

Gilead Sciences, Inc.

**Expanding Antiretroviral Treatment Coverage in the
Developing World**

Introduction

Founded in 1987, Gilead Sciences, Inc. (“Gilead”) is a biopharmaceutical maker of HIV treatments located in Foster City, California. With the approval of its first antiretroviral (“ARV”) product in the United States in 2001, Gilead recognized the pressing need to expand access to HIV treatment beyond the borders of the United States and Europe. Gilead’s desire to make ARV drugs accessible in the developing world led to its establishment of a global ARV access program in 2003 (“Access Program”). The Access Program has grown significantly since that time. Through the end of January 2010, over 700,000 patients in the developing world were receiving a generic or branded version of Viread® or Truvada®, up from just 31,000 patients at the end of 2006. This paper examines the history and evolution of the Access Program.

Beginnings of the Access Program (2003 – 2005)

Viread, Gilead’s first antiretroviral product, was approved by the U.S. Food and Drug Administration (“FDA”) in October 2001 and by the European Medicines Evaluation Agency (“EMA”) in February 2002. At the time of these launches, Gilead was already evaluating product use in the developing world. Gilead officially launched the Access Program with Viread in April 2003, adding Truvada in 2004, following FDA approval.

Since inception, the hallmark of the Access Program has been to sell ARV products at “no-profit” prices in regions throughout the developing world. Pricing is based on Gilead’s manufacturing and distribution costs. For example, in 2003, a 30-day supply of Viread cost \$39, or \$1.30 per day. In comparison, generic d4T, an older generation ARV widely used in developing world settings, cost \$5 for a 30-day supply at the time. The lower cost of d4T as compared to Viread is in part driven by a less-complex manufacturing process and significantly smaller dose.

The first countries chosen by Gilead to participate in the Access Program were the 53 countries of Africa and 15 additional countries designated “least developed” by the United Nations (“Low-Income Countries”).¹ In developing its program, Gilead was unable to find a successful developing world model to emulate. Drawing on its commercial experience, Gilead made two key decisions in the early days of the Access Program: (i) to ship ARV drugs directly from its manufacturing facilities in the United States, Canada and Europe to public and private organizations located in Low-Income Countries; and (ii) to rely upon the use of import permits to allow ARV importation into a Low-Income Country instead of seeking a new drug application approval (similar to the approvals obtained in the United States and Europe from the FDA and EMA, respectively) for an ARV in such country. The rationale for direct shipment was that Gilead would be able to pass along a lower cost to the patient without any intermediaries in the supply chain. As for import permits, Gilead believed this would expedite product availability as compared to the burdensome process of submitting separate new drug approval applications to each individual country.

Approximately one year after the initiation of the Access Program, Gilead estimated that approximately 100 patients received Viread.² In an effort to increase the impact of the program, Gilead revisited the decisions above.

First Restructuring (2005)

Limited usage of Gilead’s ARV products in the Low-Income Countries prompted Gilead’s first restructuring of the Access Program in 2005, and certain key changes:

ARV New Drug Approval: Sole reliance on permits to import ARV drugs into Low-Income Countries proved to be complicated and a time-consuming burden on the local organizations. Gilead switched course by deciding to seek new drug approval for its ARV products in as many countries as possible. To implement this strategy as expeditiously as possible, Gilead created a standard dossier to submit when seeking approval. The dossier included extensive research data to demonstrate safety and efficacy, as well as documentation to support

manufacturing quality such as FDA certification. The same dossier was submitted to all countries in the program with no customization for individual country requirements.

Manufacturing and Distribution: To provide for adequate manufacturing capacity for both Gilead's commercial operations and the Access Program, Gilead established a facility in The Bahamas to manufacture tenofovir DF, the active pharmaceutical ingredient ("API") in Viread, through a cooperative effort with PharmaChem Technologies ("PCT") and the Grand Bahama Port Authority. Gilead recognized that a manufacturing presence in Africa, the continent hardest hit by the pandemic, was also critical to improving ARV delivery efficiencies. Gilead entered into a partnership with Aspen Pharmacare ("Aspen"), a pharmaceutical manufacturer based in South Africa, to source API from the facility in the Bahamas and to manufacture and distribute Viread and Truvada in Africa. A full technology transfer to both PCT and Aspen allowed them to manufacture Gilead's ARV products in FDA-approved facilities.

