



### VOLUME 2, ISSUE 3

### NEW RECOMMENDATIONS FOR HAART IN HIV

#### In this Issue...

Treatment options in HIV infection continue to improve, as first-line ART becomes more effective, better tolerated, and more convenient.

In this issue we review current guidelines for initial antiretroviral therapy and a number of the recent studies that have influenced both the guidelines and current practice, including the ACTG 5257, NEAT 001, and SINGLE studies, as well as the phase III GS 102 and 103 fixed-dose trials.



#### Program Information

- [CME Info](#)
- [Accreditation](#)
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#### Length of Activity

- 1.0 hour Physicians
- 1.0 contact hour Nurses

#### Launch Date

August 28, 2014

#### Expiration Date

August 27, 2016

## LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Discuss the currently recommended antiretroviral regimens and the data supporting their use.
- Discuss the approach to patients with absolute or relative contraindications to nucleoside analogs.
- Describe a patient for whom a protease inhibitor-based regimen might be chosen for initial antiretroviral therapy.

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**Richard Moore, MD, MHS** discloses that he has served as a consultant for Merck.

**Michael Melia, MD** discloses that he has received grants from Merck, Gilead, Bristol-Myers Squibb, Janssen and AbbVie.

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## GUEST AUTHOR OF THE MONTH

Commentary & Reviews:



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***Guest Faculty Disclosure***

Dr. Gallant has indicated that he has received grant/research funding from Bristol-Myers Squibb, Gilead Sciences, Merck & Co., Sangamo BioSciences, Vertex Pharmaceuticals, and ViiV Healthcare. He has served as a consultant/advisor to Bristol-Myers Squibb, Gilead Sciences, and Janssen Therapeutics. He has been a paid member of the committee/panel/board at Takara Bio.

***Unlabeled/Unapproved Uses***

Dr. Gallant has indicated that there will be references to the following agents and combinations of agents not approved at the time this newsletter was written: a once-daily formulation of raltegravir (RAL); a dolutegravir (DTG)/abacavir (ABC)/lamivudine (3TC) coformulation; darunavir (DRV) and atazanavir (ATV) coformulations with cobicistat (cobi); tenofovir alafenamide (TAF); coformulated elvitegravir (EVG)/cobicistat (cobi)/tenofovir DF (TDF)/emtricitabine (FTC); and elvitegravir (EVG) and cobicistat (cobi) as stand-alone formulations.

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## COMMENTARY

While drug development in HIV infection has slowed over the last several years, treatment options continue to improve, making antiretroviral therapy (ART) more effective, better tolerated, and more convenient. There are many excellent options for first-line therapy. In the most recent version of the DHHS guidelines, discussed in this issue, the list of alternative options has been shortened, and the older categories of "other" and "acceptable" options have been eliminated because most patients can now be treated with a recommended regimen.

Recent trials of integrase strand transfer inhibitor (INSTI)-containing regimens, including ACTG 5257, suggest that starting therapy with an INSTI may be the optimal approach to initial therapy for most patients, based on the outstanding efficacy and tolerability of drugs in this class. Raltegravir (RAL) is the INSTI with the most long-term data and the fewest drug interactions. Its disadvantage is the need for twice-daily dosing, although a once-daily formulation is being developed. Elvitegravir (EVG) is given once a day and is currently the only INSTI available in a single-tablet formulation. However, EVG requires boosting with cobicistat (cobi), must be taken with a meal, and has similar drug interactions to ritonavir (RTV). Cobi inhibits tubular excretion of creatinine, causing an early rise in serum creatinine and a corresponding decline in estimated GFR (eGFR). This is not a true nephrotoxicity, but it limits the use of this combination to patients with eGFRs above 70 mL/min. Dolutegravir (DTG) is taken once daily with or without food, has few drug interactions, and is the only INSTI that was superior to comparator regimens at the primary endpoint<sup>1</sup> (discussed in detail in the papers by Walmsley et al, reviewed herein). Its superiority was based on differences in tolerability, not virologic efficacy, but it does appear to have a higher barrier to resistance than RAL and EVG, and to date no INSTI resistance has been observed in patients taking DTG for initial therapy. DTG also inhibits tubular excretion of creatinine, but to a lesser degree than cob. It is not yet available in a single-tablet regimen, but a DTG/abacavir (ABC)/lamivudine (3TC) coformulation is expected to be approved this year. The need for HLA B\*5701 screening and the continued controversy about the possible association of ABC with myocardial infarction will be issues with this regimen; but in patients with high viral loads, the lower efficacy of ABC/3TC compared to TDF/FTC that has been observed with both efavirenz (EFV) and atazanavir/ritonavir (ATV/r)<sup>2</sup> taken with a meal does not appear to be a concern when ABC/3TC is combined with DTG.

