



Enabling broad access to best-in-class HIV treatment – Best practice for originators

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Years of experience show that licensing is highly effective for ensuring that many more people in low and middle income countries, particularly in sub-Saharan Africa, can access life-saving medicines for HIV.

This paper describes the ‘best practice’ licensing models that originator companies should employ to enable broad access, including: signing licences as early as possible; broadening the geographic scope of licences; and, limiting the use of licence terms that restrict generic medicine manufacturers. It further explores how originator companies can go beyond licensing and engage in broader supportive initiatives that help ensure their licences have maximum impact. This includes: registering products widely and quickly; maintaining branded supply at affordable prices; generating clinical data to address needs in low and middle income countries; and, engaging when requested in technology transfers.

These activities should be underpinned with strong governance structures for access to ensure an integrated approach that is successful for increasing access to HIV treatment. Importantly, these best practices have the potential to serve as models to also broaden access to key medicines targeting other high-burden diseases in low and middle income countries.

Introduction

Generic antiretroviral medications (ARVs) are the mainstay of HIV treatment in low and middle income country (LMIC) markets. These products have enabled the tremendous scale-up in access to HIV treatment observed in recent years: as of June 2017, approximately 20.9 million people living with HIV had access to treatment, up from just 7.7 million as of December 2010.¹

Where products are still on patent, this scale-up is achieved through a predominant mechanism whereby companies voluntarily

license their patented products on a non-exclusive basis. Known as ‘voluntary licensing’, this mechanism allows generic medicine companies to manufacture and commercialise the products on clearly-defined terms. Since its founding in 2010 by Unitaid, the Medicines Patent Pool (MPP) has played, and continues to play, an instrumental role in ARV licensing, by working with partners to secure non-exclusive licences on publicly-available terms that are conducive to promoting access in LMICs. Today, almost all ARVs have voluntarily been licensed. The 2016 Access to Medicine

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Index found that, of 20 companies evaluated, Gilead and GSK (via ViiV Healthcare) exhibit the leading performance in access-oriented licensing for HIV products.²

Over the years, we have seen that when core principles are followed, licensing effectively promotes access through price reductions, development of optimal fixed-dose combinations (FDCs) of molecules that are patented by different originator companies, and improvements in production capacity to meet the scale of demand in LMICs.³ Such practices have been critical to enable faster access to new ARVs in LMICs, supporting progress towards UNAIDS' 90-90-90 treatment targets to help end the AIDS epidemic.

While licensing has been shown to be an effective mechanism for enabling access to ARVs, there is much more that can and should be done. Success in licensing depends on the continued efforts and collaboration of a range of global health actors, from pharmaceutical companies to national governments, non-governmental organisations, community advocacy groups and global health donors.

This paper outlines best practices that originators can engage in to support the aim of maximising access to these products, along with examples of how these practices have been applied. This includes actions companies should take to ensure the terms of their licences support access, as well as broader activities companies can engage in to maximise the impact of their licences.

Licensing model – 4 best practices in licensing ARVs

1. Licence as early as possible to multiple manufacturers

Licensing programmes should be established as early as possible in the product development cycle with multiple manufacturers. This helps generic medicine manufacturers make plans to file for approval more quickly via a Stringent Regulatory Authority (e.g., European Medicines Agency [EMA] or United States Food and Drug Administration [FDA]) and the World Health Organization (WHO) Prequalification of Medicines Programme.

Impressively, the first generic version of dolutegravir (DTG) – recommended as a first-line therapy by WHO – gained tentative approval by the FDA just three years after ViiV Healthcare (the innovator) received its FDA approval. This is the shortest timeline to date, thanks to a licence signed within a year after ViiV Healthcare's FDA filing.⁴ Another prime example is bicitegravir (BIC), a pipeline candidate for which Gilead agreed a MPP licence in late 2017,⁵ just months after it submitted marketing applications for a once-

daily, single-tablet regimen containing BIC to the EMA and FDA.^{6,7} Note that in the latter case, licensing occurred prior to first regulatory approval.

2. Broaden the geographic scope of licences

Although typically, all low income countries and many middle income countries are included in the scope of licences, countries continue to be excluded, especially upper-middle income countries outside of sub-Saharan Africa. This leaves many patients without access to affordable ARVs, particularly where large income disparities exist.