Addition of Lower Middle-Income Countries: Low-Income Countries either have per capita gross national incomes ("GNI") of less than \$1,000 (as determined by the World Bank) and/or an extremely high prevalence of HIV infection. Because of the global spread and reach of the pandemic, Gilead realized that the scope of the Access Program had to be extended beyond Africa to include countries that were not classified as Low-Income Countries. To this end, Gilead expanded the program to include Low-Income Countries in Asia, Europe, Latin America, Caribbean and Middle East, as well as those countries with per capita GNI of more than \$1,000 but less than \$3,000 and/or high prevalence of HIV infection ("Lower Middle-Income Countries"). As a result, the program grew from 68 to 97 countries. To continue to make product available at the lowest possible price and taking into account the Lower Middle-Income Countries' ability to pay, Gilead also introduced a tiered pricing structure as follows:

- ▶ *Low-Income Pricing Tier:* Viread and Truvada available at "no-profit" pricing, \$17 and \$26.25 per month, respectively.
- ▶ *Lower Middle-Income Pricing Tier:* Viread and Truvada available at \$30 and \$45 per month, respectively.

However, implementing the steps above did not significantly increase patient utilization rates. By end of 2006, there were 31,000 patients on Gilead's ARV products, a modest improvement from previous levels, but well below the potential need for the product.

Through Gilead's own experiences through the start and the restructuring of the program, and interaction and input from external entities such as non-governmental organizations ("NGOs") who worked actively in these markets, many of the shortcomings of the early model were recognized:

Regulatory Strategy for New Drug Approval: Gilead's decision to submit regulatory dossiers did not result in new drug approval in many countries. While Gilead's approach was to submit a standard dossier to all countries, the requirements differed from country to country, ranging from as few as 10 to more than 4,000 pages, with varying format and content requirements. The standard dossiers were often rejected, or sat idle, because they did not conform to local requirements or because Gilead lacked a local agent. Gilead also discovered that some countries require that drugs be listed on national formularies before submission of a new drug approval, and many have local labeling requirements, meaning that FDA or EMEA labeling is not applicable.

Lack of local expertise: When launching the Access Program in 2003, Gilead underestimated the value of in-country partnerships. This contributed to the inability to leverage local expertise to further the impact of the program. For example, in many cases local expertise and presence were necessary to help manage the registration process, providing a resource to answer relevant questions and to respond to gaps in submissions.

Addition of Viread to WHO Treatment Guidelines: Gilead was late to recognize that Viread would not achieve widespread clinical use until the drug was added to the World Health Organization's ("WHO") prequalification and essential medicines lists. Furthermore, Gilead did not appreciate the impact this would have on country-level

adoption of Viread and Truvada in national treatment guidelines. With the two-year review time at WHO, Viread and Truvada were not included on the lists until May 2007.

Medical Education: Gilead assumed that Viread's attributes (efficacy, tolerability, low rate of resistance, convenience and versatility) and steep discounted prices would automatically generate demand. Gilead's pivotal clinical trials for Viread also demonstrated a significant safety and tolerability advantage over d4T. However, due to a lack of knowledge about the product at local levels, its absence from local treatment guidelines and the availability of lower-cost d4T, the anticipated demand for Viread never materialized. This highlighted the need for local engagement and a formal medical education initiative.

Demand and Supply Management: Due to the complexity in forecasting demand for Access Program markets, Gilead built unnecessarily high levels of product inventory and realized a financial loss.

International Climate: During the first few years after launch of the Access Program, a number of key players and programs now involved in expanding ARV treatment were not in place or were just starting out, and overall funding for these efforts was limited. For example, the Clinton HIV/AIDS Initiative and the Global Fund to Fight AIDS, Malaria and Tuberculosis only began issuing grants in May 2003; at the same time, The President's Emergency Plan for AIDS Relief (PEPFAR) was approved by the U.S. Congress. Additionally, international organizations and many countries were slow to acknowledge the desperate need to increase ARV access in the developing world. Only a few countries had national HIV treatment plans, and those that did had limited resources to implement them. This lack of funding also necessitated the use of lower-cost drugs.

