

Analysis of ViiV/MPP Dolutegravir Licenses – Pluses and Minuses

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The recently announced adult and pediatric licenses from ViiV Healthcare Co. to the Medicines Patent Pool on the promising new integrase inhibitor, dolutegravir, will substantially increase access for people eligible for antiretroviral therapy, but they are not perfect.

The pediatric license, covering children under age 18, achieves the highest level of effective coverage yet achieved, with 99.3% of pediatric patients covered. However, this coverage still leaves 40,000 of an estimated 4 million children living with HIV in low- and middle-income countries uncovered.ⁱ (Note: dolutegravir is only approved in the US for children over the age of 12, so expansion of coverage to younger children will depend on regulatory approvals and the development of pediatric formulations.)

The effective coverage of the adult license, which covers people 18 and older, which include abacavir as well as dolutegravir, and which includes both countries explicitly included in the licensed territories and countries where sales of dolutegravir and some fixed dose combinations will be permissible, is 93.4%. Unfortunately, the exclusion of 14 countries because of granted or pending patents leaves approximately 2.2 million adults uncovered.

Licensed Territory

Non-Royalty Countries: Sub-Saharan Africa, Least Developed and Low-Income Countries (67 Countries)

Afghanistan, Angola, Bangladesh, Benin, Bhutan, Botswana, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Dem. Rep., Congo Rep, Côte d'Ivoire, Djibouti, East Timor, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Ghana, Gambia, Guinea, Guinea-Bissau, Haiti, Kenya, Kiribati, Lao People's Dem. Rep., Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Myanmar, Namibia, Nepal, Niger, Nigeria, Republic Kyrgyz, Republic of North Korea, Rwanda, Samoa, São Tomé and Príncipe, Sénégal, Seychelles, Sierra Leone, Solomon Islands, Somalia, South Africa, South Sudan, Sudan, Swaziland, Tanzania, Tajikistan, Togo, Tuvalu, Uganda, Vanuatu, Yemen, Zambia and Zimbabwe

These are the countries that have traditionally benefited from ViiV's voluntary licenses.

Royalty Countries (6 countries)

Egypt*, India*, Indonesia, Philippines, Turkmenistan and Vietnam*.

The License Agreement permits sales in royalty countries only within the public market, broadly defined.ⁱⁱ This restriction leaves the more lucrative private sector to ViiV where it can sell without competition.ⁱⁱⁱ To prevent product diversion, generic licensees must

differentiate their medicines and packaging and they have additional contractual obligations to prevent or respond to product diversion, Sub-License Agreement, paragraph 8 provisions. There are tier-based royalties within the royalty countries but royalties will only be payable in countries where a patent has been granted. As indicated by the *'s above, patents are still pending and not yet granted in Egypt, India, and Vietnam. As long as that is true, sales could be made in the public market with no risk and in the private market with risk of post-grant liabilities depending on national law. If and when royalties are payable, India, Vietnam and the Philippines are Tier 1 countries and will pay a 5% royalty on net sales. Indonesia and Egypt are Tier 2 countries and will pay a 7½% royalty; Turkmenistan is a Tier 3 country and will pay a 10% royalty.

Countries outside the territory where the DTG Compound patent is not granted and thus generic supply will be permissible (53 countries)^{iv}

Albania, Anguilla, Argentina*, Belize, Bolivia, Bosnia, British Virgin Islands, Costa Rica‡, Cuba, Dominica*, Dominican Republic‡, Fiji, Ecuador‡, El Salvador*, Georgia*, Grenada, Micronesia, Guatemala*, Guyana, Honduras*, Iran*, Iraq, Jamaica*, Jordan, Kosovo, Lebanon*, Libya‡, Macedonia, Maldives, Marshall Islands, Mayotte, Montenegro, Montserrat, Nauru, Nicaragua*, Pakistan*, Palau, Panama*, Papua New Guinea, Paraguay*, Peru‡, Serbia, St. Lucia*, St. Vincent*, Sri Lanka, Suriname, Syria*, Thailand‡, Tonga, Tunisia‡, Uzbekistan*, Venezuela and West Bank and Gaza

These are countries where is no granted or pending patent on the dolutegravir compound and thus where generic licensees may freely sell dolutegravir without violating the License Agreement. However, many of these countries do have abacavir patents (see countries marked with an *), and thus abacavir cannot be sold in these countries nor can a combination product containing dolutegravir and abacavir. Other countries in the list above have pending applications on the dolutegravir/lamivudine/abacavir combination (see countries marked with an ‡).^v The License Agreement would not allow manufacture, sale, or supply of this combination once the patent is granted, though single dose dolutegravir could still be sold. Although ViiV is pursuing registration and commercialization of this combination, it is not clear that this would be a preferred regimen compared to tenofovir/lamivudine/dolutegravir.