ViiV Healthcare includes all lower-middle income countries in its paediatric and adult DTG licences, plus some upper-middle income countries outside sub-Saharan Africa in the paediatric licence. The paediatric licence is royalty-free. Under the terms of the adult licence, ViiV Healthcare only receives royalties from sales in certain territories (countries exempt from royalties are low income countries, Least Developed Countries and sub-Saharan African countries). Furthermore, in

some middle income countries, the size of the royalty depends on the gross national income per capita of the country in question.^{2,8}

3. Allow for novel combinations

Provisions that allow products to be included in FDCs without prior approval from the licensor are an important means to accelerate the development of improved treatment regimens. This is particularly useful when optimal FDCs contain molecules that are patented by different companies. All MPP licences now include such provisions.⁹

Such provisions made it possible for generic medicine manufacturers to develop ‘TLD’, a combination that includes Gilead’s tenofovir disoproxil fumarate (part of the current standard of care in LMICs), ViiV Healthcare’s DTG (a newer medicine offering important clinical and cost-savings benefits over existing treatments), and lamivudine (which is more widely used in LMICs than Gilead’s product, emtricitabine).^{10,11} Both Aurobindo and Mylan

received tentative approvals for TLD from the FDA in August 2017.^{12,13} Since then the governments of South Africa and Kenya, together with UNAIDS, CHAI, the Bill & Melinda Gates Foundation, Unitaid, the UK Department for International Development, PEPFAR, USAID, and the Global Fund, with Aurobindo and Mylan have announced a ceiling price agreement supporting affordable access to TLD in LMICs.¹⁴

4. Limit terms that place restrictions on generic licensees

Originator companies should limit the use of licence terms that place restrictions on generic licensees. In addition to the best practices described, they can work to include a range of terms in their licences that are conducive to promoting access. These include allowing licensees to produce both active pharmaceutical ingredients (APIs) and finished dosage forms; source APIs without restriction; and, obtain waivers on data exclusivity.

Going beyond the licence – 4 practices that support access

To ensure broad and uninterrupted access, originator companies need to look beyond the terms of their licences and engage in supportive activities that encourage uptake of their products by populations in need. Best practices are given below with the caveat that specific initiatives will depend on several factors, including the product in question, how it fits within current treatment guidelines, and the makeup of the health system where it is deployed.

1. Register widely and quickly across licensed territories and maintain registrations

Often, national drug regulatory authorities will expedite reviews of generic medicine filings if the innovator has already registered the product in-country. It is therefore best practice for originators to register and maintain a broad set of registrations in

licensed markets. Among the 20 companies measured by the 2016 Access to Medicine Index, Gilead is the only company to publish the registration status of the majority of its products for high-burden diseases in full detail.^{2,15}

2. Maintain branded supply capability at affordable prices as appropriate

Originator companies should take measures to ensure their products are available where needed, should cases arise where provision of generic medicine is insufficient. This may occur if generic medicine manufacturers do not face strong enough incentives to supply low income markets (for example due to low required volumes). Originators and generic medicine manufacturers share the responsibility to ensure access in these cases.

Originators should work to enable access in



these instances by selling the branded product at prices that are affordable to countries and population segments within them.

Alternatively, where populations have no ability to pay for ARVs, donation programmes may be an appropriate short-term means to ensure access, provided there are plans in place to support sustainable access to products in the future. This is particularly important given that people living with HIV will require treatment for life.

There have been cases in which companies have facilitated generic competition for their ARVs, while maintaining branded supply in the same territories (e.g., Johnson & Johnson, ViiV).²

When originators do choose to supply ARVs in regions where they are also licensed they should ensure they do not impede the ability of generics to effectively compete.

3. Generate clinical data early in drug development that addresses needs of specific populations in LMICs

After a new ARV is first approved for the developed world, further research is often required in pregnant women, children and patients co-infected with tuberculosis to generate sufficient evidence to allow for inclusion in WHO treatment guidelines. This is an important step in paving the way for use in LMIC settings. However, generating clinical data is not within the typical business model of generic medicine manufacturers. Therefore, leading originators should undertake these studies, ideally as part of initial product development. This helps ensure products with characteristics that meet the needs of specific populations in LMICs are available as quickly as possible.

