TDF/FTC<br><br>Lop/rtv dosing: 15% qd, 11% bid/qd, 74% bid</td><td>96 Week Results
<table>
<tr><th></th><th>Drv/rtv</th><th>Lop/rtv (all)</th><th>Lop/rtv (BID)</th><th>p value</th></tr>
<tr><td>VL < 50</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Overall</td><td>79%</td><td>71%</td><td>72%</td><td>0.01<br>0.04</td></tr>
<tr><td>Baseline VL >100K</td><td>76%</td><td>63%</td><td></td><td>0.02</td></tr>
<tr><td>Baseline VL <100K</td><td>81%</td><td>75%</td><td></td><td>NS</td></tr>
<tr><td>Baseline CD4 <200</td><td>79%</td><td>66%</td><td></td><td>0.01</td></tr>
<tr><td>Baseline CD4 >200</td><td>79%</td><td>75%</td><td></td><td>NS</td></tr>
<tr><td>CD4 change</td><td>+188</td><td>+171</td><td></td><td>NS</td></tr>
<tr><td>Virologic Failure</td><td>12%</td><td>17%</td><td></td><td>0.04</td></tr>
</table>
Virologic response in the non-virologic failure censored population: 93% (drv/r) vs. 87% (lop/r) p=0.02</td></tr>
<tr><td>CASTLE</td><td>atv/rtv (300/100) QD (n=440) vs. lop/rtv BID (n=443) + TDF/FTC</td><td>96 Week Results
<table>
<tr><th></th><th>Atv/rtv</th><th>Lop/rtv</th><th>p value</th></tr>
<tr><td>VL < 50</td><td></td><td></td><td></td></tr>
<tr><td>Overall</td><td>70%</td><td>63%</td><td><0.05</td></tr>
<tr><td>Baseline VL >100K and CD4 <100</td><td>74%</td><td>66%</td><td><0.05</td></tr>
<tr><td>CD4 change</td><td>+268</td><td>+290</td><td>NS</td></tr>
</table>
Higher discontinuation rates in lop/rtv arm due to GI side effects (capsule formulation used); on treatment difference of 89% (atv/r) vs 88% (lop/r)</td></tr>
<tr><td>ACTG 5142</td><td>Efv (n=250) vs. Lop/rtv (n=253) + 2NRTIs (also included an Efv + Lop/rtv arm)</td><td>96 week results
<table>
<tr><th></th><th>EFV</th><th>Lop/rtv</th><th>p value</th></tr>
<tr><td>VL < 50</td><td>89%</td><td>77%</td><td>P=0.003</td></tr>
<tr><td>CD4 change</td><td>+230</td><td>+287</td><td>P=0.01</td></tr>
</table>
No difference in time to first-treatment limiting adverse events</td></tr>
</table>

<table>
<tr>
<td>STARMRK</td>
<td>Ral (400mg BID) vs. EFV (600mg QD) + TDF/FTC (n=563)</td>
<td>96 Week Results
<table>
<tr><th></th><th>RAL</th><th>EFV</th><th>95% CI</th></tr>
<tr><td>VL < 50</td><td>86%</td><td>82%</td><td>-1.9, 10.3</td></tr>
<tr><td>CD4 change</td><td>+189</td><td>+163</td><td>NS</td></tr>
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**Table 3. Issues for Consideration of Preferred and Alternative Regimen Components**

| | Atazanavir/ ritonavir | Darunavir/ ritonavir | Efavirenz/ tenofovir/ emtricitabine | Raltegravir | Lopinavir/ ritonavir | Fosamprenavir/ ritonavir | Rilpivirine/ tenofovir/ emtricitabine | Elvitegravir /cobicistat /tenofovir /emtricitabine |
|---|---|---|---|---|---|---|---|---|
| **Dosing/ Frequency** | 300/100 mg every day | 800/100mg every day | 1 Tablet every day | 400mg twice daily | 800/200mg every day OR 400/100 mg twice daily | 700/100mg twice daily or 1400mg/200mg every day | 1 Tablet every day | 1 Tablet every day |
| **Food Considerations** | With food | With food | None | None | None | None | With food | With food |
| **Pill burden**[a] | 3 pills/day | 4 pills/day | 1 pill/day | 3 pills/day | 5 pills/day | 5 pills/day | 1 pill/day | 1 pill/day |
| **Adverse effects** | Hyper-bilirubinemia (usually asymptomatic), nausea, rash, prolonged PR interval | Rash (10%; contains sulfa moiety), diarrhea (6%), nausea, headache, ↑LFTs, ↑amylase, hyperlipidemia | CNS adverse effects; ↑LFTs; false positive results on cannabinoid and BZD screening assays; potential teratogen | Nausea, headache, diarrhea, pyrexia, CPK elevation, Severe Skin and hypersen-sitivity reactions | GI intolerance (QD>BID), asthenia, ↑LFTs, hyperlipidemia (esp TG), prolonged PR interval, QT prolongation | GI intolerance, rash, headache, ↑LFTs, hyperlipidemia | Depression, insomnia, headache and rash. | Diarrhea, nausea, headache, and renal adverse events |
| **Potential for Drug interactions**<br><br>**Unique interactions** | 3A4 substrate and inhibitor<br><br>TDF, H2 blockers, PPIs | 3A4 substrate and inhibitor<br><br>carbamazepineph enobarbital, phenytoin, pravastatin, paroxetine, sertraline | 3A4 substrate, inducer and inhibitor | UGT1A1 mediated interactions | 3A4 substrate and inhibitor | 3A4 substrate inhibitor and inducer | 3A4 substrate<br><br>Use of PPI is contraindicated<br><br>Caution should be used when administered with other agents that can cause QTc prolongation | Elvitegravir is CYP3A substrate and modest inducer of CYP2C9; Cobicistat is an inhibitor of CYP3A and CYP2D6 as well as the transporters P-gp, BCRP, OATP1B1 and OATP1B3 |
| **Hepatic considerations** | Dose adjust for hepatic insufficiency (C-P >7) | Not recommended with severe hepatic impairment (C-P class C) | Use with caution in hepatic insufficiency | Use with caution in severe hepatic insufficiency | Use with caution in hepatic insufficiency | Dose adjust for hepatic insufficiency (C-P >5) | pharmacokinetics has not been adequately evaluated in individuals with severe hepatic impairment | Not recommended with severe hepatic impairment (C-P Class C) |
| **Cost / year** | $8026[b] | $7795[b] | $12,667 | $8,018 | $5951 | $7,097[b] | $13,475 | $21,041 |
| **Cost/year for Regimen (with TDF/FTC)**[c] | $16,037 | $15,806 | $12,667 | $16,029 | $13,962 | $15,108 | $13,475 | $21,041 |

Prices obtained Nov-Dec 2012; [a] includes tenofovir/emtricitabine pill burden; [b] includes ritonavir pricing; [c] tenofovir/emtricitabine

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