Triumeq\textsuperscript{®}: The Newest Single-Tablet Regimen for HIV Treatment Naive Patients

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INTRODUCTION
Over 1 million people in the United States are infected with HIV.\textsuperscript{1} The rates of deaths resulting from HIV have decreased, from 45,000 in 1996 to under 10,000 in 2010, due to increased treatment options. At the same time, rates of newly diagnosed individuals demonstrates that HIV remains a major health concern.\textsuperscript{2} This concern is even more prominent in places such as El Paso County, where rates of newly diagnosed individuals have increased from 10.1% in 2008 to 14.1% in 2013.\textsuperscript{3}

Due to the growth and success of efficacious HIV treatment options, tolerability and convenience of regimens have become key factors for healthcare professionals when deciding initial regimens. As a result of the significant impact a patient’s adherence has on the success of antiretroviral therapy, single-tablet combination regimens have become the focus of many pharmaceutical companies in recent years. Triumeq\textsuperscript{®} is the newest single-tablet regimen, which combines a 2\textsuperscript{nd} generation integrase inhibitor (INSTI), dolutegravir, with the dual nucleoside reverse transcriptase inhibitors (NRTI) backbone, abacavir and lamivudine.\textsuperscript{4} This is a significant development in antiretroviral therapy, as Triumeq\textsuperscript{®} is the first single-tablet regimen that does not contain the dual NRTI backbone, tenofovir and emtricitabine. Additionally, dolutegravir has demonstrated promising data with regards to efficacy and resistance.\textsuperscript{5,6}

CURRENT GUIDELINES
The Department of Health and Human Services and International Antiviral Society – USA practice guidelines recommend that optimal HIV treatment should consist of two nucleoside reverse transcriptase inhibitors (NRTI) in combination with a third active antiretroviral drug from the following drug classes: an integrase inhibitor (INSTI) or a boosted protease inhibitor (PI), specifically ritonavir-boosted darunavir.\textsuperscript{7,8} The guidelines were updated in 2014 to endorse the use of the 2\textsuperscript{nd} generation INSTI, dolutegravir, in combination with two NRTIs as a first-line regimen for treatment-naive patients. This coincides closely with the August 2014 FDA approval of, Triumeq\textsuperscript{®}.\textsuperscript{4} Most recently, the April 2015 guidelines no longer recommends Atripla\textsuperscript{®} (efavirenz/emtricitabine/tenofovir) and Complera\textsuperscript{®} (rilpivirine/emtricitabine/tenofovir) as first-line options for treatment-naive patients. Consequently, Stribild\textsuperscript{®} (elvitegravir/cobicistat/tenofovir/emtricitabine) and Triumeq\textsuperscript{®} are the only twosingle-tablet combination regimens recommended as first-line for treatment-naive patients.

TRIUMEQ\textsuperscript{®} (dolutegravir/abacavir/lamivudine)

CLINICAL Efficacy
Triumeq\textsuperscript{®} is the newest one-pill, once-a-day, fixed dose combination regimen and the FDA approval was based partially on three pivotal randomized-controlled trials comparing dolutegravir with current first-line options in treatment-naive HIV patients.\textsuperscript{4} In the SINGLE trial, dolutegravir plus abacavir/lamivudine combination once daily was compared with Atripla\textsuperscript{®}.\textsuperscript{9} At 48 weeks, sustained virologic response was demonstrated in 88% of the dolutegravir-group versus 81% in the efavirenz group.\textsuperscript{9} This is significant as the dolutegravir plus abacavir/lamivudine regimen is the first regimen to show one-year superiority over Atripla\textsuperscript{®}. The dolutegravir group also resulted in statistically significant shorter times to viral suppression and greater increases in CD4 counts compared with the Atripla\textsuperscript{®} group.\textsuperscript{9}

The FLAMINGO trial, which compared dolutegravir with ritonavir boosted darunavir, significantly demonstrated at 48 weeks, sustained virologic response in 90% of dolutegravir patients versus 83% of darunavir patients.\textsuperscript{7} Again, this is the first time a regimen has demonstrated superiority toritonavir-boosted darunavir. Both the SINGLE and FLAMINGO trials established superiority of