Two nonnucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz (EFV) and rilpivirine (RPV) are recommended for initial therapy. The fixed-dose combination of EFV/TDF/FTC has been a popular starting regimen for many years and has a wealth of clinical data and experience supporting its use. However, enthusiasm for EFV is waning, primarily because of the short- and long-term neuropsychiatric side effects and the availability of other better-tolerated regimens, including two (soon to be three) single-tablet regimens. A recent analysis of multiple ACTG trials found that EFV was associated with a two-fold increased risk of suicidality, which includes suicidal ideation, attempted suicide, and completed suicide.<sup>3</sup> Although the absolute incidence of suicidality was low, these results remind us that not all of the neuropsychiatric side effects of EFV disappear after the first few days to weeks on therapy. RPV is better tolerated, and in the STAR study, the single-tablet combination of RPV/TDF/FTC was superior to EFV/TDF/FTC in patients with baseline viral loads < 100,000 copies/mL for that reason.<sup>4</sup> However, RPV has its own drawbacks, including a higher rate of virologic failure and resistance in patients with high baseline viral loads, the potential for etravirine (ETR) cross-resistance, the need to take the medication with a full meal, and the need to avoid proton pump inhibitors.



Protease inhibitors (PIs) still have a role in initial therapy, though that role is shrinking. The most common reason for using ritonavir (RTV)-boosted PIs (PI/r), aside from the presence of transmitted NRTI or NNRTI resistance, is the high barrier to resistance. This can be important in patients with unreliable adherence, since virologic failure of a PI/r-based regimen does not result in PI resistance. Unfortunately, this means that patients at greatest risk of nonadherence are often treated with the most complex regimens. Fortunately, PI-based regimens are now easier: the two recommended regimens — the combination of either darunavir (DRV) or atazanavir (ATV) plus RTV and two NRTIs — now involve taking only three pills once daily, which will drop to two pills once the two PIs are coformulated with the pharmacologic booster, *cobi*.

The results of ACTG 5257, discussed in this issue, suggest that DRV is the most appropriate "default" PI, since it was superior to ATV from a tolerability standpoint. ATV can cause jaundice, renal insufficiency, nephrolithiasis, cholelithiasis, and greater loss in bone mineral density, but it is preferred in pregnancy and is an appropriate choice in patients with life-threatening sulfa allergies or those who have developed a rash on DRV.

My own approach is to start with an INSTI in most patients. Those who want a single tablet regimen can be treated with EVG/*cobi*/TDF/FTC. DTG plus TDF/FTC is an excellent choice for patients who don't mind taking two pills daily and when drug interactions are a concern. DTG plus ABC/3TC is appropriate for HLA B\*5701-negative patients with low cardiac risk who have kidney disease, and when the single tablet coformulation of those drugs becomes available, it will undoubtedly be more widely used.

The controversy over whether ABC increases risk of myocardial infarction has not been resolved: multiple studies have found an association, and multiple other studies have not. We are awaiting an analysis from the NA-ACCORD cohort, hoping that it will tip the scales in one direction or the other. Both the DHHS and IAS-USA guidelines recommend that ABC be avoided in patients with multiple cardiac risk factors. I sometimes use the single tablet combination of RPV/TDF/FTC in patients with viral loads < 100,000 copies/mL who do not take proton pump inhibitors or H2 blockers, although most of my patients taking this combination have been switched to it from a different initial regimen because of toxicity or the desire for simplification.