The New Model (2006 – Present)

Driven by lessons learned in the early years of the program, Gilead further restructured its Access Program by increasing program oversight and accountability, creating essential internal and external resources and improving regulatory, medical education, distribution and forecasting activities. This led to the following changes:

Internal Restructuring Efforts

Gilead decided that accomplishing its goal could only be achieved if a dedicated team was formed to focus solely on the Access Program, leading to the creation of "International Access Operations" ("IAO"). IAO was removed from commercial operations; however, the team maintained its full operational responsibilities. This allowed the team to focus on its mission without any competing commercial priorities. The IAO's guiding principle was to enhance access in all eligible countries through appropriate mechanisms while operating in a fiscally responsible manner. Its operational focus included entering into or expanding strategic regional partnerships, pursuing ARV new drug approvals, effectively managing supply and demand and increasing knowledge and understanding of ARV products throughout the developing world.

The IAO consists of a *Program Lead*, three *Regional Leads*, a *Medical Education Lead* and a *Business Analytics and Demand Forecasting Lead*. The IAO team also draws on Gilead resources in legal, business operations and contract compliance, finance, government affairs, information technology, manufacturing, medical affairs, public affairs, quality assurance, regulatory and research and development. The team's success is assessed by metrics that include the number of patients treated, the number of countries in which ARV products are registered, the expansion of medical education programs and the implementation of operational improvements to increase the availability of Gilead's medicines in the regions of the Access Program.

Partnerships

Regional Distribution Network

One of the key lessons learned in the early years was the need for local presence to drive the registration, distribution, medical education and forecasting activities. To achieve this, Gilead began establishing a network of distributors in 2006. Over time, Gilead has entered into partnerships with 11 local distributors to form a global network with reach across all of the Program's 130 countries. The distributors work across five designated regions:

- ▶ *Africa:* Aspen Pharmacare (the largest distributor in the Access Program network)
- ▶ *Asia-Pacific:* Anspec, IDS Group, Piramal Healthcare and Traphaco
- ▶ *Eastern Europe:* Delta Medical and Medicopharmacia
- ▶ *Middle East:* Quadri Pharma
- ▶ *Latin America and the Caribbean:* Gador S.A., Puerto Rico Pharmaceutical, Inc. and Stendhal

These distributors were selected by Gilead to participate in the Access Program based on their knowledge of local environments and their ability to operate under low margin conditions. Final selection was made only after a thorough due diligence process was conducted that evaluated their ability to: (i) accelerate the regulatory process by leveraging their knowledge of local systems; (ii) manage supply and logistics; (iii) provide medical education; (iv) maintain oversight of safety data reporting for product usage in their territories; and (v) operate in compliance with Gilead's standards of appropriate business conduct. In order to keep the Access Program costs low (but at the same time ensure that these distributors participate), Gilead permits each distributor to add a nominal markup to the end price of each ARV product. Some of these distributors have also been engaged to distribute in Gilead's commercial (non-Access Program) markets.

The Regional Leads are the critical links between Gilead and these 11 partners. They assist the distributors in negotiating agreements, facilitating training of local sales teams, conducting regional medical education programs, securing registration for Gilead's drugs and making product supply available for distribution. Gilead is able to leverage expertise developed for its commercial markets by providing technical, medical and marketing support to each distributor to help build their capabilities to provide comprehensive, region-specific medical education and training for physicians and health ministries, while keeping their margins low.

Generic Drug Makers

Another key element of Gilead's partnership strategy is its agreements with Indian generic drug manufacturers. The rationale for this collaboration is multifaceted. The key strength of the generics is manufacturing high volume of product at a lower cost of production combined with experience in distribution in Africa and other Low-Income Countries. This complements Gilead's strengths in innovative R&D and manufacturing. Additionally, by extending the license to multiple Indian generic manufacturers, Gilead attempted to create competition in the market to help drive costs down, even if only a subset of the companies are able to translate Gilead's technology transfer into final product. Finally, these partnerships were also driven by the realization that Gilead (and Aspen manufacturing on behalf of Gilead) alone did not have enough bandwidth to supply ARV products to Access Program markets in a cost-efficient manner.

As a result, in 2006, Gilead entered into non-exclusive licenses with 11 Indian generic drug companies to allow the licensees to produce tenofovir, API in both Viread and Truvada, and generic versions of Viread and Truvada. As of January 2010, Gilead had 13 licensing partners.

The agreements permit the licensees to: (i) sell Viread and Truvada in local Indian markets and to export the products to 94 additional countries, including Thailand; (ii) seek API from, or sell API to, other Gilead licensees; and (iii) seek API from Gilead's own API supplier. The licensees are free to establish their own prices for their generic products, but pay

Gilead a royalty of 5 percent on the sale of finished products. They owe no royalty on the manufacture or sale of API. The royalty terms keep the structure of the agreement simple; royalty on API would have been too complex to record. By not charging a royalty on API, Gilead's hope was to encourage its partners to source API from fewer sources, thus creating manufacturing efficiencies on API and further driving down cost.