Excluded territories with granted or pending patents

Countries outside the adult territory where there are compound patents granted on DTG (15 countries)

Armenia, Azerbaijan, Belarus, Bulgaria, China P.R., Colombia, Hungary, Kazakhstan, Mexico, Moldova, Mongolia, Morocco, Romania, Turkey and Ukraine^{vi}

These are countries where sale or supply of dolutegravir is clearly prohibited by the License Agreement and where infringement could lead to a termination of the generic license for the offending licensee. Because of this patent blockage, the CS advocates could pursue a coordinated strategy for compulsory licensing in these countries. Fortunately, the

Licensing Agreement clearly allows supply where a compulsory license has been issued, paragraph 2.4.

Countries outside the adult territory in which there are compound patents pending on DTG (3 countries)

Algeria, Brazil and Malaysia^{vii}

The Licensing Agreement prohibits manufacture, sale, and supply in a territory only with respect to granted and in-force patents. Thus generic licensees could undertake at-risk commercialization in these three countries, subject to national laws governing penalties that might arise from infringement during the patent-pending period. There would be no royalties with respect to such sales. However, it is unclear whether generic companies would undertake this risk.

Countries in the Paediatric License (121 countries)

Afghanistan, Algeria, Angola, Argentina, Armenia, Azerbaijan, Bangladesh, Belize, Benin, Bhutan, Bolivia, Botswana, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Chile, Colombia, Comoros, Congo DR, Congo Rep, Costa Rica, Cote d'Ivoire, Cuba, Djibouti, Dominican Republic, East Timor, Ecuador, Egypt, El Salvador, Equatorial guinea, Eritrea, Ethiopia, Fiji, Gabon, Gambia, Georgia, Ghana, Guatemala, Guinea, Guinea-Bissau, Guyana, Haiti, Honduras, India, Indonesia, Iran, Iraq, Jamaica, Kenya, Libya, Madagascar, Malawi, Malaysia, Maldives, Mali, Marshall Islands, Mauritania, Mauritius, Micronesia, Moldova, Mongolia, Morocco, Mozambique, Myanmar, Namibia, Nauru, Nepal, Nicaragua, Niger, Nigeria, Pakistan, Samoa, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Solomon Islands, Somalia South Africa, South Sudan, Sri Lanka, Sudan, Swaziland, Syria, Tajikistan, Tanzania, Thailand, Togo, Tonga, Tunisia, Turkmenistan, Tuvalu, Uganda, Ukraine, Uzbekistan, Vanuatu, Venezuela, Vietnam, West Bank and Gaza, Yemen, Zambia and Zimbabwe^{viii}

Additional positive terms in the ViiV/MPP Licenses

Early access

- One of the great advantages of the ViiV/MPP Licenses is that they allow early access to a promising new treatment within a few months of having first been approved in the US. Historically, LMICs have faced long delays in access to licensed ARVs.

Full disclosure of license agreements

- As has been true with all of its licenses, the ViiV/MPP licenses are publicly available on the MPP website.^{ix}

Royalties

- **No royalties need be paid in the 63 licensed adult territories, even in countries that might otherwise have a patent.** This provision secures the MPP's

commitment that no country shall be worse off in terms of provision of medicines because of an MPP license. Since ViiV had previously had a no-royalty policy concerning these 63 Sub-Saharan and low-income countries, that policy was preserved.

- **No royalties paid in the 53 countries where there is no dolutegravir compound patent granted.** Under the License Agreement, paragraph 2.4, and Sub-License Agreement, paragraph 2.5, sub-licensees are permitted to carry on activities, including manufacture, sale, or supply, outside of the Territory if such activities would not infringe any Non-Territory patent [granted and in force]. Accordingly, no royalties are due on sales in countries outside the licensed territory where supply of that market would not infringe a patent.
- **Tiered royalties in royalty territories, but only once patents are granted.** As discussed above, royalties need only be paid when granted and patents are still pending in Egypt, India, and Vietnam.^x
- **No royalties are due on any licensed pediatric sales.** Under the Pediatric License Agreement, no royalties are due on sales in the territory nor in sales outside of the licensed territory where no patent would be infringed by the sub-licensees activity.

Unrestricted place of manufacture

- There are no restrictions on the place of manufacture, so that generic suppliers may be located outside the licensed territory and even in countries where there would otherwise be a patent bar so long as no patents are violated in the country of sale/use, Sub-License Agreement, paragraphs 2.1-2.
- In the event that a production occurs in a country where there is a patent, royalties are not payable on that basis alone, but rather is dependent on whether sales occur in licensed royalty-free countries or royalty countries.