Finally, I use PI-based regimens (usually DRV/r plus two NRTIs) when there are adherence concerns, offering a switch to simpler regimens if the patients demonstrate adherence over time.

In some patients I am unwilling to use NRTIs. Examples include patients with multiple cardiac risk factors or a positive HLA B\*5701 who also have chronic kidney disease or osteoporosis. In such patients, there is no clear guidance on the selection of an NRTI-sparing regimen. My practice is to use the untested regimen of DRV/r plus DTG plus lamivudine (3TC). The rationale is that the combination of DRV/r plus RAL may have failed more often at low CD4 counts and high viral loads because of twice daily dosing of RAL (thus the choice of DTG), or it may have failed because of an intrinsic weakness in the PI plus INSTI approach (thus the addition of 3TC). It seems unlikely that we will soon have data from additional large randomized trials of NRTI-sparing regimens. The solution to this problem may ultimately be either the approval of tenofovir alafenamide (TAF), a pro-drug of tenofovir that so far appears to have less bone and kidney toxicity than TDF,<sup>5</sup> or further evidence that ABC does not increase the risk of myocardial infarction.

### Commentary References

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## THE CHOICE OF THE INITIAL ANTIRETROVIRAL REGIMEN

Landovitz RJ, Ribaldo HJ, Ofotokun I, et al. *Efficacy and tolerability of atazanavir, raltegravir, or darunavir with FTC/tenofovir: ACTG 5257*. Program and abstracts of the 2014 Conference on Retroviruses and Opportunistic Infections; March 3-6, 2014; Boston, Massachusetts. Abstract 85.



[Presentation abstract](#)

ACTG 5257 is a large, NIH-funded clinical trial comparing three of the current recommended antiretroviral (ARV) regimens for initial therapy: raltegravir (RAL), darunavir/ritonavir (DRV/r) or atazanavir/ritonavir (ATV/r), each taken in combination with tenofovir DF/emtricitabine (TDF/FTC). The study was designed in an era when the combination of efavirenz (EFV) with TDF/FTC was the most commonly prescribed initial ARV regimen and was meant to compare the regimens typically used when EFV was not an acceptable option. Three 96-week endpoints were evaluated: virologic efficacy, tolerability, and a composite efficacy/tolerability endpoint. The three regimens were equivalent in terms of virologic efficacy. However, both RAL and DRV/r were superior to ATV/r in terms of tolerability, and RAL was also superior to DRV/r using the composite endpoint. The difference was driven primarily by discontinuations due to adverse events. Not surprisingly, there were many switches in the ATV/r arm due to hyperbilirubinemia and/or jaundice, but GI side effects were also more common with ATV/r than with DRV/r, which in turn had more GI side effects than RAL.

Although both ATV and DRV are thought of as "lipid friendly" PIs, RAL had a smaller effect on lipids than either of the PIs. ATV/r was also associated with greater loss in bone density by total body DXA,<sup>1</sup> a finding that was also observed in the earlier ACTG 5202 trial.<sup>2</sup> Whether this is because of the increase in tenofovir levels by ATV or an effect of ATV itself is not known. However, patients failing PI-based therapy in ACTG 5257 had no drug resistance, whereas the small number of those who failed in the RAL arm sometimes failed with NRTI or integrase mutations, which suggests that boosted PI-based regimens still have a role for patients with unreliable adherence.

It's worth pointing out that in this study, a twice-daily regimen (RAL plus TDF/FTC) outperformed two once-daily regimens, and that among the one-daily regimens, what was then a 4-pill regimen (DRV/r plus TDF/FTC) outperformed a three-pill regimen (ATV/r plus TDF/FTC), suggesting that tolerability trumps dosing frequency and pill burden, at least in clinical trials.

