Stemming the Tide: Can New Approaches to HIV Treatment Reverse the Trend of Rising Drug Prices in the United States?

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(See the HIV/AIDS Major Article by Girouard et al on pages 784–91.)

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The United States pays the highest prices for prescription medications in the world, with total spending of $374 billion in 2014, an increase of 13% over the prior year [1]. Standard branded 3-drug antiretroviral therapy (ART) regimens for the treatment of human immunodeficiency virus (HIV) infection cost >$30 000/year. In this issue of Clinical Infectious Diseases, Girouard et al present a new strategy to lower ART costs. They evaluate the cost-effectiveness and budget impact of 2-drug dolutegravir (DTG) and lamivudine (3TC), in place of standard 3-drug therapy with DTG, 3TC, and abacavir (ABC). Two-drug therapy would either be given as initial treatment, or as maintenance treatment for virologically suppressed patients.

The investigators used the average wholesale price (AWP) of $31 800/person/year for branded DTG/ABC/3TC, with a cost of branded DTG and generic 3TC of $22 900/person/year. They then applied a 23% and 70% discount on branded and generic drugs, respectively, based on a Medicaid drug price report comparing average manufacturer price to AWP [2]. This yielded annual costs of $24 500 for branded DTG/ABC/3TC and $15 200 for DTG + 3TC. Thus, the removal of ABC and use of generic 3TC resulted in an estimated savings of $9300/person/year. With univariate and multivariate sensitivity analyses, wide ranges were applied to key assumptions, including 48-week virologic suppression rates, subsequent virologic failure rates, and Medicaid-discounted ART costs. They found that the incremental cost-effectiveness ratio was $22 500/quality-adjusted life year (QALY) for 2-drug maintenance therapy, and >$500 000/QALY for standard 3-drug therapy. With 50% uptake among patients newly starting ART in the United States, cost savings would total $550 million for induction-maintenance therapy within 5 years, with savings of >$3 billion if 25% of currently suppressed patients in the United States were switched to DTG + 3TC maintenance.

Preliminary data on the use of DTG + 3TC are encouraging. The 24-week results of the Dolutegravir-Lamivudine as Dual Therapy in Naïve HIV-Infected Patients: A Pilot Study (PADDLE) were presented at the 15th European AIDS Conference in October 2015, after the study by Girouard et al was completed [3]. This proof-of-concept study evaluated the antiviral efficacy, safety, and tolerability of a DTG + 3TC regimen in 20 HIV-infected, ART-naive adults who were hepatitis B surface antigen negative, with no resistance to nucleoside medications. The median CD4 count at baseline was 407 cells/µL (interquartile range [IQR], 296–517 cells/µL), with median HIV type 1 RNA load of 24 128 copies/mL (IQR, 11 686–36 794 copies/mL). All participants had viral load <400 copies at week 3, and <50 copies at week 12.

The PADDLE study was implemented after the publication of 3 fully powered randomized clinical trials that found that a boosted protease inhibitor (PI) + 3TC was noninferior to standard 3-drug ART. The Global Antiretroviral Design Encompassing Lopinavir/r and Lamivudine vs. LVP/r (GARDEL) study evaluated lopinavir/ritonavir + 3TC in treatment-naive patients initiating ART, the Study to Evaluate the Activity and Tolerability of Lopinavir/Ritonavir and Lamivudine Bitherapy in HIVI Patients with Viral Suppression (OLE) study evaluated lopinavir/ritonavir + 3TC in virologically suppressed patients with no history of drug resistance, and the Simplification to Atazanavir/Ritonavir + Lamivudine as Maintenance Therapy (SALT) study evaluated maintenance therapy with atazanavir/ritonavir + 3TC [4–6]. Although these PI-based results are encouraging, a DTG-based 2-drug regimen may be preferable, as DTG has fewer drug interactions and side effects than PI-based regimens, and also has a higher barrier to resistance.

Girouard et al recommend that, if further pilot study data demonstrate high rates of virologic suppression with the
DTG + 3TC regimen, a large-scale randomized noninferiority study be undertaken to evaluate the efficacy of dual therapy. We agree with this recommendation. Although results of dual therapy with DTG are encouraging to date, the numbers are small and follow-up time is short. Furthermore, results from dual PI-based therapy may not be duplicated with a DTG-based regimen. If dual therapy is shown to be noninferior, the study costs would rapidly be recouped, due to lower ART costs. In addition, this strategy could reduce long-term medication toxicity and preserve ABC for use for later regimens.

