Preparing for Generics in the U.S.

May 9, 2013 By Tim Horn

Advocacy efforts surrounding the development, optimization and availability of generic antiretrovirals (ARVs) has primarily focused on nations in the global south, where highly effective regimens are available for less than $200 per patient, per year, and as a result, 14 million life-years have been saved, including nine million in sub-Saharan Africa, since 1995. With patent expirations pending over the next four to five years for several Department of Health and Human Services (HHS)-preferred and -alternative ARVs,* attention to the potential for cost savings--along with the safety, efficacy and convenience of generic options to be made available in the U.S.--is now critical.

According to mathematical modeling published by Rochelle Walensky, MD, and colleagues, an Atripla (efavirenz, emtrictabine and tenofovir DF)-comparable regimen consisting of generic lamivudine (approved in 2011), generic efavirenz (expected to become available in 2014-2015), and brand-name brand tenofovir (Viread; not expected to go off patent until at least 2017), prescribed as individual once-daily tablets, was associated with a 50 percent reduction in drug costs and savings of $920 million in the first year of availability alone.

Of potential concern is Walensky and colleagues' conclusion that this regimen would be associated with reduced efficacy, resulting in 4.4 months of life lost per patient lifetime. This finding was based on two assumptions: 1) the increased pill burden would hinder adherence and reduce viral suppression, leading to worse outcomes, and 2) lamivudine is potentially inferior to emtricitabine and may increase the frequency of drug resistance, potentially affecting viral suppression efficacy in second-line therapy.Lamivudine is, however, considered a safe and effective alternative to emtricitabine by the World Health Organization (WHO), which also considers lamivudine in combination with efavirenz and tenofovir DF to be a preferred first-line regimen for adults and adolescents with HIV in its 2010 guidelines (and the preferred first-line regimen in its 2013 guidelines still under review). Additionally, half-life and potency differences between lamivudine and emtricitabine are likely negated when either are combined with highly effective agents with long half-lives, notably efavirenz and tenofovir DF.

Limited data are available confirming that once-daily coformulations are associated with higher adherence rates compared with once-daily regimens involving two or more pills. According to one recent analysis, though participants taking once-daily regimens had higher adherence compared with participants taking twice-daily regimens, there was no difference among those taking Atripla compared with those taking once-daily regimens of multiple pills. Moreover, of the four preferred initial combination regimens for ARV-naïve HIV-infected adults and adolescents specified in the

U.S. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, two require three tablets once a day and one requires twice-daily dosing.

As single-tablet, once-daily regimens are highly desirable because of their convenience, preference among people with HIV and healthcare providers, and potential for lower out-of-pocket insurance copayments, the study and development or importation of U.S. Food and Drug Administration-approved fixed-dose combination tablets will remain a priority as safe and effective agents come off patent over the next few years. Yet the immediate reality is the anticipated approval and availability of generic efavirenz; even if combined with the branded coformulation of tenofovir and emtricitabine (Truvada), savings in the U.S. were modeled by Walensky and colleagues to be $560 million in the first year alone.

The timing of the patent expirations for standard-of-care ARV options for is notable. With roughly one in four people with HIV in the U.S. receiving effective antiretroviral therapy, largely due to poor HIV testing uptake and engagement in care, strategies are being enacted to improve clinical care outcomes. These efforts, however, will coincide with full implementation of the Patient Protection and Affordable Care Act (ACA), under which thousands of uninsured people with HIV will be permitted to enroll in Medicaid or be required to maintain coverage through a private health insurance plan.

As of late April, however, only 20 states and the District of Columbia plan to expand Medicaid eligibility as per ACA recommendations; 15 will not expand and the rest remain undecided. As for people with HIV enrolling in private insurance places, recent ACA rules allowed states--many hostile to ACA--to regulate minimum drug formulary compositions. Finally, with the uncertain future of the Ryan White CARE Act beyond its September 2013 expiration, it remains unclear to what extent people with HIV utilizing Medicaid or private insurance will be able to access AIDS Drug Assistance Programs to defray out-of-pocket HIV prescription costs.

Because a large percentage of Medicaid, private insurance, and Ryan White expenditures are directly related to prescription drug costs, compounded by growing political intolerance for disease-specific funding and nationwide efforts to reduce health care spending in the U.S., a shift toward generic ARVs is not so much a desire as it is a necessity.

The availability of a single generic formulation is generally not enough to substantially lower the price of ARVs; market competition is what drives down prices for generic compounds and their brand-name equivalents. Indeed, Walensky and colleagues' cost-savings outcomes are dependent on a 75 percent reduction in pricing, similar to that seen when leading drugs for other diseases came off patent and market competition ensued: simvastatin for hypercholesterolemia (66 percent price reduction), methylphenidate for attention-deficit hyperactivity disorder (72 percent price reduction), and the anticoagulant warfarin (85 percent price reduction).

Ensuring market competition--initially as generics become available for use with brand-name drugs and, eventually, as generic fixed-dose combination regimens are allowed with additional patent expirations--will need to be an advocacy priority, with the understanding that this may

necessarily limit patient and provider choice of regimen options through Medicaid, ADAP, and private insurance formulary restrictions and generic prioritization. When patient or provider prescribing requirements do not allow for generic substitutions, such as for those who cannot tolerate efavirenz or those who must use single-tablet regimens to maintain excellent adherence, access to affordable brand-name drugs must remain feasible.

Importantly, mechanisms need to be put into place to ensure that savings to the U.S. health care system that result from the availability of generic ARVs are diverted to programs needed to improve universal HIV testing, implement engagement-in-care best practices, and provide effective treatment for coinfections such as hepatitis C. Ensuring that HIV treatment cost savings are reabsorbed by other HIV programs is imperitive, considering that the objectives of the 2010 National HIV/AIDS Strategy are to be financed explicitly by repurposed rather than new funds.

* U.S. patent expirations of HHS-preferred and -alternative antiretrovirals (does not include potential extensions): lamivudine (2009), efavirenz (2012), ritonavir (original capsule formulation, 2012), abacavir (2012), emtricitabine (2016), lopinavir/ritonavir (2016), atazanavir (2017), and tenofovir (2017).

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