Know-how

- There is no know-how licensed in these agreements, though there are provisions for grantbacks of know-how on improvements.

Registration

- ViiV waives all NCE (data) exclusivity or other regulatory exclusivity so as to permit generic licensees to register generic equivalents with regulatory authorities, paragraph 5.8.
- Obligations to register products in licensed territories and – where not patent infringing – non-licensed territories rests with generic licensees, Sub-License Agreement, paragraph 4.1.
- Generic licensees are required to meet WHO prequalification or stringent regulatory authority standards or to obtain temporary approvals from a WHO Expert Review Panel, essentially meeting Global Fund quality standards, id. paragraph 4.2.
- Generic licensees are also required to seek marketing and other required approvals from national drug regulatory authorities, id. paragraph 4.3.
- Generic licensees shall not sell or offer a compound product for sale prior to having

received regulatory approval, id. Paragraph 2.10.

Grantback Rights

- Generic licensees are required to notify ViiV and the MPP concerning any improvements, paragraph 9.1.
- Generic licensees are also required to grant a perpetual, irrevocable, worldwide, royalty free, and non-exclusive license to any improvement, improvement patent and related know-how. The MPP may not further sublicense the grantback rights without entering in good-faith negotiations with the generic licensee who made the improvement. Paragraph 9.2.

Fixed-dose combinations

- The Sublicense Agreement specifically licenses a combination product containing dolutegravir and abacavir, paragraph 1.22.
- The Sublicense Agreement also permits pharmaceutical combinations and compositions containing dolutegravir and other active ingredients, as long as no non-licensed patent of ViiV is violated, paragraph 1.22.
- Specifically, since the patent on lamuvidine has expired and since dolutegravir is licensed by ViiV and tenofovir is either licensed by Gilead or is being produced and used widely because of the absence of in-force patents, it should be possible to manufacture, market and supply a relevant once-a-day fixed-dose combination in a very large market once the combination receives regulatory approval.^{xi}
- As stated previously, ViiV has filed combination patent applications on DTG/3TC/ABV in many countries, though it is granted so far only in South Africa, Mongolia, and Turkey

Conclusion and next steps

The ViiV/MPP licenses are not perfect – no license that serves less than a 100% of PWAs in low- and middle-income countries is fully acceptable. Nonetheless, these licenses have been carefully crafted to allow early access tens of millions of patients who might benefit from what may well be one of the lowest-cost, most-effective, most tolerable, and most resistance-proof antiretrovirals on the market. Future challenges include: (1) identifying and motivating qualified generic producers to develop dolutegravir products, pre-qualify them at the WHO and register them broad in territories where sale is permissible; (2) expediting the adoption of dolutegravir and fixed-dose combinations thereof in WHO Guidelines and in treatment guidelines in low- and middle-income countries; (3) validating and registering pediatric use of dolutegravir for children under the age of 12; (4) developing appropriate pediatric formulations; and (5) overcoming patent barriers where non-territory patents prevent generic competition.

ⁱ UNAIDS reports HIV infections in children under 0-14 at 3.3 million. It separately calculates the number of “adolescents” 10-19 at 2.1 million. Obviously there are redundancies in these two figures, but we know that the definition includes governments and state institutions/programs, NGOs, UN-related organizations, international NOGs such as MSF, funding mechanisms such as UNITAID, PEPFAR, and the Global Fund, and other not-for-profit treatment programs.

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- iii If ViiV does not meet reasonable demand in the private market following product approval in a royalty country, it will bargain in good faith with the MPP to expand the scope of public market licenses to include the private market as well. Licensing Agreement, paragraph 2.6.
- iv This list has been provided by the MPP in response to a request for information, along with assurances that the absence of granted or pending patents has been confirmed. Any generic seeking to market in any of the listed countries should independently verify this information.
- v ViiV's patents listed in the Pediatric License, Appendix D, in 2011 are presumed to be on the DTG/3TC/ABV combo.
- vi Although Ukraine is not listed as a country with a non-territorial patent, there are credible reports, including from the Ukrainian patent office that it dolutegravir is in fact patented there.
- vii Even though this information was not provided by ViiV, the MPP did discover these pending patents during its investigations on this license.
- viii This coverage includes three countries not included in the previous ViiV/MPP pediatric abacavir license: Peru, Ukraine, and Venezuela. Presumably, the MPP and ViiV will now expand the abacavir license to include these three additional territories.
- ix <http://www.medicinespatentpool.org/current-licences/>.
- x The use of tiered royalties and sector segmentation to expand the geographical scope of MPP licenses was one of the recommendations from the Outcome report: Civil Society meeting on the MPP and voluntary licenses (Johannesbury 9-10, 2012).
- xi This analysis will not undertake an analysis of the market that could thereby be served, but it is very large.