By end of 2006, Gilead proceeded with licensing agreements with the following ten Indian generic companies: Alkem, Aurobindo, Emcure, FDC Ltd., Hetero, Matrix, Medchem, Ranbaxy, Shasun and Strides. One company, JB Chemicals and Pharmaceuticals, declined to participate after initially entering into the agreement. Aptuit Laurus, Sequent and Cadila Healthcare were added in 2009. As of this date, Matrix is the only company who has brought a product to market. Over 388,000 patients – approximately 55 percent of all patients in the developing world on tenofovir – had received a Matrix product as of the end of 2009. In October 2009, the WHO added generic tenofovir manufactured by Matrix to its list of prequalified medicinal products. Matrix has also received tentative FDA approval for its generic tenofovir and tenofovir-containing regimens, including generic Atripla,[®] testifying to the quality of its products. Aurobindo and Hetero have also obtained tentative FDA approvals, although they have not recorded any sales as of January 2010. There has already been a 50 percent decrease in price as compared to Gilead's price with the possibility of further reduction with increased competition; however, this is also expected to result in lower margins for manufacturers that may limit the number of companies that produce the generic version.

These partnerships also prompted Gilead to revisit its original agreement with Aspen. In November 2007, Gilead and Aspen entered into a new agreement providing Aspen with a license to produce generic ARV products, along the same terms as those granted to the Indian generics. Gilead thereby secured a generic manufacturer based in Africa, further increasing the efficiency of the Access Program.

Country-by-Country Registrations

The success of the Access Program is dependent on having Gilead's ARV products receive full regulatory approval in all Access Program countries. Though complex and time-consuming, country-specific dossiers continue to be essential to seeking regulatory approval. Regulatory approval and registration of a drug product are also critical from the perspective of each national government's health ministry and the adoption of Gilead's products in national treatment guidelines. This, in turn, enables Gilead and its regional distributors to engage in medical education activities to help promote awareness and appropriate use of product.

The role of the regional distributor is critical in accelerating the regulatory process by leveraging their local knowledge of local systems and by managing the necessary on-the-ground logistics. Dedicated Gilead internal resources and important support from the distribution network have resulted in significant regulatory progress. By January 2010, Viread had regulatory approval in 82 countries, as compared to 18 countries at the end of 2006. Likewise, Truvada is now approved in 77 countries, up from eight countries at the end of 2006.

Gilead currently posts information about ARV registration filing dates and regulatory approvals on its website at www.gilead.com/access_developing_world, enabling transparency in communication of regulatory status.

Increased Emphasis on Medical Education

To increase the knowledge and understanding of its ARV products in the developing world, Gilead has made several key adjustments since inception of the Access Program. Initially, Gilead attempted to provide medical education in these markets directly; however, it became clear that Gilead did not have the resources or the local knowledge and expertise to provide this information. The current approach focuses on educating Gilead's distributors and leveraging relationships with key opinion leaders in the markets to provide them with necessary resources and materials to deliver medical education.

The Medical Education Lead has become a dedicated resource to support the development and implementation of key initiatives. As a result, Gilead has increased the number of educators disseminating information through its distribution partnerships. Each distributor has undergone an intensive training in medical education, ARV products, safety, reporting and Gilead's anti-corruption policies. Ongoing training courses are conducted on a consistent basis. Gilead also relies on its distribution partners to conduct regional healthcare research programs and independent education programs. These programs provide training to both Gilead's regional partners and to healthcare professionals and government health ministries regarding the safe and effective use of Gilead's products. Second, to expand the availability of ARV-related educational materials, Gilead has developed an online portal, from which its distribution partners can download medical research reports, journal articles, promotional materials and other documents for training purposes and for distribution to physicians, patients and policymakers. Select materials are translated into several of the primary languages spoken in the regions of the Access Program.

