INNOVATIVE APPROACHES FOR PHARMACEUTICAL POLICY RESEARCH IN DEVELOPING COUNTRIES:

THE VIEW THROUGH A MARKET LENS

Brenda Waning

The research presented in this PhD thesis was conducted under the umbrella of the Utrecht World Health Organization (WHO) Collaborating Centre for Pharmacoepidemiology and Pharmaceutical Policy Analysis, which is based at the Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, The Netherlands. The Collaborating Centre aims to develop new methods for independent pharmaceutical policy research, evidence-based policy analysis and conceptual innovation in the area of policy making and evaluation in general. The research was conducted in collaboration with the Boston University School of Medicine and the Boston University School of Public Health.

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Innovative Approaches for Pharmaceutical Policy Research in Developing Countries: The View Through a Market Lens

Innovatieve methoden voor farmaceutisch beleidsonderzoek in ontwikkelingslanden vanuit een marktperspectief

Proefschrift

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Chapter 1

Beyond Conventional Wisdom: Innovative Research Methods To Promote Evidence-Based Pharmaceutical Policies And Improve Access To Medicines In Developing Countries

Brenda Waning

1. Framing Access To Medicines Issues

Despite substantial gains over the past few decades, more than two billion people, one-third of the world's population, still lack access to basic essential medicines [1-4]. The issue of access to medicines in developing countries was placed on the global agenda by the World Health Organization (WHO) over thirty years ago [1] and remains a priority issue today. The United Nations aims "[In cooperation with pharmaceutical companies,] to provide access to affordable essential drugs in developing countries" by 2015 as noted in Millennium Development Goal 8E [5].

The WHO access to medicines framework was first described in the *2000-2003 WHO Medicines Strategy* and included four major components: rational selection, affordable prices, sustainable financing, and reliable health and supply systems (Figure 1) [6-7].

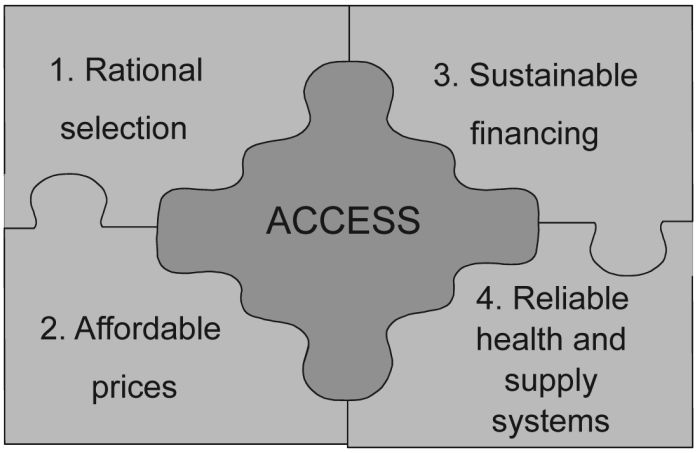

Figure 1. Access to medicines framework*

** WHO Medicines Strategy 2000-2003*

The framework was originally created to guide national policy makers on how to approach access to medicines issues in their countries. The WHO drafted a checklist of key actions policy makers could undertake in each of the four domain areas [6]. Examples of key actions included development of national treatment guidelines and essential medicines lists (rational selection), supporting price competition in the local market and implementation of generics policies (affordable prices), expansion of health insurance and increases in public funding for essential medicines (sustainable financing), and creation of efficient public-private-nongovernmental organization mix approaches (reliable supply systems) [6]. This framework was created at a time when most efforts to increase

access to medicines were funded by national governments and focused on public sector health service delivery.

But 2002 marked a dramatic shift from nationally-focused initiatives to global approaches, especially in the areas of HIV/AIDS, tuberculosis and malaria. Large-scale global health initiatives such as the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM) [8], the United States (US) President's Emergency Plan for AIDS Relief (PEPFAR) [9], and later UNITAID [10] were established to deliver preventive, diagnostic, and treatment services for HIV/AIDS, tuberculosis, and malaria in developing countries. Over the past decade, unprecedented funding in excess of US $63 billion has been poured into these "mega funds" [11-14].

2. Research On Pharmaceutical Policies And Access To Medicines

Sound pharmaceutical policies are promoted by WHO as powerful tools to facilitate access to essential medicines in developing countries [15]; however, little research has been conducted to assess positive and negative impacts of such policies.

The research to date has focused largely on the effects of national pharmaceutical policies. The majority of those studies, however, have been small in scale and utilized simplistic pre- and post-measurement methodologies evaluating a single intervention through a few outcome measures; they do not reflect the reality of complex health system and policy environments. A 2009 systematic review to assess the effects of pharmaceutical policies on rational medicine use reported a dearth of studies from developing countries and noted that most studies lacked sufficient methodological rigor [16]. In 2010 a bibliometric study on access to medicines publications found little evidence for access interventions [17], while Frost and Reich's review on barriers to access found very few studies exploring access in a comprehensive manner reflective of real world conditions [18]. Even less research has been conducted to examine the implications of global policies set by donors and international organizations, despite the unprecedented amount of funding poured into the newly established large global health initiatives.

There are many possible explanations for the dearth of pharmaceutical policy research at national and global levels. Historically, pharmaceutical data sources in developing countries have been limited and unreliable. Even when information is available, it is often not accessible in a manner that can be easily used for research purposes. Information is often recorded on bits and pieces of paper, pharmacy stock cards, and invoices. Few governments have information systems to store information in an easily accessible fashion.

The global public health community emphasized the creation of simple tools to facilitate data collection and analysis for untrained researchers, but did not place equal emphasis on the adoption of new methodological advances for pharmaceutical policy research. Few academic institutions offer training in pharmaceutical policy research for developing countries. Whereas there was a clear demand for evidence-based decisions in the clinical arena, there was a complacency and acceptance that reliable and timely evidence could not be generated to support the dynamic and complex pharmaceutical policy environment.