This study by Girouard et al is important, offering the rare potential to save costs without sacrificing quality of care, and highlighting the enormous impact of ART prices in the cost-effectiveness of HIV therapy. Another strategy to consider in future economic analyses is the use of generic ABC and 3TC in 3-drug regimens, although the impact on treatment adherence would need to be considered, due to separate medication formulations. In the future, it is possible that pill burden could be reduced with the provision of generic co-formulated ABC + 3TC. However, the costs saved from the use of generic ART regimens will depend on future medication prices. Currently the average wholesale price of generic ABC and 3TC are only 10% and 14% lower than the branded drugs, respectively. However, the range of costs paid for these medications in the United States is wide, depending on the payer and the negotiated rates, discounts, and rebates (Table 1). Prices also vary widely between retail pharmacies. For example, the website GoodRx (www.goodrx.com) compares retail prices for prescription medications in the United States. On 10 November 2015, the price for generic abacavir on this site varied from $234 to $438/month, and the price for generic lamivudine varied from $175 to $336/month. Hopefully, the prices for these medications will decline as more generic producers enter the marketplace.

In discussing strategies to lower the cost of ART, it is worthwhile to highlight the successful experience of the US President’s Emergency Plan for AIDS Relief (PEPFAR). PEPFAR was created in 2003 to provide HIV treatment for patients in low- and middle-income countries with a high burden of HIV. In 2004, the US Food and Drug Administration (FDA) initiated an expedited review process, which includes rapid evaluation of antiretroviral medications from any manufacturer internationally, to issue tentative approval for use outside of the United States if the medications meet FDA standards. By 2012, the average time for FDA evaluation and tentative approval of generic antiretrovirals had been reduced to 2 months, and >150 drug products had been approved. Due to the use of generic medications, the cost of ART in PEPFAR programs dropped from $1100/person/year in 2004 to $334/person/year in 2012 [8]. In 2014, ABC costs in PEPFAR-supported countries were about 5% of the AWP for generic ABC in the United States ($345/person/year in South Africa, $284 in Haiti, and $274 in Cambodia) [7]. Lamivudine costs in PEPFAR countries were about 1% of the AWP for the generic medication in the United States ($48/person/year in South Africa, $47 in Cambodia, and $44 in Haiti). Margins are thin with these low prices, which are possible only through bulk procurement. However, if costs for generic ART medications in the United States could be decreased even to a level that was 10-fold higher than the PEPFAR costs, the budget impact would be substantial.

If some portion of these cost savings could be shifted to supporting services to improve engagement and retention in care, it could have major impact on the HIV epidemic in the United States. Currently, the Centers for Disease Control and Prevention estimates that of the 1.2 million people living with HIV in the United States, 86% are aware of their diagnosis, 40% are engaged in care, 37% are prescribed ART, and 30% have suppressed viral loads [9]. In comparison, of the estimated 204,899 individuals who were living with HIV in Rwanda in 2013, 86% were in care, 63% had initiated ART, and 52% had suppressed viral loads [10]. Although patient characteristics are very different in Africa and the United States, many PEPFAR-supported programs provide community-based support to help patients overcome barriers to remaining in care. A recent study found that interventions to improve retention in care in the United States could be cost-effective, with large population impact [11]. Yet, with future budget cuts, if existing ancillary services that help maintain the current level of care engagement are cut, it could

### Table 1. Monthly Treatment Costs for Abacavir and Lamivudine

<table>
<thead>
<tr>
<th>Medication</th>
<th>US–AWP (B); US–Discounted Price (G)</th>
<th>US–GoodRx (US)</th>
<th>Haiti (US)</th>
<th>Cambodia (US)</th>
<th>South Africa (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>$670 (B); $603 (G)</td>
<td>$516 (B); $181 (G)</td>
<td>$234 (G)</td>
<td>$24</td>
<td>$23</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>$499 (B); $430 (G)</td>
<td>$384 (B); $129 (G)</td>
<td>$175 (G)</td>
<td>$4</td>
<td>$4</td>
</tr>
</tbody>
</table>

**Abbreviations:** AWP, average wholesale price; B, brand name; G, generic; US, United States.

a Discounted from AWP 70% for generic drugs and 23% for brand name.
b Lowest price on GoodRx (www.goodrx.com) on 10 November 2015 (lowest price for both abacavir and lamivudine was at Walgreens). c Median treatment cost, World Health Organization global price reporting mechanism, 2014 [7].
have a further negative impact on the epidemiology of HIV in the United States.

In conclusion, the findings of the cost-effectiveness analysis of DTG + 3TC presented by Girouard et al are novel and compelling. If the ongoing DTG + 3TC pilot studies demonstrate high rates of virologic suppression, this would provide strong justification for a fully powered clinical trial. Two-drug strategies offer real potential to reduce HIV treatment costs, not only in the United States but in other countries as well. As the United States and other countries are moving toward AIDS elimination by 2030 with the available treatment and prevention tools, having highly active and cost-effective ART is going to be an essential part of this initiative.

Notes

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References


8. Venkatesh KK, Mayer KH, Carpenter CC. Low-cost generic drugs under the President’s Emergency Plan for AIDS Relief drove down treatment cost; more are needed. Health Aff (Millwood) 2012; 31:1429–38.

