Patents and profits: A disparity of manufacturing margins in the Tenofovir value chain

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The epidemiology of infectious diseases is critically affected by their treatment; left untreated, most infectious diseases with an appreciable reproduction number will continue to infect new hosts until all such hosts are infected or have acquired some kind of immunity. This profile is especially true for HIV, which in South Africa has maintained a high level of new infections despite our efforts to reduce incidence through behavioural changes and other strategies. Broader and earlier treatment, and the use of wider prophylaxis, would stop the spread of the virus and eventually wind the clock back on the epidemic.

Early access to treatment is, however, neither uniform nor even considered as a desired regimen under the present guidelines. Affordability is almost certainly an important factor, and it is being argued that the so-called Treatment as Prevention (TasP) protocols are neither practical nor affordable. Central to this debate is the molecule tenofovir disoproxil fumarate (TDF), which is used in both the prophylaxis and treatment regimens.

The history of TDF and the way in which this remarkable molecule has been managed by Gilead Sciences is a unique story, which exemplifies the impressive success of international procurement agencies in securing a rock bottom TDF price without touching Gilead’s more than considerable margins in the markets of the developed world. This bifurcation of the pharmaceutical market is almost unique and reflects the more nuanced trading conditions and intellectual property rights of the last 10 years as compared to the previous 50.

Discovery, development and commercialisation of TDF

In a recent article, published in the African Journal of Aids Research (1), it is reported that over the twelve years from 2001 (when it was first registered by the Food and Drug Administration) to 2012, the number of patients that use the product in all its forms (Atripla, Viread, Truvada, etc.) has grown from less than 5,000 to an estimated 4.5 million, equivalent to an increase in the demand for the active pharmaceutical ingredient (API) from 0.5 to 490 tonnes per annum. This astonishing growth is the consequence of both the extent of the HIV epidemic and the high tolerability of TDF relative to the older antiretrovirals, making it a preferred treatment option.

The discovery of Tenofovir arose from the work of Professor Antonín Holý of the Institute of Organic Chemistry and Biochemistry in Prague, Czech Republic, on a family of nucleosides known as acyclic nucleoside phosphonates, which were found to be excellent reverse transcriptase inhibitors. Realising their drug potential, Professor Holý established a partnership with Professor Erik de Clercq of the Rega Institute for Medical Research in Leuven, Belgium, who assessed the compounds’ antiviral activity (2). This collaboration proved to be hugely successful and resulted in several new drugs, including the discovery of Tenofovir which was patented in 1986.

The subsequent development and commercialisation of TDF is covered in the original article (1). Although originally a Bristol Myers Squibb (BMS) project, the intellectual property was eventually relinquished to Dr John Martin who left BMS to establish Gilead Sciences. The latter company could be described as a one-molecule wonder, given the extent of its reliance on TDF. For instance, it has a string of patents and products based on single or multiple formulations of the molecule including Viread, Truvada, Atripla, Complera and Stribild. From 2008 onwards, more than 80% of its revenue has been linked to TDF-containing products, and over the period 2001 to 2011, TDF in its various forms has generated for Gilead more than US$31 billion revenue at a gross margin of 80%, equivalent to a gross profit of US$25 billion (1).

Management of the TDF market

At present, Gilead supplies an estimated 650,000 patients at an average treatment cost of US$4,200 per person per year (pppy). At the other end of the spectrum, generic manufacturers supply about 3.5 million patients at an average treatment cost of US$41 pppy (1% of the branded cost). The high prices of the branded products are secured predominantly in the developed countries (USA, EU, Japan, etc.) whereas the generic prices pertain to the middle and lower income countries (including South Africa). Given that Gilead does not manufacture the API but secures this material from the same or similar sources as the generic formulators, it is clear who earns the bulk of the profit in this market. A detailed analysis of the TDF value chain, from preparation of the API to sale of the formulated product, has shown as expected that manufacturing margins are highly skewed in favour...
of the originator, with the latter’s 2011 profit being US$3.2 billion vs. US$4 million for API manufacturers and US$39 million for formulators (1).

The secret of how Gilead has managed to retain high revenue and profit levels lies in its management of the TDF market through the Gilead Access Programme (GAP). The latter programme has two components, namely distribution of their own branded product at reduced prices and licensing partnerships with generic manufacturers. The licensing partnerships, which now supply 75% of the market by volume, include Cipla, Aurobindo, Mylan, Hetero, Emcure, Laurus, Sequent, Shasun, Macleods, Desano, Lupin and Aspen Pharmacare.

Apart from protecting its lucrative markets, GAP has also enabled Gilead to deflect criticism of its failure to provide essential medicines for the poor, hence risking the possibility of compulsory licensing. The programme’s achievements have been assured through the combined impact of tight market control in developed countries and high levels of competition between generic companies elsewhere. In this respect, it could be described by the company as being a huge success, resulting in declining input costs, strong revenue growth and high profitability over the last 12 years. Even though pharmaceutical companies may market their access programmes as philanthropy on the basis of the associated price discounts and increased patient enrolment in developing countries, it is apparent that in the case of TDF the programme also made good business sense.

Notwithstanding Dr Martin’s initial insight in respect of the market potential for acyclic phosphonates, the persistence of exorbitant gross margins (> 98%) on Gilead’s branded products appears unjustified. Moreover the low margins for generic producers may undermine their sustainability in the medium term. The analysis argues for a more rational approach to drug pricing, including possible regulation in developed countries, and more sustainable earnings for the generic producers. The latter issue is especially topical and urgent in view of the growing role for TDF in pre- and post-exposure prophylaxis programmes.

Note: the reader is referred to the original article for more information on all aspects of the above discussion.

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