Whatever the reason, in the absence of methodologically sound research on pharmaceutical policies in developing countries, decision makers at national and global levels are seldom armed with the evidence they need to make informed and strategic decisions. Instead, policies are typically based upon unchallenged conventional wisdoms that become tightly integrated into daily practice at policy and programme levels. These conventional wisdoms are individuals' assumptions and opinions that get passed on to others and become accepted norms and standards of practice. Common conventional wisdoms include beliefs that purchase volumes are the sole and biggest driver of medicine prices and that regulatory price controls offer reasonable approaches to lower medicine prices.

3. Changes In The Global Health Landscape: Transparency, Accountability, And A Shift Towards Market-Based Approaches

Transparency And Accountability Arrangements To Promote Spending Efficiency

The global health landscape is rapidly evolving. Donors and international organizations have recently adopted policies and practices to ensure that both donors and recipients are accountable for efficient use of funds. These accountability mechanisms include independent financial audits, progress-based disbursements of funds, and commitments to transparency of information. Proposals, grant agreements, funding disbursements, board proceedings, and purchase transactions for medicines and diagnostics are now readily available in the public domain [8, 19-20].

Similar initiatives have been established to promote information disclosure on medicines at national level, as well. The World Bank has been a long-time advocate of greater transparency in the pharmaceutical sector as a means of combating corruption and improving

governance [21-22]. The WHO launched the Good Governance project in 2004 which aims to strengthen health systems and prevent corruption through several approaches, including the promotion of transparency and accountability in regulatory and supply management systems for medicines [23]. The Medicines Transparency Alliance, established by the United Kingdom Department for International Development in 2007, uses a multi-stakeholder approach in seven pilot countries to increase the amount of publicly available information on medicine prices, quality, and availability; and thereby promote transparency and accountability in government spending on medicines [24].

Market-based approaches to improve access to medicines

In another recent shift in the global health landscape, donors and international organizations are now approaching access to medicines and diagnostics from a market perspective. Whereas public health initiatives were historically based upon building and rebuilding public sector supply systems, donors and international organizations are now looking to intervene directly through existing market channels to increase access to medicines and other health commodities.

From its beginnings in 2002, the GFATM has recognized the importance of monitoring market dynamics to inform its own decision-making processes [19]. The GFATM changed the global health landscape by requiring reporting and then publicly posting transactional data for commodities procured with its funds, thereby reducing the information asymmetry historically inherent in the pharmaceutical sector [19, 25]. For the first time, information on what medicines were being purchased, including suppliers and prices, was available on the Fund's website. But reporting rates were estimated to be well below 50% and the absence of standardized reporting formats and quality assurance resulted in inconsistent reporting of data that was sometimes of dubious quality. The GFATM formed a Market Dynamics Committee in 2009 to advise the executive board and Secretariat on how to improve the quality and use of this data. The Committee is also expected to provide recommendations on how the Fund could better exert its influence to improve the market for commodities (medicines, diagnostics, and prevention items) used in its HIV/AIDS, tuberculosis, and malaria programs [26].

Other international organizations have adopted similar market-based approaches. The Bill and Melinda Gates Foundation, established in 2000, funds many projects aimed at creating a more efficient marketplace for health technologies in developing countries [27]. The Clinton HIV/AIDS Initiative quickly emerged in 2002 after the establishment of the GFATM, developing and implementing innovative market-based interventions designed to lower prices for medicines and diagnostics for HIV/AIDS [28]. The United Kingdom Department for International Development employs market-based

approaches in many of its projects as does the US-funded Supply Chain Management Systems (SCMS) procurement arm of PEPFAR. At the local level, the World Bank and the United Nations Industrial Development Organisation provide technical assistance to countries to determine if and under what circumstances local production of medicines might result in increased access to essential medicines at affordable prices [29-30]. Finally, UNITAID, a Geneva-based donor and WHO partnership created in 2005, is the first international organization designed specifically and solely to identify and address market shortcomings as a means of improving access to diagnostics, medicines and preventive items used for HIV/AIDS, tuberculosis, and malaria [31].

4. The Close-Up View Of Pharmaceutical Policy Through A Market Lens

The Accelerating Access Initiative, a collaboration of multiple international agencies and pharmaceutical manufacturers, was launched in 2000 to develop tiered or differential pricing schemes for antiretroviral (ARV) medicines used to treat HIV/AIDS in developing countries [32]. While this marked an important first step in promoting access to HIV/AIDS medicines, it was insufficient to support the massive scale-up of HIV/AIDS treatment begun by the GFATM in 2002. Prices charged by innovator companies, despite tiered pricing schemes, were extremely high and unaffordable to developing countries. Innovator companies had little incentive to develop and produce formulations specifically suitable to low-resource setting environments.

Market-based approaches to public health gained popularity immediately after the realization that universal access to HIV/AIDS treatment could not be realized through purchase of innovators' ARVs. The emergence of an Indian generic pharmaceutical industry offered promise as a means to provide lower-priced, quality medicines to people in developing countries. Market-based strategies were developed to promote ARV price reductions, generic competition, and formulation innovation.

Beyond HIV/AIDS, the Access to Medicines Index, which first appeared in 2008, began tracking and ranking pharmaceutical manufacturers according to their efforts to increase access to essential medicines in poor countries [33]. By 2010, pharmaceutical companies were taking note of the Index and making serious efforts to improve their ranking [34], but connecting the policies of manufacturers to actual improvements in access to medicines remains elusive.