<table>
<thead>
<tr>
<th>Integrase Strand Transfer Inhibitor-Based Regimens:</th>
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<tr>
<td>• Dolutegravir/abacavir/lamivudine—only for HLA-B*5701 negative patients</td>
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<tr>
<td>• Dolutegravir plus tenofovir/emtricitabine</td>
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<tr>
<td>• Elvitegravir/cobicistat/tenofovir/emtricitabine—only for patients with pre-therapy CrCl &gt;70 ml/min</td>
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<td>• Raltegravir plus tenofovir/emtricitabine</td>
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<tr>
<td>Protease Inhibitor-Based Regimen:</td>
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<tr>
<td>• Darunavir/ritonavir plus tenofovir/emtricitabine</td>
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dolutegravir with the comparator. The SPRING-2 trial showed noninferiority when comparing once daily dolutegravir with twice-daily raltegravir at 96 weeks.

SAFETY
In the SINGLE trial, the dolutegravir group demonstrated statistical superiority to Atripla, primarily due to the higher discontinuation rate because of adverse events in the Atripla group. The dolutegravir group exhibited a generally more favorable safety profile than the Atripla group, with specifically less CNS adverse events and lipid profile changes. The most common adverse events reported for dolutegravir group were nausea, diarrhea, nasopharyngitis, headache, and insomnia.

The lack of the tenofovir component in Triumeq, may allow this regimen to be an option for patients with renal dysfunction, although the package insert does not recommend in patients with a creatinine clearance less than 50ml/min. Although slight increases in creatinine serum concentrations have been initially noted in patients on dolutegravir, these increases remain stable during follow-up and combined analysis of the SINGLE and SPRING-2 trials found no significant difference in renal safety when compared to efavirenz or raltegravir.

There are also disadvantages to this regimen. The abacavir component requires patients to receive HLA-B*5701 genetic testing before initiation in order to identify those at risk for developing abacavir-associated hypersensitivity reactions. It should also be noted that controversy exists regarding the impact of abacavir on cardiovascular disease and risk for myocardial infarction. However, this link is currently unclear and there remains conflicting data on whether abacavir should be avoided in patients with cardiovascular disease.

RESISTANCE
Results from numerous trials demonstrate promising resistance data with the use of dolutegravir. In the SINGLE trial, none of the dolutegravir arm patients developed resistance mutations to dolutegravir upon early virological failure. Results from the VIKING trial demonstrate that unlike elvitegravir, dolutegravir demonstrates a significantly greater barrier to resistance; dolutegravir remains active in the majority of patients possessing 1st-generation INSTI associated resistance mutations. This indicates that Triumeq may be a better regimen option for treatment-experienced patients than Striibild, which contains elvitegravir.

However, there are still concerns regarding whether the genetic barrier to resistance with dolutegravir is comparable to that of a boosted PI regimen, in which patients very rarely develop resistance. There are clinical trials in progress that are evaluating this concern. The results of these trials will help determine whether Triumeq should be used in patients with high risk for poor adherence, which facilitates resistance development.

ADDITIONAL CONSIDERATIONS
Triumeq does not have food requirements or concerns regarding meal fat content, which is an advantage over Striibild and other therapy options. Another potential advantage to Triumeq is that dolutegravir is metabolized primarily through the UGT1A1 enzyme and minimally via CYP3A4, which reduces the drug-drug interactions with dolutegravir when compared to other antiretroviral agents. Additionally, there are no significant drug interactions with proton pump inhibitors, methadone nor oral contraceptives. However, similar to Striibild, administration of antacids, calcium, and/or other cation-containing supplements should be separated from dolutegravir administration due to reduction of dolutegravir serum concentrations.

The cost of a 30-day supply of Triumeq is $2650, which is slightly less than Striibild at $2950. Fortunately, both single-tablet regimens are available through the Texas HIV Medication Program.

PLACE IN THERAPY
With the recent approvals of two new single-tablet regimens over the last 5 years and more co-formulations in the pipeline, healthcare providers are being provided with various treatment options for treatment-naive HIV patients. Triumeq demonstrates superiority in comparison to the previous first-line regimens Atripla and ritonavir-boosted darunavir regimen. In addition, Triumeq may be a better option in renal impairment that Striibild. Although, the mandatory genetic screening test for HLA-B*5701 is a disadvantage to Triumeq, the minimal risk for significant drug-drug interactions and promising resistance data are both persuasive points for the use of Triumeq.

Acknowledgements: Grecia Heredia, PharmD

REFERENCE

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