Managing Variability in Supply and Demand

As discussed earlier, Gilead learned over time that accurate demand forecasting is critical to ensuring an uninterrupted supply of ARV products to patients. ARV demand forecasting in the developing world presents unique challenges. Demand can rapidly change due to a variety of unpredictable factors, such as highly variable and uncoordinated funding sources for the purchase of HIV medications, government tenders to procure medications, various local treatment guidelines, infrastructure challenges and political conditions. Gilead's lead time for production of finished ARVs can be several months, making it difficult to react to such rapid demand changes. In addition, regulatory specifications in many Access Program countries require product labels and package inserts to be in the local language.

To tackle supply and demand variability, Gilead's Business Analytics and Demand Forecasting Lead developed internal processes to manage and communicate demand requirements. Gilead also invested in an information technology tool to track and communicate changes in demand and distributor inventory consistently across regions. And Gilead has expanded its collaborations with global health organizations, such as the Clinton HIV/AIDS Initiative and the WHO, to inform its global planning efforts and better estimate the volume of current and future demand for its ARV products.

Additional Thoughts

Economics

The mission of the Access Program is to enhance access without incurring any financial loss in running the operation as measured by calculation of a net margin metric. The net margin is impacted by revenue from royalty, as well as product sales. Primary costs incurred are from manufacturing, staffing, administration and investments in medical education programs.

In 2007, the Access Program had a net loss of \$5 million, driven in large part by the excess inventory that Gilead had produced in anticipation of a significant uptake in demand. The demand did not materialize and Gilead was forced to sell the product at a discount to cover its manufacturing cost and to clear its inventory.

In 2008, lean operations, royalty revenues and sales to low- and lower middle-income markets had driven the transition to break even in net margin, thereby achieving the financial objective of the access program (fiscal responsibility).

Success of the Gilead Model

Gilead's operational approach is also starting to become adopted by companies that aim to expand access to medicines in hard-to-reach and resource-constrained settings.

In 2007, for example, Tibotec Pharmaceuticals provided a royalty-free voluntary license to Aspen for darunavir for sub-Saharan Africa and in December 2008, Tibotec announced that it had signed a royalty-free, non-exclusive license

agreement with Emcure Pharmaceuticals Ltd. of India to distribute darunavir in that country. What remains to be seen is how effective these agreements will be given that multi-country, competitive approaches have not been utilized. Similar to Gilead, Merck now posts its developing world ARV registrations on its company website.

Challenges

By enabling Indian generic manufacturers to produce tenofovir, Gilead is creating a significantly greater supply of low-cost tenofovir and, at the same time, increasing the competition for its branded products. This competition may lead to erosion of margins and put greater pressure on Gilead's network of distribution partners who are focused on selling branded Viread and Truvada. As the generic market grows, there are also questions about management and support of critical medical education and regulatory/pharmacovigilance activities.

The current state of forecasting demand for HIV drugs poses a significant challenge to delivering medicines and encouraging sustainable programs. The competitive tender process often required for global ARV procurement can have a strain on forecasting depending on how it is implemented. For instance, there is a high level of uncertainty surrounding tender issuance and volumes quoted may not be ultimately procured. Lead times are variable, making supply chain planning and execution difficult.

Political will and commitment at the government level will continue to be an important aspect of the global community's ability to address the growing needs of the millions of individuals affected by HIV/AIDS. Without growth in national-level healthcare expenditure it will be difficult to develop sustainable programs. For example, while Gilead offers no-profit prices, countries still must budget adequately to purchase product. Additionally, as governments are further pressured to expand healthcare for their populations, those countries in Gilead's Upper Middle-Income tier (GNI of less than \$10,000) will lobby for consideration for lower tier pricing. The key challenge Gilead faces is to have governments respect both the established pricing tiers and the generic approach. These represent some of the external factors outside of Gilead's immediate control.

Summary

Gilead's innovation in new operational approaches has directly translated into a greater capacity to deliver its ARV drugs to the developing world. In 2006, 97 countries participated in the program, Viread was registered in 18 countries, Truvada was registered in eight countries, and approximately 9,000 developing world patients were receiving Gilead's products. As of January 2010, 130 countries participated in the program, Viread was registered in 82 countries, Truvada was registered in 77 countries and over 700,000 developing world patients were receiving Gilead's products (branded and generic). The number of distributors worldwide grew from 2 in 2006 to 11 in 2008.

References

- 1 United Nations Conference on Trade and Development. UN List of Least Developed Countries. Available at: <http://www.unctad.org/Templates/Page.asp?intItemID=3641&lang=1>
- 2 Hamilton, D. A 'Good Deed' for AIDS Hits Obstacles. *Wall Street Journal*. June 30, 2006.