Market-based approaches specific to pharmaceutical policy may be a natural fit in this particular public health environment, given that medicines and diagnostics are, in fact,

commodities that are developed, produced, bought, and sold within a market and public health context. The ultimate price of a medicine is the result of a complex interaction between the organization of the supply side of the market and demand-side needs and preferences [35] (Figure 2). The supply side of a pharmaceutical market is typically comprised of numerous developers and producers (e.g., of active principle ingredients, intermediaries, excipients, and final formulations), packagers, and distributors. While the ultimate demand for medicines comes from consumers, between the supply and demand sides are interactions that take place at public and private sector health facilities, at public and private pharmacies, with private physicians and health-care providers and with drug sellers that, together, dictate the ultimate market for a given medicine.

To complicate things further, there are an infinite number of market determinants, some of which are demonstrated in Figure 1. On the supply side, market determinants include: regulatory frameworks; trade agreements; patents and other intellectual property issues; production complexity and efficiency; market structure and competition; price mark-ups; supplier knowledge; medicine quality, safety, and efficacy; perception of patient preferences; and research and development. On the demand side, market determinants include: product acceptability; marketing influence; provider/patient knowledge, attitudes, and perceptions; disease epidemiology; health systems infrastructure and technical capacity; standard treatment guidelines; ability-to-pay; and education level of people needing medicines. Determinants of supply-demand interactions include norms, standards, policies and guidelines of donors and organizations, product registration, donor fund flow, information exchange (including the degree of information asymmetry), and supply chain management systems.

All of these factors individually and collectively influence the ultimate size, shape, and function of pharmaceutical markets. In access to medicines initiatives, market approaches aim to promote "healthy" market conditions whereby manufacturers have incentives to invest and innovate, while at the same time supply quality public health products at affordable prices and in acceptable formulations that enable the maximum number of people to access them. But little research has been conducted to describe how developing country markets evolve and which policies are most successful in shaping markets to support access to medicines goals. The discipline of market-based pharmaceutical policy research is new and therefore requires the identification and application of new data sources and suitable analytic methods.

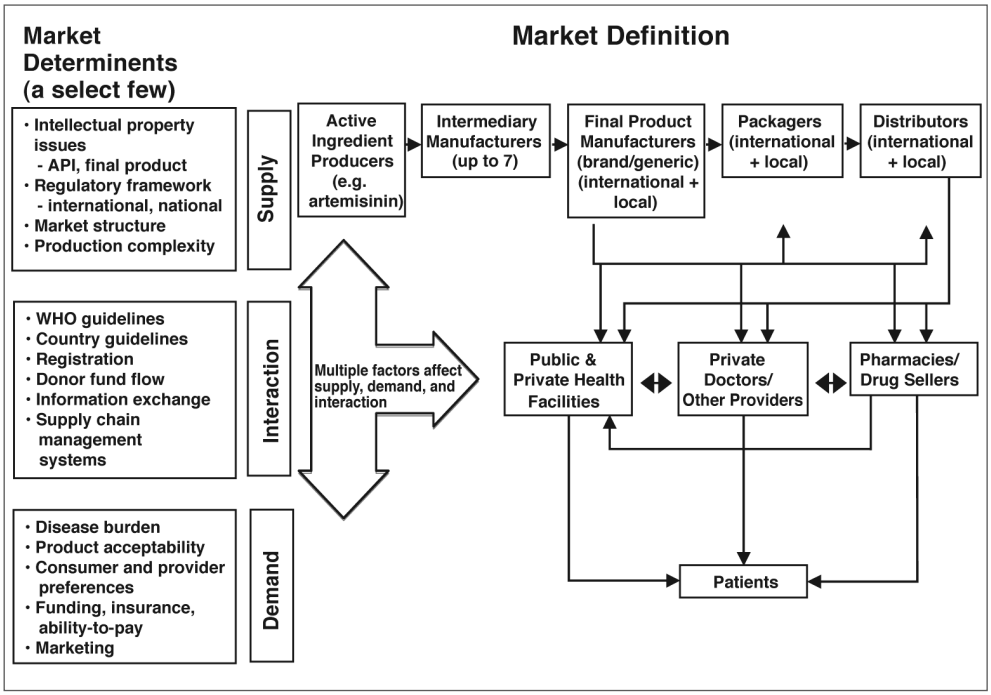

Figure 2. Definition and determinants of pharmaceutical markets*

**adapted from Ross-Degnan*

5. Information Is There For The Taking: New Resources Offer Untapped Potential For Pharmaceutical Policy Research And Market-Based, Access To Medicines Initiatives

Pharmaceutical markets and policy environments are inherently complex and dynamic. As such, their description and monitoring require timely information from many sources. While historically this information has been largely unavailable, with the information yields of large, donor-funded global health initiatives, it soon became evident that this vast amount of information could be translated into real-time data sources. At national level, information in the form of databases to house national insurance schemes for medicines began to emerge. At both global and national levels, this newly available information provided a window to view interactions between national/local policies, markets, and access to medicines.

It was also clear that this rich new vein of information has, so far, been woefully underutilized, even by the very organizations which are collecting and posting it. Global health initiatives taking market-based approaches are very new, with little precedent or research to guide their decision-making, so it's not surprising that few organizations have yet made optimal use of information they are collecting or defined how they will monitor markets and intervene in them. Likewise, the underuse of this information by civil society organizations, academics and others has meant very little actual accountability for billions of dollars of donor and government spending – accountability that was meant to be built into the programs from the start. Similarly, governments were collecting and storing medicines insurance claims data, but not utilizing this data to predict or measure impacts of their own policy decisions.

It became evident to me that this growing vein of raw data is there for the probing. From the perspective of an academic perch, looking at real-world pharmaceutical policy questions on one hand and the ever-mounting deposits of reported information on the other, I realized the untapped potential of newly available resources. In this information and accountability era, pioneering academic researchers now have the opportunity to dig deeper and chart new territory in the area of pharmaceutical policy research. Researchers must envision anew and capitalize upon this publicly available information to develop new data sources and innovative methodological approaches to examine the impacts of pharmaceutical policies on market evolution and access to medicines.