The results of ACTG 5257, along with those of other first-line therapy trials, including STARTMRK (RAL).<sup>3</sup> GS 102 and GS 103 (elvitegravir/cobicistat/TDF/FTC, discussed below), SINGLE (discussed below), and FLAMINGO<sup>4</sup> (dolutegravir) all suggest that starting therapy with integrase inhibitor-based regimens may be the best approach for the majority of patients.

### References

1. Brown T, Moser C, Currier J, et al. [Bone density changes after antiretroviral initiation with protease inhibitors or raltegravir](#). 21st Conference on Retroviruses and Opportunistic Infections (CROI 2014). Boston, March 3-6, 2014. Abstract 779LB.

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2. 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;203:1791-801.
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## THE CONTINUED SEARCH FOR THE "NUKE-SPARING REGIMEN"

Raffi F, Babiker AG, Richert L, et al. *First-Line RAL + DRV/r Is Non-Inferior To TDF/FTC + DRV/r: The NEAT001/ANRS143 Randomised Trial*. Program and abstracts of the 2014 Conference on Retroviruses and Opportunistic Infections; March 3-6, 2014; Boston, MA. Abstract 84LB.



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Since the mid-1990s, the standard of care for first-line antiretroviral therapy (ART) has been two nucleoside analog reverse transcriptase inhibitors (NRTIs) plus a third agent—currently a nonnucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), or an integrase strand transfer inhibitor (INSTI). The recommended dual NRTI "backbones" are tenofovir DF/emtricitabine (TDF/FTC) and abacavir/lamivudine (ABC/3TC). However, TDF can cause nephrotoxicity, including proximal tubulopathy, and greater initial loss in bone mineral density than other agents, and ABC cannot be used in patients who test positive for HLA B\*5701 and is not recommended in patients with multiple cardiac risk factors because of a possible association with risk of myocardial infarction. Zidovudine/lamivudine (AZT/3TC) is not recommended because of its toxicity, which includes gastrointestinal side effects, fatigue, anemia, lipoatrophy, lactic acidosis, and hepatic steatosis.

The optimal choice of therapy for patients who have contraindications to NRTIs remains unclear. NEAT 001/ANRS 143 attempted to address this question in a large, randomized trial comparing the NRTI-sparing combination of raltegravir (RAL) plus once-daily darunavir/ritonavir (DRV/r) with a meal, versus the standard comparator of DRV/r plus TDF/FTC. At 96 weeks, the NRTI-sparing regimen was noninferior to the standard regimen. However, RAL plus DRV/r was inferior to DRV/r plus TDF/FTC in patients with baseline CD4 counts < 200 cells/mm<sup>3</sup> (P = 0.02) and narrowly missed criteria for inferiority in those with baseline viral load > 100,000 copies/mL (P = 0.09). These results support an earlier noncomparative study (ACTG 5262) of the same NRTI-sparing regimen, in which participants with baseline viral loads > 100,000 copies/mL had an unacceptably high rate of virologic failure.<sup>1</sup>

The reason for these findings is unclear, but there are a several potential explanations:

1. An inherent problem with NRTI-sparing regimens or two-drug regimens in general. This is unlikely. In ACTG 5142, the combination of lopinavir/ritonavir (LPV/r) plus efavirenz (EFV) was as effective as standard comparators, although it was associated with more side effects and lipid elevation.<sup>2</sup> In the GARDEL study, the combination of LPV/r plus 3TC was as effective and better tolerated than the standard combination of LPV/r plus 2 NRTIs.<sup>3</sup>
2. An inherent problem with the combination of a boosted PI plus an INSTI. This is possible, but there is no mechanism to explain what the weakness would be. The

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combination of LPV/r plus RAL was effective in the PROGRESS study,<sup>4</sup> but the sample size and number of participants with high viral loads were small.

3. A problem with the specific regimen chosen. Would once-daily dolutegravir (DTG) have been more effective than twice-daily RAL in combination with once-daily DRV/r? The more convenient and symmetrical dosing might have resulted in greater adherence and better results. On the other hand, the "asymmetrical," twice-daily regimen of RAL plus TDF/FTC outperformed two once-daily regimens in ACTG 5257, discussed above.