For example, questions have emerged about the safe and effective use of tenofovir alafenamide (TAF) in patients co-infected with tuberculosis, in pregnant and breastfeeding women, and in children. These populations are generally a smaller consideration in high income countries (where case burden is minimal) than in LMICs, and as such, the data needed to answer these questions to enable TAF to be included in WHO treatment guidelines, will only be available in 2020.¹⁴ Thus, although generic medicine companies are expected to gain regulatory approvals for TAF-containing products by 2019, patients in LMICs markets are unlikely to receive treatment before 2021.

Some companies engage in collaborative R&D to address needs where commercial incentives are low. For example, ViiV Healthcare has been involved in the development of the clinical data package for the use of DTG in children in LMICs.¹⁶ AbbVie is working in partnership with the Drugs for Neglected Diseases Initiative and others to develop a FDC that combines the four drugs needed to treat paediatric HIV (lopinavir, ritonavir, 3TC and abacavir) into an easy-to-use, heat-stable formulation with a tolerable taste.¹⁷

4. Engage in technology transfers where requested

Originators should also provide consultancies and technology transfers, where requested by generic medicine manufacturers. Bristol-Myers Squibb has a technology transfer agreement to support the Brazilian government in becoming the sole supplier of atazanavir in Brazil.¹⁸ Gilead provides licensing partners with full technology transfer packages, for example for TAF.¹⁹ Ideally, licensors should begin technology transfers in advance of regulatory approval to help licensees build production capacity as soon as possible.

Supporting access activities with strong governance

A company's access to medicine governance structure elaborates strategies across all of its functions, from licensing to R&D, registration, supply and pricing. Leading originator companies think about access in a holistic manner, with specific targets and outcome measurements, all supported by effective governance and senior-level sponsorship for access initiatives. Such features underpin the viability and success of activities originators take to support access to their products in LMICs.

The 2016 Access to Medicine Index found that the companies with the strongest performance in access-oriented licensing for HIV – Gilead and GSK (via ViiV Healthcare) – both have detailed strategies for increasing access to medicine. These strategies include a set of programmes with time-bound quantitative and qualitative targets that contribute to company-wide access goals. The companies measured by the Index are all mature with regard to access governance, according to the expectations set by the Index: the standards described were achieved by 17 out of 20 companies evaluated.²

Conclusion

Looking forward, licensing will continue to play a critical role in ensuring rapid access to the most effective HIV treatments globally. To continue our progress towards the 90-90-90 treatment goals, originator companies need to adopt the licensing best practices and access-supporting activities explored here as early in product development as possible. These must

be conducted in alignment with global public health needs and paired with strong access governance and continued collaboration to ensure the most important products reach all patients in need. Beyond HIV, these best practices can serve as a model for strategies to significantly increase access to key medicines in LMICs.

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About the Access to Medicine Foundation

The Access to Medicine Foundation is an independent non-profit organisation based in the Netherlands. It aims to advance access to medicine in low and middle income countries by stimulating and guiding the pharmaceutical industry to play a greater role in improving access.

About Clinton Health Access Initiative

Founded in 2002, by President William J. Clinton and Ira C. Magaziner, the Clinton Health Access Initiative, Inc. ("CHAI") is a global health organization committed to saving lives, reducing the burden of disease and strengthening integrated health systems in the developing world. Learn more at www.clintonhealthaccess.org

