Recommendation on Integrase Inhibitor Use in Antiretroviral Treatment-Naive HIV-Infected Individuals from the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents (October 30, 2013)

Introduction

In the February 12, 2013, version of the Health and Human Services (HHS) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, the Panel recommendations on initial combination regimens for the antiretroviral therapy (ART)-naive, HIV-infected patient include raltegravir (RAL) plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) as the preferred integrase strand transfer inhibitor (INSTI)-based regimen, and elvitegravir (EVG)/cobicistat (cobi)/TDF/FTC as an alternative regimen for patients with estimated creatinine clearance (CrCl) ≥70 mL/min. Since the release of the Guidelines, a new INSTI, dolutegravir (DTG), was approved for use in ART-naive and ART-experienced patients. Additionally, long-term follow-up data (up to 144 weeks) from randomized clinical trials have demonstrated the durable safety and efficacy of EVG/cobi/TDF/FTC.

On the basis of these new findings, the Panel now recommends the following 4 INSTI-based regimens as preferred regimens for ART-naive patients (arranged in order of drug approval):

- Raltegravir 400 mg twice daily plus tenofovir 300 mg/emtricitabine 200 mg once daily **(AI)**
- Elvitegravir 150 mg/cobicistat 150 mg/tenofovir 300 mg/emtricitabine 200 mg once daily in patients with estimated CrCl ≥70 mL/min **(AI)**
- Dolutegravir 50 mg once daily plus abacavir 600 mg/lamivudine 300 mg once daily in patients who are HLA B*5701 negative **(AI)**
- Dolutegravir 50 mg once daily plus tenofovir 300 mg/emtricitabine 200 mg once daily **(AI)**

Rationale for Upgrading Elvitegravir/Cobicistat/Tenofovir/Emtricitabine to a Preferred INSTI-Based Regimen

Since the inclusion of co-formulated EVG/cobi/TDF/FTC as an alternative INSTI in the February 2013 guidelines, 96 week data from 2 Phase 3 clinical trials have been published,[1,2] and additional data through 144 weeks have been presented.[3,4] In these studies, EVG/cobi/TDF/FTC remained non-inferior to co-formulated efavirenz (EFV)/TDF/FTC[3] and to ritonavir-boosted atazanavir (ATV/r) plus TDF/FTC at Week 144.[4] No additional occurrences of proximal renal tubulopathy were reported in the EVG/cobi/TDF/FTC-treated participants in either study beyond 24 weeks. Additionally, following early, modest increases in serum creatinine observed with EVG/cobi/TDF/FTC therapy, there were no further increases in creatinine levels through Week 144.[3,4] These data, along with post marketing clinical experience with the co-formulated product, are the basis for the Panel's decision to recommend EVG/cobi/TDF/FTC as a preferred regimen for ART-naive patients.

Dolutegravir-Based Regimens for Treatment-Naive Patients

In 3 Phase 3 randomized controlled trials, DTG 50 mg once daily plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) was compared to 3 Guidelines-designated preferred regimens:

1. DTG versus RAL, administered either with investigator-selected abacavir/lamivudine (ABC/3TC) or TDF/FTC;[5]
2. DTG plus ABC/3TC versus EFV/TDF/FTC;[6] and
3. DTG versus ritonavir-boosted darunavir (DRV/r), administered either with investigator-selected ABC/3TC or TDF/FTC.[7]

The primary endpoint for these trials was the proportion of patients with HIV RNA <50 copies/mL at Week 48. DTG was found to be non-inferior to RAL at Week 48 and also at Week 96.[5,8] DTG-based regimens were also found to be superior to DRV/r- and EFV-containing regimens, largely because of more discontinuations for adverse events or other reasons in the comparator arms. No emergent DTG resistance has been observed thus far in clinical trials of DTG in treatment-naive patients.

Overall, DTG was well tolerated in clinical trials, with insomnia and headache of moderate to severe intensity (in 3% and 2% of patients, respectively) being the most commonly reported adverse effects. Cases of hypersensitivity reaction have been reported in clinical trials. DTG decreases tubular secretion of creatinine without affecting glomerular function, with increases in serum creatinine observed within the first 4 weeks of treatment (mean change from baseline in serum creatinine of 0.11 mg/dL after 48 weeks); no discontinuations due to drug-related renal adverse events have been seen to date.[9]

Summary

In summary, all three approved INSTIs have been shown in randomized clinical trials to be non-inferior to other preferred ART regimens for treatment-naive patients. Each INSTI-based regimen has distinctive characteristics; certain clinically relevant features are summarized below and in Table 1.

- **Raltegravir** remains a preferred INSTI because it has the longest clinical trial and post-marketing experience and has been shown to have durable potency. However, it requires twice daily dosing.
- **Elvitegravir** is available as a fixed-dose combination product that is taken as a single-tablet, once-daily regimen. It must be given with food. The fixed-dose combination product includes cobi, which is a potent CYP3A4 inhibitor that may result in drug-drug interaction with other concomitant medications. Additionally, the fixed-dose combination product is only approved for patients with estimated creatinine clearance of ≥70 mL/min.
- **Dolutegravir** is the most recently approved INSTI. It can be given once daily with or without food. In randomized trials, DTG was non-inferior to RAL and was superior to both DRV/r and EFV (because of fewer drug discontinuations in those who received DTG). However, DTG has the shortest duration of follow-up and limited post-marketing experience to date.

Table 1. Comparison of 4 INSTI-Based Regimens

	RAL + TDF/FTC	EVG/cobi/TDF/FTC	DTG + ABC/3TC	DTG + TDF/FTC
Comparators in Randomized Trials	EFV/TDF/FTC	EFV/TDF/FTC ATV/r + TDF/FTC	EFV/TDF/FTC DRV/r + 2 NRTI RAL + 2 NRTI	DRV/r + 2 NRTI RAL + 2 NRTI
Follow-Up Data	>5 years	144 weeks	48–96 weeks	48–96 weeks
Post-Marketing Experience	6 years	1 year	Minimal	Minimal
Dosing Frequency	Twice daily	Once daily	Once daily	Once daily
Numbers of Tablets Per Day	3	1	2	2
Meal Consideration	None	Take with a meal	None	None
CYP 3A4 Interactions	No	Yes • cobi—potent CYP3A4 inhibitor • EVG—CYP3A4 substrate	No • DTG—minor CYP3A4 substrate	No • DTG–minor CYP3A4 substrate
CrCl and Dosing	Dosage adjustment for TDF and FTC if CrCl <50 mL/min	Not recommended if CrCl <70 mL/min	Dosage adjustment for 3TC if CrCl <50 mL/min	Dosage adjustment for TDF and FTC if CrCl <50 mL/min
HLA B*5701 (+) Patients	No concern	No concern	Do not use this regimen.	No concern

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ATV/r = atazanavir/ritonavir; cobi = cobicistat; CrCl = creatinine clearance; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; RAL = raltegravir; TDF = tenofovir disoproxil fumarate

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