6. Goal and objectives of this thesis

The main goal of this thesis is to further develop methodological approaches for examining pharmaceutical policy and access to medicines issues in developing countries. Conceptually, I adopt a framework to assess pharmaceutical policies in the market context of pharmaceutical supply, demand, and supply-demand interactions.

Specific objectives include (1) identifying new data sources: Whenever possible, I have used existing data that was collected from routine reporting requirements for non-research purposes by numerous organizations engaged in global health. In so doing, I have replicated real-world policy research settings where timely guidance based on relevant data is critical and policy makers cannot wait for original data collection and long-term prospective study results. Another major objective is (2) to use analytic methods not frequently applied to pharmaceutical policy research in developing countries, namely interrupted time-series, cost-accounting, competition, market trends, product diffusion, and market segmentation analyses. My research covers both national and global

pharmaceutical policies and access issues, differentiating between data needs and approaches best suited for each level.

In addition, I had as objectives: (3) to determine which policy strategies increase access to medicines (for example, by looking at the relationship between medicine purchase volume and price, by describing relationships between global policies and temporal trends in market dynamics, by analyzing price competition in private rural pharmacies, etc.); (4) to provide a model for knowledge transfer and incorporation of evidence into international pharmaceutical policy; (5). to demonstrate that such knowledge transfer can bypass the usual, slow academic publication process and rapidly influence pharmaceutical policy and outcomes; (6).to demonstrates the importance of building an evidence base to support strategic, informed pharmaceutical policies that improve access to medicines in poor countries; and (7). to discern from these findings future directions and challenges for access to medicines initiatives.

7. Thesis outline and preview

In addition to this introductory chapter, this thesis contains seven studies across three chapters (chapters 2-4) plus a discussion chapter and summary. In **Chapter 2** I utilize new, locally relevant data sources and methodological applications to examine the market effects of national pharmaceutical policies. The first study uses medicines claims from a national health insurance system to analyze medicine price competition in private pharmacies triggered by a public-sector rural pharmacy network initiative in Kyrgyzstan. The second study utilizes financial and inventory records from pharmacy outlets and cost accounting methods to examine minimum medicine mark-ups needed to balance medicine affordability and sustainability of pharmacy businesses in rural Kyrgyzstan.

Chapter 3 introduces new data sources and methods for describing and examining predictors of antiretroviral medicine prices at the global level. In these two studies I harness information from more than twenty existing data sources, developing innovative mechanisms to clean, validate and transform information into a landmark market intelligence data set. This analytic data set and the resulting analyses provide the basis not only for our research but also for ensuing policy decisions and practice changes made by several donors and international organizations, described later in Chapter 5. The first study describes the rapid emergence of a vibrant and competitive market for antiretroviral medicines following the establishment of global funding initiatives for treatment of HIV/AIDS. The second study examines the impacts of large-scale global policies on prices of antiretroviral medicines and in so doing refutes conventional wisdom around mechanisms to lower medicine prices.

In **Chapter 4** I demonstrate the need to expand the dialogue about access to medicines beyond the effects of policies on medicine prices. Using the same analytic data set I developed for the studies in Chapter 3, I present the first series of publications describing relationships between global policies and temporal trends in market dynamics as they relate to access to medicines. The first study shows how changes in first-line antiretroviral medicine markets are interconnected with the WHO's HIV/AIDS treatment guidelines, antiretroviral quality approvals by the WHO Prequalification Programme and the United States Food and Drug Administration, and group purchase arrangements. The second study demonstrates the fragility of the pediatric antiretroviral market and the limited diffusion of new, better-adapted pediatric antiretroviral medicines, despite successful donor incentives to spur development innovation. In the third study I conduct market segmentation analyses to quantify the role Indian generic antiretroviral medicine manufacturers have played in the global provision of HIV/AIDS medicines, providing reliable and timely information for policy dialogue as India engages in bilateral and regional free trade agreements aiming to impose stricter restrictions on intellectual property for medicines.

In **Chapter 5**, I draw on key findings from all research, discuss the implications of these findings as well as the real-world policy changes that have already resulted from them, and suggest next steps to improve the quality and utility of pharmaceutical policy research in developing countries.

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Chapter 2

Local Data For Local Policy: New Data Sources And Methods To Inform National Policy On Access To Medicines

Chapter 2.1

Towards Equitable Access To Medicines For The Rural Poor: Analyses Of Insurance Claims Reveal Rural Pharmacy Initiative Triggers Price Competition In Kyrgyzstan

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Abstract

Background

A rural pharmacy initiative (RPI) designed to increase access to medicines in rural Kyrgyzstan created a network of 12 pharmacies using a revolving drug fund mechanism in 12 villages where no pharmacies previously existed. The objective of this study was to determine if the establishment of the RPI resulted in the unforeseen benefit of triggering medicine price competition in pre-existing (non-RPI) private pharmacies located in the region.

Methods

We conducted descriptive and multivariate analyses on medicine insurance claims data from Kyrgyzstan's Mandatory Health Insurance Fund for the Jumgal District of Naryn Province from October 2003 to December 2007. We compared average quarterly medicine prices in competitor pharmacies before and after the introduction of the rural pharmacy initiative in October 2004 to determine the RPI impact on price competition.

Results

Descriptive analyses suggest competitors reacted to RPI prices for 21 of 30 (70%) medicines. Competitor medicine prices from the quarter before RPI introduction to the end of the study period decreased for 17 of 30 (57%) medicines, increased for 4 of 30 (13%) medicines, and remained unchanged for 9 of 30 (30%) medicines. Among the 9 competitor medicines with unchanged prices, five initially decreased in price but later reverted back to baseline prices. Multivariate analyses on 19 medicines that met sample size criteria confirm these findings. Fourteen of these 19 (74%) competitor medicines changed significantly in price from the quarter before RPI introduction to the quarter after RPI introduction, with 9 of 19 (47%) decreasing in price and 5 of 19 (26%) increasing in price.