We don't know the best approach to patients who can't take NRTIs. Some argue that despite its weaknesses, the NEAT 001 combination is preferred because data exist demonstrating acceptable efficacy. Others make extrapolations, using DTG rather than RAL, for example, or adding one of the "benign" NRTIs, lamivudine or emtricitabine. One promising solution to the problem is tenofovir alafenamide (TAF), which shows promise in early studies as a form of tenofovir without significant renal or bone toxicity.<sup>5</sup> However, until that drug is approved, clinicians will have to use the available data to choose NRTI-sparing regimens in patients who need them.

### References

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4. Reynes J, Trinh R, Pulido F, et al. [Lopinavir/ritonavir combined with raltegravir or tenofovir/emtricitabine in antiretroviral-naïve subjects: 96-week results of the PROGRESS study](#). *AIDS Res Hum Retroviruses*. 2013;29:256-65.
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## ANOTHER WIN FOR DOLUTEGRAVIR

Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med*. 2013;369:1807-18.



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Walmsely S, et al. Program and abstracts of the 2014 Conference on Retroviruses and Opportunistic Infections; March 3-6, 2014; Boston, MA. Abstract 543.

Dolutegravir (DTG), the third approved integrase strand transfer inhibitor (INSTI), has done well in every trial in which it has been studied. In SPRING-2<sup>1</sup> it was noninferior to raltegravir (RAL) in combination with two nucleoside reverse transcriptase inhibitors (NRTIs). In FLAMINGO,<sup>2</sup> it was superior to darunavir/ritonavir (DRV/r) in combination with two NRTIs based on greater tolerability. The VIKING study demonstrated activity of double-dose DTG in some patients with resistance to raltegravir (RAL) and elvitegravir (EVG),<sup>3</sup> and SAILING-2 found that DTG was superior to RAL in ART-experienced, INSTI-naïve patients.<sup>4</sup>

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The SINGLE trial is a phase III, double-blind comparison of DTG plus abacavir/lamivudine (ABC/3TC) versus efavirenz/tenofovir DF/emtricitabine (EFV/TDF/FTC). The DTG-based regimen was superior to the EFV-based regimen at the 48-week primary endpoint and again at 96 weeks. DTG was superior to EFV in patients with baseline viral loads < 100,000 copies/mL and was noninferior in those with higher baseline viral loads (> 100,000 copies/mL). Superiority was driven primarily by tolerability, with fewer patients discontinuing therapy because of adverse events.

It is notable that none of the initial therapy trials- SPRING-2, FLAMINGO, or SINGLE - have demonstrated any INSTI resistance in patients failing therapy with a DTG-based regimen. This is in contrast to studies of RAL- or EVG-based regimens, where integrase mutations have been observed with failure. Although this could be explained in part by the fact that resistance testing was performed earlier in the case of virologic failure in most DTG trials compared to trials of the other INSTIs, it is becoming accepted that DTG has a higher barrier to resistance than RAL or EVG. What is not known is how its resistance barrier compares with that of the boosted PIs. It has become clear over the course of multiple clinical trials and years of clinical experience that patients without baseline PI resistance do not develop PI mutations with virologic failure. We cannot say that yet about DTG.

DTG-based regimens are now recommended for initial therapy in the DHHS antiretroviral guidelines and appear to be attractive choices for many patients. The only real drawback is the lack of a single-tablet coformulation, although a coformulation of DTG/abacavir (ABC)/lamivudine (3TC) is expected to be approved soon. It will have the advantages of being the only non-TDF-containing single-tablet regimen and a regimen with relatively few drug interactions (in contrast to EVG/cobicistat/TDF/FTC). However, the coformulation with ABC means that HLA B\*5701 prescreening will be required, and guidelines continue to recommend that ABC be avoided in patients with a high risk of myocardial infarction. Patients who are not good candidates for ABC can still take the two-tablet, twice-daily combination of DTG plus TDF/FTC.

