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Indian manufacture of new generic antiretrovirals: implications for global access to anti-HIV drugs

"The Indian decision suggests that in the future, developing-world patent offices may take a tougher stance than industrialized countries as to which drugs merit patents."

India's ruling on patent protection

India recently rejected patent applications on two antiretrovirals (ARVs), darunavir and tenofovir, which ensures the continued generic manufacturing of these drugs at substantially reduced costs compared with proprietary formulations [1]. The ruling by India's Patent Office (IPO) to reject the exclusive licensing of the nucleoside reverse-transcriptase inhibitor tenofovir (Gilead Sciences, CA, USA) and protease inhibitor (PI) darunavir (Tibotec Pharmaceuticals, NJ, USA) also allows other countries to import generic versions produced in India. Cipla, the Mumbai-based generic drug manufacturer, had filed cases against both companies. Even before the anticipated outcome, Gilead had already offered 13 Indian drug manufactures the licensing rights to manufacture tenofovir, but with the caveat that the Indian manufacturers purchase the active drug ingredient from Gilead and that the product be sold only to the poorest 95 countries (which does not include middle-income countries, such as China and Brazil). The patent rejection potentially opens up the market for generic drug manufactures to further drive down the cost of these two ARVs, and may have wider implications for the future development and distribution of ARVs.

India's role in expanding access to generic ARVs

India is not the first country to reject a patent on tenofovir, but rather, this decision follows a similar one made by Brazil and the US Patent Office. India's decision highlights section 3(d) of India's patent law, prohibiting 'evergreening', in which multinational pharmaceutical companies can make small, trivial changes to existing medicines in order to extend the period of a patent monopoly on a drug. This practice by pharmaceuticals has the impact of preventing

the entry of generic competitors into the market and keeping drug prices high [101]. India is currently bound by the World Trade Organization (WTO) Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement, which safeguards intellectual property rights by providing a 20-year warranty securing the inventor exclusive rights [2,3]. In line with the WTO obligations, India has granted Pfizer and Tibotec the rights for the entry-blocking drug maraviroc, and the new non-nucleoside reverse transcriptase inhibitor etravirine, respectively [3]. The concern is that new Indian patent laws that comply with the WTO obligations will impede the development of generic versions of HIV drugs, pitting patients against patents.

Since the 1970s, the Indian Patents Act has allowed the production of generic versions of drugs where a slight modification in manufacturing could qualify a drug for a new patent [4]. This provision has allowed Indian drug manufacturers to coformulate ARVs at prices as low as 4% of the brand-name versions. Although the current generation of coformulated ARVs will continue to be available at reduced costs, the question is, what will be the future of new generic ARVs that are likely to be needed to maintain continued access to an expanded formulary of affordable HIV therapy?

Need for greater access to generic ARVs in resource-limited settings

Today, HAART continues to be made ever more sustainable, effective and simpler, but the need for treatment on a global scale has grown with the continued rise in the number of HIV-infected individuals [5]. The number of individuals receiving HAART must be put within the larger context of the estimated 33 million who are currently living with HIV [102]. Although close to 4 million individuals are estimated to

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be currently receiving antiretroviral therapy (ART), this only represents approximately 31% of the population in need of treatment [3,102]. Nevertheless, based on the experience of Brazil, even after producing generic ARVs, the costs of providing scaled-up HAART rises over time as individuals develop progressive disease, standards of care change and new drugs become available [6]. A current debate exists as to whether HIV treatment should be utilized at higher CD4⁺ T-cell counts to minimize the chronic effects of untreated HIV disease [7]. Consequent changes in treatment guidelines will result in increasing the need of ARVs around the world.

“Developing nations will need to balance the needs of patients who need access to these drugs at reduced prices while still rewarding innovation through patent protection.”

Owing to the continued decline of CD4⁺ T-cell counts in untreated patients, the vast majority of currently HIV-infected individuals will be in need of treatment within the next decade. This means that by 2015 most of the 38 million currently HIV-infected patients will have become eligible for treatment based on current WHO treatment guidelines. A question that nations with a high HIV burden will have to consider is that with a growing number of patients failing first-line HAART and requiring second-line therapy, how should the need of second-line HAART be balanced with the unmet need of patients who are still requiring first-line HAART? When scaling-up ART, nations must develop means of negotiating a balance between sustainability of treatment programs and equitable access in order to provide structured, indefinite, chronic HIV care [8].

Evidence for an expanded ARV drug formulary

A large formulary of readily available ARVs is crucial to transform HIV infection from a fatal disease into a chronic illness [4]. In addition, despite the proven safety, tolerability and efficacy of generic ARVs [9,10], these drugs must be monitored for proven bioavailability and bioequivalence in addition to satisfactory manufacturing, distribution and administration [11]. The availability of fixed-dose generic therapeutics, such as lamivudine, stavudine and nevirapine, as a single combination for less than US\$1 a day, had set the stage for the further expansion of HAART across the developing world. However, any optimism

generated for this regimen as a global, universal, first-line treatment has now been tempered by the realities of stavudine- and nevirapine-associated toxicities. A more promising option may be a fixed-dose combination of tenofovir, emtricitabine and efavirenz, which is a simple, safe and well-tolerated regimen [12]. Tenofovir is increasingly becoming a key HIV/AIDS drug, recommend by the WHO for improved first-line treatment regimens owing to price negotiations undertaken through public and private donors.

Despite the increasing availability of fixed-dose, generic, first-line regimens, second-line regimens continue to be up to 10-times the cost of first-line agents due to a lack of adequate generic formulations. Darunavir is a new and expensive agent, which is needed in patients experiencing treatment failure. As a larger number of patients initiate ART across the developing world, failure of first-line treatment is inevitable among patients [13]. The Indian National AIDS Control Organization (NACO) is currently providing free access to second-line ARVs to 5000 patients with first-line drug resistance. It is estimated that in the near future, the rate of 5-year switching could range between 5 and 40%, based on the individual country [14]. However, only a quarter of patients in resource-limited settings and on second-line therapy are on drug combinations recommended by current WHO guidelines, in contrast to patients on first-line HAART, where almost all patients are on recommended combinations [15]. Therefore, there is a need to rapidly expand the formulary of second-line PI regimens that are in concordance with the WHO guidelines as part of national treatment programs [17]. Given the improved treatment outcomes of patients initiating second-line PI containing HAART, further efforts are needed to improve the timely diagnosis of treatment failure on first-line therapy and expand access to second-line regimens.

Implications of the Indian ruling on future HIV drug development

Scale-up of ART may soon be replaced with the new mantra of sustainability, which requires a wide armamentarium of ARVs to meet the needs of patients who have been living with HIV for decades. It is conceivable that in the near future companies could legally challenge the current decisions by the IPO through filing a second patent application. Multinational pharmaceuticals could face considerable financial losses and a reduced market share in developing-world markets with the generic manufacturing of

established by branded pharmaceuticals, though it has been suggested that these prices remain substantially higher compared with those offered through CHAI [3,17]. The US FDA under US President's Emergency Plan for AIDS Relief (PEPFAR) allows for the purchase of generic ARVs to be provided outside the US.

“This provision has allowed Indian drug manufacturers to coformulate ARVs at prices as low as 4% of the brand-name versions.”

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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