Conclusions

The RPI served as a market driver, spurring competition in medicine prices in competitor pharmacies, even when they were located in different villages. Initiatives designed to increase equitable access to medicines in rural regions of developing and transitional countries should consider the potential to leverage medicine price competition as a means of achieving their goal. Evaluations of interventions to increase rural access to medicines should include impact assessment on both formal and informal pharmaceutical markets.

Background

Equitable access to medicines remains a challenge in developing and transitional countries, especially among the rural poor. Pharmacies in densely populated areas are always more lucrative, often leaving sparsely-populated rural regions without access to reliable sources of medicines within reasonable proximity. Even when pharmacies are physically present, medicines are often unaffordable, and their availability can be erratic because of failing public financing and supply chain management systems [1-11]. Understanding that a large number of people in developing countries seek care and medicines from the private sector, numerous private sector interventions have been mounted; however, a 2007 systematic review of private sector interventions on quality and utilization of care by the poor revealed an insufficient evidence base for those wishing to increase access to health services through private sector interventions [12].

One of the more commonly used mechanisms to address inequities in rural access to medicines has been the establishment of revolving drug funds, whereby a capital investment allows for the initial purchase of medicines and revenues from medicine sales or user fees are used to replenish stock. Sustainable and successful schemes have been described across Africa, South East Asia, and the Former Soviet Union [13-22]. More frequently, however, the literature reveals the failure of revolving drug funds to accomplish their objectives [14,15,22-34].

The design and management challenges of revolving drug funds that Cross et al [22] described in 1986 remain relevant today, nearly a quarter of a century later. Most noteworthy for our study is the inability of most schemes to adopt a business approach to their operations and practices, including a failure to assess the potential market and insufficient planning and marketing [22]. The concept of revolving drug funds has evolved into more sophisticated, business-focused initiatives, such as the Tanzanian Accredited Drug Dispensing Outlets and the Ghanaian CAREshops [6,35]. However, we have found no evidence that either these more advanced initiatives or the traditional revolving drug funds have been described or evaluated with regard to their impact on the existing pharmaceutical market in a given region.

Kyrgyzstan, like many developing and transitional countries, struggles to ensure access to medicines in rural regions. Approximately 64% of Kyrgyzstanis live in predominantly mountainous rural regions [36]. In participatory research sessions involving more than 80% of households in Naryn Province (n = 27,266), rural residents prioritized geographic access to pharmacies as the number one determinant of health in their communities [37]. In 2004, it was estimated that more than 300 rural villages in Kyrgyzstan had no physical access to pharmacies and medicines [38]. A number of factors underlie this absence of rural pharmacies: all pharmacies were privatized during health reforms

following the dissolution of the Soviet Union, and would-be entrepreneurs believed pharmaceutical markets in rural regions were insufficient and unviable. A shortage of pharmacists in rural areas, combined with national policies that mandate pharmacies be staffed by pharmacists, created yet another deterrent to starting rural pharmacies.

When pharmacies are present in rural Kyrgyzstan, medicines are often unaffordable to the poor. The Kyrgyzstan Mandatory Health Insurance Fund covers medicines for approximately 80% of the population [39]. This insurance benefit, however, is administered through contracted private pharmacies concentrated in highly populated regions, and although rural residents are eligible for the medicines insurance benefit, they live too far away from contracted pharmacies to actually access it. Meanwhile,outpatient medicine purchases were the fastest growing component of out-of-pocket health expenditures from 2000 to 2003, increasing more than two-fold over this time period [40]. A 2005 evaluation in Jumgal District found that out-of-pocket costs for treatment of hypertension can represent up to 71% of non-food consumption per capita [38].

In 2005, the Kyrgyz Ministry of Health responded to the pharmacist human resource issue by changing the law to allow nurses to dispense medicines in pharmacies in rural regions after completing a two-week training course. A non-governmental organization (NGO), in collaboration with the Kyrgyz-Swiss Health Reform Support Project, Jumgal Village Health Committees, and the Kyrgyzstan Mandatory Health Insurance Fund, launched a rural pharmacy initiative (RPI) in Jumgal District. The RPI established pharmacies in 12 villages under a revolving drug fund mechanism. The RPI pharmacies were located in government-owned clinics and contracted with nurses already in the clinics to dispense medicines. To avoid disrupting the private market, the RPI management refrained from setting up pharmacies in Chaek, the district center, where a few pharmacies already existed. These private pharmacies also had outlets in two larger villages in Jumgal. A description of key features of the RPI is provided in Table 1.

While no distinct policy was created to establish medicine prices in the RPI, the management applied minimal mark- ups sufficient to cover their estimated operating costs. Retail mark-ups initially averaged approximately 30-50% for most medicines. Surprisingly, as the rural pharmacy initiative emerged, the private pharmacies in the district center appeared to be changing their prices on key medicines in order to compete with the new RPI pharmacies in area villages. Anecdotal reports and interviews with owners of private pharmacies in Chaek suggested that the RPI had an unplanned impact on overall medicine prices, even in the district center where the RPI was not operating.

The potential of these types of rural pharmacy initiatives to induce medicine price competition has profound implications for Kyrgyzstan and beyond. While scores of studies have been conducted to describe the unaffordability of medicines [7,9,11], few publica-

tions provide evidence-based guidance on how to decrease medicine prices so they are more affordable. The purpose of this study, therefore, is to determine if the RPI actually achieved the unforeseen benefit of triggering price competition in nearby private competitor pharmacies.

Methods

We obtained six lists of medicines covered by the Kyrgyz Mandatory Health Insurance Fund from 2002-2007 along with pharmaceutical claims data (n=162,999 claims) for the period October 2003-December 2007 for the districts Ak Taala, Alai, At Bashi, Jumgal, Kochkor, Naryn, Tok-togul, and Ton. We cleaned insurance claims data in several steps, excluding the following: reimbursement equaled zero; those where patient co-pay plus reimbursement did not equal total reimbursement; those with invalid package sizes; and those where the difference in published and actual reimbursement rates exceeded 20%.