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2. Clotet B, Feinberg J, van Lunzen J, et al. [Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection \(FLAMINGO\): 48 week results from the randomised open-label phase 3b study](#). *Lancet*. 2014 Mar 31. pii: S0140-6736(14)60084-2.
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## THE ELVITEGRAVIR/COBICISTAT/TENOFOVIR/ EMTRICITABINE "QUAD"

Clumeck N, Molina JM, Henry K, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. *J Acquir Immune Defic Syndr*. 2014;65:e121-4.

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Wohl DA, Cohen C, Gallant JE, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF versus single-tablet regimen efavirenz/emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. *J Acquir Immune Defic Syndr*. 2014;65:e118-20



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Elvitegravir (EVG) is an integrase strand transfer inhibitor (INSTI) that is administered once daily and requires pharmacologic boosting with the CYP3A4 inhibitor, cobicistat (cobi), which has drug interactions that are similar to those of ritonavir (RTV). It is currently available only in a single-tablet formulation with cobin, tenofovir DF (TDF), and emtricitabine (FTC), which is a recommended regimen for initial therapy in the DHHS guidelines based on the results of two phase III comparative trials: GS 102, in which it was compared with efavirenz (EFV)/TDF/FTC, and GS 103, in which it was compared with atazanavir/ritonavir (ATV/r) plus TDF/FTC. In both trials it was noninferior to the comparators, with nonsignificant differences favoring the EVG-based regimen by intention-to-treat analysis.

In GS 102, the EVG-containing regimen demonstrated noninferiority with the EFV-containing regimen at 48, 96, and 144 weeks, with few virologic failures in either arm. At 144 weeks, there was a non-significant difference in efficacy of 4.9% favoring the EVG regimen. The EVG combination had advantages over EFV in terms of side effects, mainly because of the difference in neuropsychiatric effects. Although there had been some discontinuations because of renal toxicity during the first year of the study, no new cases of proximal tubulopathy were identified after the first 24 weeks, and serum creatinine remained stable after the expected increase through week 4, which is a result of cobin's inhibitor of tubular excretion of creatinine, discussed above. Resistance was observed in 3% of patients, with no new emergent mutations after week 96.

In GS 103, the EVG-containing regimen demonstrated noninferiority compared with the ATV/r-containing regimen at 48, 96, and 144 weeks, with few virologic failures in either arm. At 144 weeks, there was a nonsignificant difference in efficacy of 3.1% favoring the EVG regimen. As in GS 102, no new cases of proximal tubulopathy were identified after the first 24 weeks, and serum creatinine remained stable after week 4. Differences in serum creatinine and eGFR between the EVG and comparator arm were less pronounced in GS 103 than in GS 102 because RTV, a component of the comparator arm in GS 103, also inhibits tubular excretion of creatinine, though to a lesser degree than cobin.

Because serum creatinine can be expected to rise during the first month of therapy, with an average increase of approximately 0.15 mg/dl, EVG/cobi/TDF/FTC is not recommended for patients with baseline eGFRs of < 70 mL/min, and it should be discontinued if the eGFR falls below 50 mL/min. Continued declines in eGFR after the first four weeks should not be attributed to cobin, and the evaluation should include markers of TDF-associated tubular toxicity.

EVG and cobin are currently available only in the four-drug coformulation, but approval of standalone formulations is expected later this year, which will allow cobin to be used as a pharmacoenhancer for protease inhibitors. Coformulations of cobin with ATV and with DRV are expected to be approved shortly after approval of cobin. EFV and cobin are also being studied in coformulation with FTC and tenofovir alafenamide (TAF), discussed above.

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## INITIAL THERAPY AND LABORATORY MONITORING IN THE NEW DHHS TREATMENT GUIDELINES

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services.