References

1. UNAIDS. UNAIDS fact sheet: Latest statistics on the status of the AIDS epidemic. 2017;(July):8. <http://www.unaids.org/en/resources/fact-sheet>.
2. Access to Medicine Foundation. *Access to Medicine Index 2016*. Haarlem; 2016. <http://accesstomedicineindex.org>.
3. Amole CD, Middlecote C, Prabhu VR, Kumarasamy N. Can the generic antiretroviral industry support access to a universal antiretroviral regimen? *Curr Opin HIV AIDS*. 2017;12(4):390-397. doi:10.1097/COH.0000000000000382.
4. Clinton Health Access Initiative A. Aurobindo Pharma receives US FDA tentative approval for Dolutegravir, allowing the product to be launched in the PEPFAR market. <http://www.aurobindo.com/docs/press-room/press-reports/aurobindo-chai-press-release-on-dolutegravir-ta-for-launch-in-pepfar-market.pdf>. Published 2016. Accessed November 24, 2017.
5. Gilead. Gilead Announces New License Agreement With the Medicines Patent Pool for Access to Bictegravir. <http://www.gilead.com/news/press-releases/2017/10/gilead-announces-new-license-agreement-with-the-medicines-patent-pool-for-access-to-bictegravir>. Published 2017. Accessed November 13, 2017.
6. Gilead. European Medicines Agency Validates Gilead's Marketing Application for Fixed-Dose Combination of Bictegravir, Emtricitabine and Tenofovir Alafenamide for Treatment of HIV. <http://www.gilead.com/news/press-releases/2017/7/european-medicines-agency-validates-gileads-marketing-application-for-fixeddose-combination-of-bictegravir-emtricitabine-and-tenofovir-alafenamide-for-treatment-of-hiv>. Published 2017. Accessed November 13, 2017.
7. Gilead. Gilead Submits New Drug Application to U.S. Food and Drug Administration for Fixed-Dose Combination of Bictegravir, Emtricitabine and Tenofovir Alafenamide for HIV Treatment. <http://www.gilead.com/news/press-releases/2017/6/gilead-submits-new-drug-application-to-us-food-and-drug-administration-for-fixeddose-combination-of-bictegravir-emtricitabine-and-tenofovir-alafenamide-for-hiv-treatment>. Published 2017. Accessed November 13, 2017.
8. ViiV Healthcare. ViiV Healthcare extends Medicines Patent Pool licence agreement for dolutegravir to cover all lower middle-income countries.

- <https://www.viivhealthcare.com/media/press-releases/2016/april/viiv-healthcare-extends-medicines-patent-pool-licence-agreement-for-dolutegravir-to-cover-all-lower-middle-income-countries.aspx>. Published 2016. Accessed November 13, 2017.
9. Medicines Patent Pool. Licences in the MPP. <https://medicinespatentpool.org/what-we-do/global-licence-overview/licences-in-the-mpp/>. Accessed November 13, 2017.
 10. Medicines Patent Pool. DOLUTEGRAVIR – ADULT (DTG). <https://medicinespatentpool.org/licence-post/dolutegravir-adult-dtg/>. Accessed November 22, 2017.
 11. Medicines Patent Pool. TENOFOVIR DISOPROXIL FUMARATE (TDF). <https://medicinespatentpool.org/licence-post/tenofovir-disoproxil-fumarate-tdf/>. Accessed November 24, 2017.
 12. U.S. Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products: New Drug Application (NDA): 209618. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=209618>. Accessed November 22, 2017.
 13. U.S. Food & Drug Administration. Drugs@FDA: FDA Approved Drug Products: New Drug Application (NDA): 209670. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=209670>. Accessed November 22, 2017.
 14. Clinton Health Access Initiative. *ARV Market Report: The State of the Antiretroviral Drug Market in Low- and Middle-Income Countries, 2016-2021.*; 2017. <https://clintonhealthaccess.org/2017-arv-market-report/>.
 15. Gilead. HIV/AIDS. <http://gilead.com/responsibility/developing-world-access/hiv-aids>. Accessed November 13, 2017.
 16. Unitaid. CHAI seeks generic manufacturer for paediatric HIV drug dolutegravir. <https://unitaid.eu/news-blog/request-proposal-selecting-generic-manufacturer-develop-paediatric-dolutegravir-dtg/#en>. Published 2017. Accessed November 22, 2017.
 17. Drugs for Neglected Diseases Initiative. Two “4-in-1” LPV/r/ABC/3TC. <https://www.dndi.org/diseases-projects/portfolio/two-4-in-1-lpv-r-based-fixed-dose-combinations/>. Accessed November 24, 2017.
 18. Bristol-Myers Squibb. Patents, Licensing and Technology Transfer. <https://www.bms.com/about-us/responsibility/access-to-medicines-in-the-developing-world/patents-licensing-and-technology-transfer.html>. Accessed November 22, 2017.
 19. Gilead. Gilead Sciences Policy Position: Intellectual Property and Patient Access. 2014. https://www.gilead.com/~media/files/pdfs/policy-perspectives/intellectual-property-and-patient-access_1022141.pdf?la=en. Accessed November 24, 2017.