Differences in published and actual reimbursement prices result from a delay in actually distributing the revised published lists to the more than 300 contracted pharmacies throughout the region. We then excluded all non-Jumgal claims and all claims for medicines not on the list of top 30 selling medicines by volume, resulting in a final analytic data set of 18,012 Jumgal claims, which included 6,795 and 11,217 claims from RPI and competitor pharmacies, respectively (Figure 1).

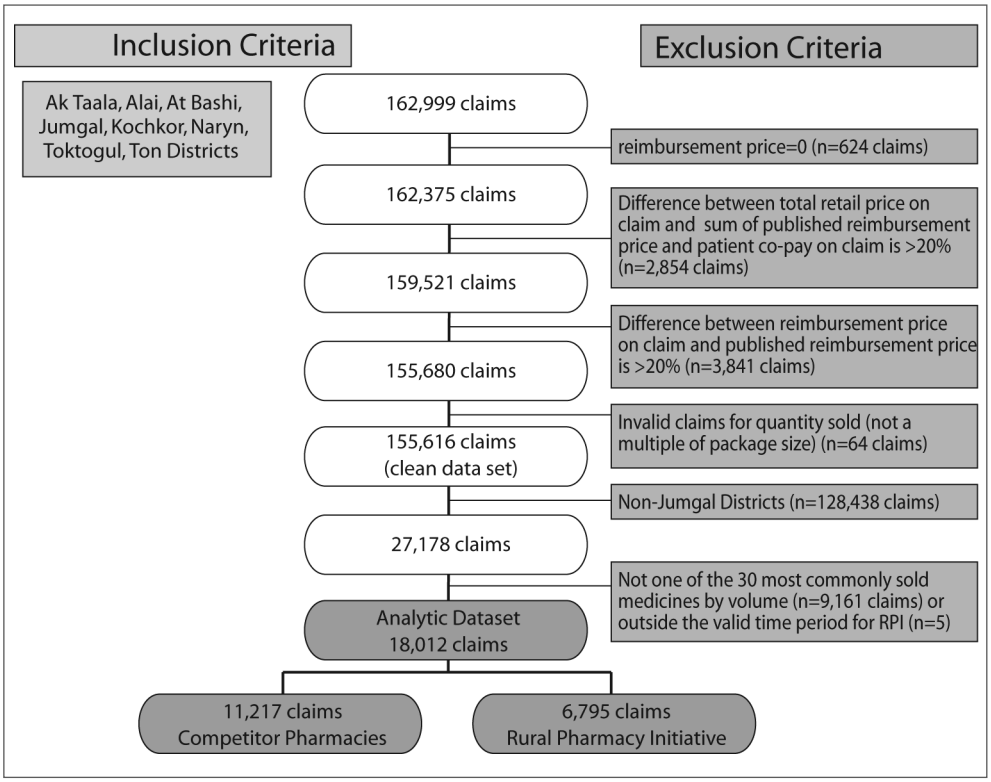

Figure 1. Creation of an analytic data set from medicines insurance claims

We examined RPI and competitor prices using both simple descriptive and multivariate analyses. Since the RPI was first introduced in October 2004, this study period allows for a one-year observation period of competitor medicines prices before the introduction of the RPI and more than three years of observation for both RPI and competitor pharmacies afterwards. All prices are provided as price per unit (price per tablet or price per injection) in Kyrgyz Som.

For descriptive purposes, we calculated competitor price changes by comparing their average price for the last quarter observed in the study to their average price in the quarter preceding the first RPI price observed. Competitor final price changes are presented as *percent price changes* (Figure 2, Table 2) and calculated as follows:

$$((\text{average price}_{\text{last quarter}} - \text{average price}_{\text{quarter before RPI introduction}})/\text{average price}_{\text{quarter before RPI introduction}}) \times 100.$$

We plotted examples of competitor price changes for medicines that exhibited price decreases, price increases, and no price changes (Figures 3, 4, 5, and 6). The Health

Insurance Fund reimbursement prices are provided as a reference but are not meant to be an indicator of retail prices. The reimbursement price is the amount reimbursed to pharmacies by the Health Insurance Fund, whereby the patient pays the difference between the retail and reimbursement prices. Each medicine has a unique reimbursement price, ranging from 30-100% of the retail price. These reimbursement prices are changed regularly but these changes are typically not related to changes in retail prices.

We conducted multiple regression analysis on 19 of the top 30 selling medicines which met our sample size inclusion criteria that required at least seventeen quarters of competitor price data, including three quarters of data before RPI introduction and at least nine quarters of RPI price data. In quarters with missing data due to sparse purchases, we imputed the price and number of transactions using the adjacent quarters.

We estimated competitor prices for 3 time periods: the immediate price change from the quarter before the RPI was introduced to the quarter after the RPI was introduced (Table 3, Column B), quarterly trends prior to the RPI introduction (Table 3, Column C), and the long term quarterly price trends after the RPI introduction (Table 3, Column D). When quarterly price trends before RPI introduction are equal to quarterly price trends after RPI introduction, we present the overall quarterly rate of change (Table 3, Column E). Statistical significance is defined as $p \leq 0.05$.

We conducted model-checking diagnostics, including a test for residual autocorrelation, to ensure our model was appropriate for our distribution. Our model takes into account price dispersion because it utilizes all price values, not just average price. But we present the average price to facilitate interpretation of the results. We conducted all descriptive and multivariate analyses using SAS 9.1 (SAS Institute, Carey, NC).