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RECOMMEND TO A COLLEAGUE

NEWSLETTER ARCHIVE

The Department of Health and Human Services (DHHS) antiretroviral therapy guidelines were updated on May 1, 2014. The new version, which continues to recommend antiretroviral therapy (ART) for all patients regardless of CD4 count or viral load, includes a number of important changes related to the selection of the initial regimen and subsequent laboratory monitoring.

1. **"Recommended Regimens"**: The panel abandoned the term "preferred regimens" in part because of the addition of regimens that are recommended only in patients with baseline viral loads < 100,000 copies/ml. The argument is that those regimens have been shown to be highly effective in patients with lower viral loads, but that restriction makes the term "preferred" less appropriate. The recommendations for patients at any viral load are:

a. *NNRTI-based regimens*: efavirenz/tenofovir DF/emtricitabine (EFV/TDF/FTC)

b. *PI-based regimens*: darunavir/ritonavir (DRV/r) plus TDF/FTC; atazanavir/ritonavir (ATV/r) plus TDF/FTC

c. *INSTI-based regimens*: dolutegravir (DTG) plus TDF/FTC; DTG plus abacavir/lamivudine (ABC/3TC); elvitegravir (EVG)/cobicistat (cobi)/TDF/FTC; raltegravir (RAL) plus TDF/FTC

Patients with baseline viral loads < 100,000 copies/mL can start therapy with any of the above regimens or with EFV plus ABC/3TC; rilpivirine (RPV)/TDF/FTC; RPV plus ABC/3TC; or ATV/r plus ABC/3TC

2. **"Alternative Regimens"**: The number of alternative regimens has been shortened, and the category of "Other Regimens" has been eliminated, reflecting the fact that most patients can now be treated with a recommended regimen. Current alternative regimens include DRV/r plus ABC/3TC; lopinavir/ritonavir (LPV/r) plus ABC/3TC, LPV/r plus TDF/FTC, and RAL plus ABC/3TC.

3. **Agents "Not Recommended"**: Zidovudine (AZT), nevirapine (NVP), unboosted ATV, ritonavir-boosted fosamprenavir (FPV/r), ritonavir-boosted saquinavir (SQV/r) and maraviroc (MVC) have been added to the list of agents that are not recommended for initial therapy, either because of toxicity (AZT, NVP, SQV/r), pill burden (SQV/r) or insufficient efficacy or efficacy data (NVP, ATV, FPV/r, MVC).

4. **Laboratory monitoring**: Recognizing that the viral load is the most important measure of response to ART, the new guidelines deemphasize the importance of CD4 monitoring, and point out that these two tests should no longer be linked. Current recommendations are that the CD4 count be monitored every three to six months before initiating ART, three months after initiating ART, every three to six months during the first two years of ART, and yearly after two years on ART if the viral load is consistently suppressed and the CD4 count is in the 300-500 cells/mm<sup>3</sup> range. In virologically suppressed patients with CD4 counts > 500 cells/mm<sup>3</sup>, continued CD4 monitoring is optional. The guidelines also point out that more complex and costly lymphocyte subset panels that include markers other than CD4 (eg, CD8, CD19) should not be ordered, as the results are not used in clinical decision-making. Patients are sometimes concerned about the reduction in frequency of CD4 count monitoring, and clinicians may order unnecessary CD4 counts for that reason alone. However, just as we taught our patients to care about their CD4 counts through education, we can and should re-educate them that viral load monitoring is far more important than CD4 monitoring in the era of universal ART.

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- As the demographics of HIV have shifted to include many older adults, clinicians require education regarding the treatment of common comorbidities.
- Clinicians may be unclear about issues specific to the diagnosis and treatment of women with HIV.
- Many clinicians require education regarding current treatment and new emerging hepatitis C medications in patients coinfecting with HIV/HCV who require antiretroviral therapy.
- Clinicians may need an update on current recommendations for the treatment of HIV with HAART.

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The target audience (clinicians) for this initiative includes infectious disease (ID) specialists, primary care physicians (PCPs), nurse practitioners (NPs), physician assistants (PAs), and other health care practitioners whose work/practice includes treating patients with HIV.

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