Results

Descriptive analyses reveal that prices for 21 of 30 (70%) competitor medicines changed by at least 10% to mimic RPI prices after the introduction of the RPI. Prices for 17 of 30 (57%) competitor medicines decreased at least 10%, with price decreases ranging 10-64.3% (Figure 2). Prices for 4 of 30 (13%) competitor medicines increased more than 10%, with price increases ranging 12.1-222.2%, apparently in response to RPI prices introduced at higher rates than those charged by competitors. Nine of 30 (30%) competitor medicines revealed price changes +/-9.9% after the RPI introduction.

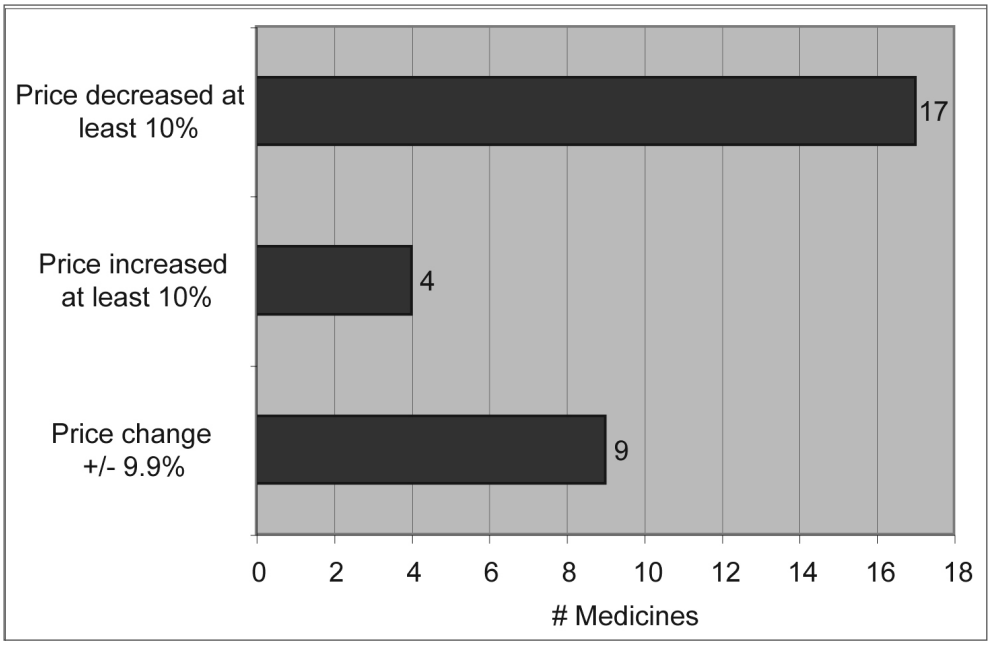

Figure 2. Competitor medicine price changes after the RPI introduction

Detailed information on specific medicine price changes is provided in Table 2. Among the seventeen competitor medicine prices that decreased at least 10% after RPI introduction, six, seven, and four medicines showed price reductions of 41-64%, 20-40%, and 10-19%, respectively. Among the four competitor medicines that increased more than 10% after RPI introduction, three were iron-containing medicines.

Two examples where competitor medicine prices decreased after RPI introduction are provided in Figures 3 and 4. Figure 3 reveals dramatic competitor price reductions for metronidazole 500mg vaginal suppositories where the competitor price decreases immediately from 11.9 Kyrgyz Som/suppository prior to RPI introduction to 7.9 in the following quarter. The quarterly trends continue downward to a final price of 6.5 Kyrgyz Som/suppository at the end of the study period.

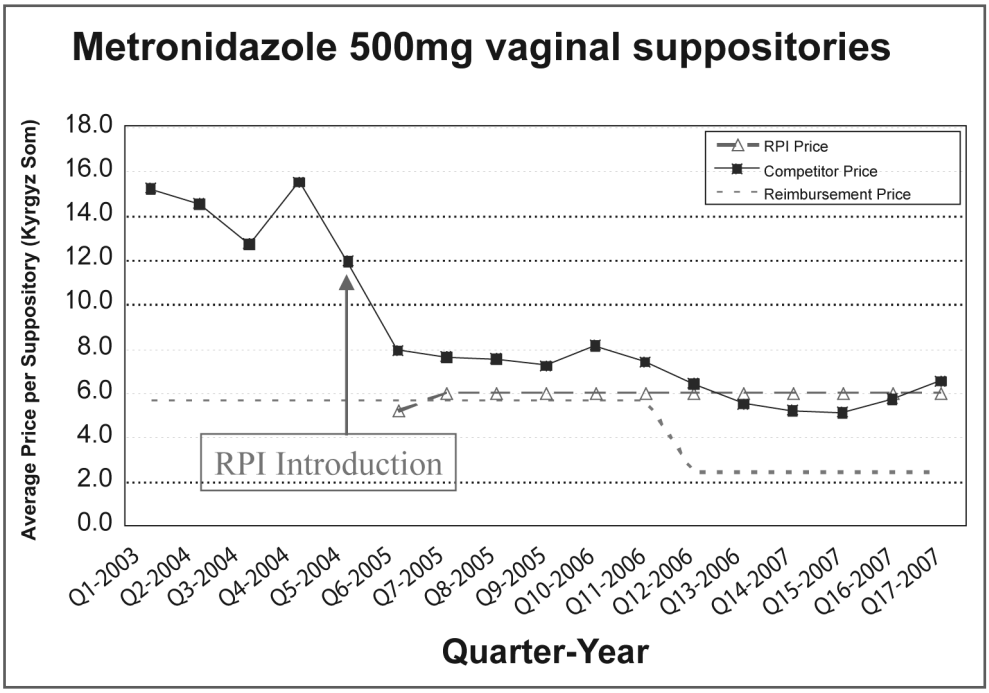

Figure 3. Price changes for metronidazole 500mg vaginal suppositories

In Figure 4, the competitor price for enalapril 20mg tablets (Ednyt®) was 10.5 Kyrgyz Som/tablet in the quarter prior to the introduction of RPI pharmacies. The RPI entry price was 5.4 Kyrgyz Som but they soon increased their price to 8.1 Kyrgyz Som. A few quarters later, the competitors priced their product to mimic the RPI prices, also ending at 8.1 Kyrgyz Som at the end of the study.

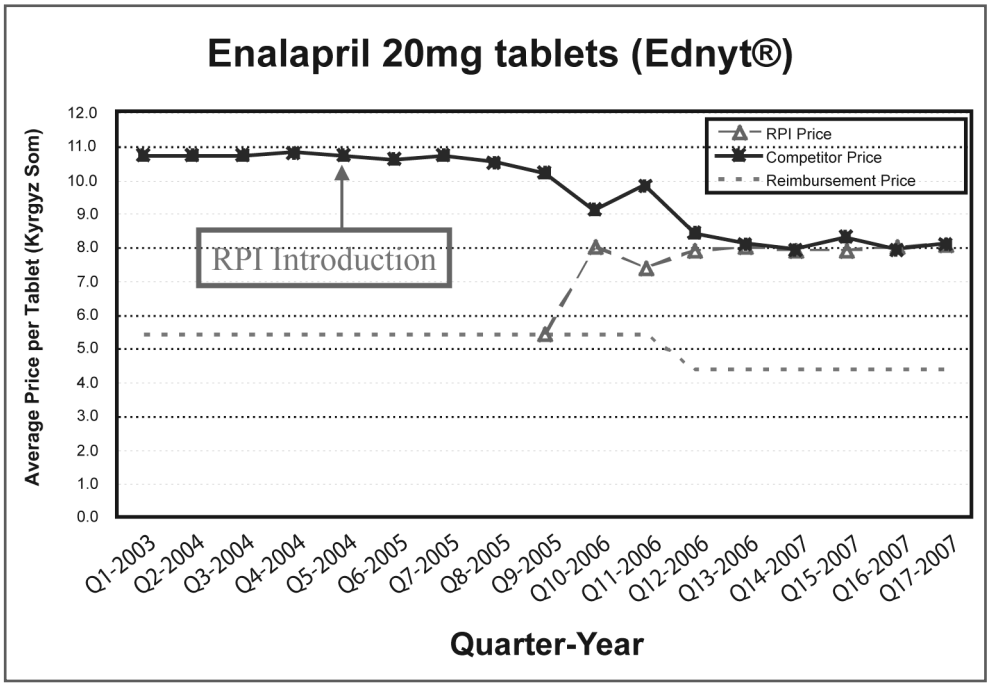

Figure 4. Price changes for enalapril 20mg tablets (Ednyt®)

Figure 5 illustrates dramatic price increases observed for tablets containing iron and ascorbic acid (Gyno-Tardyferon®) in response to these products being sold at higher prices in RPI pharmacies. Competitor prices increased from 3.8 Kyrgyz Som/tablet to 8.2 Kyrgyz Som/tablet after the RPI pharmacies introduced the product at the price of 8.2 Kyrgyz Som/tablet.

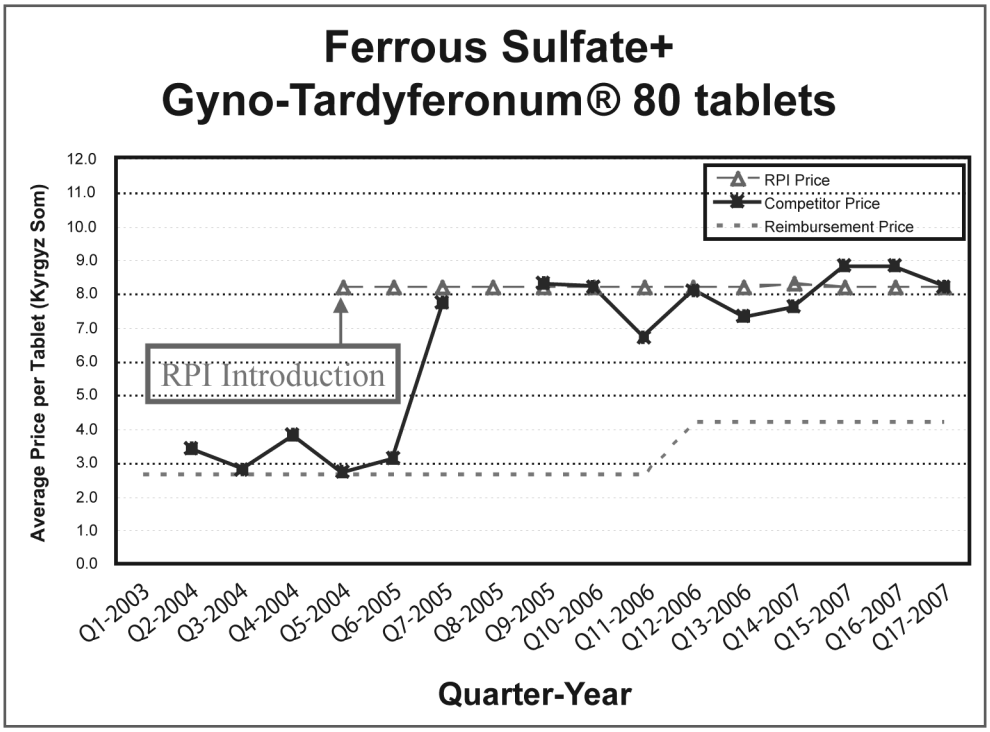

Figure 5. Price changes for ferrous sulfate+ascorbic acid (Gyno-Tardyferon®) tablets

Lastly, figure 6 provides an example of a medicine that exhibits no overall price change from the quarter before the RPI is introduced and the end of the study period. While competitor prices fall for a brief period of time, the pharmacies eventually revert to prices charged prior to the introduction of the RPI.

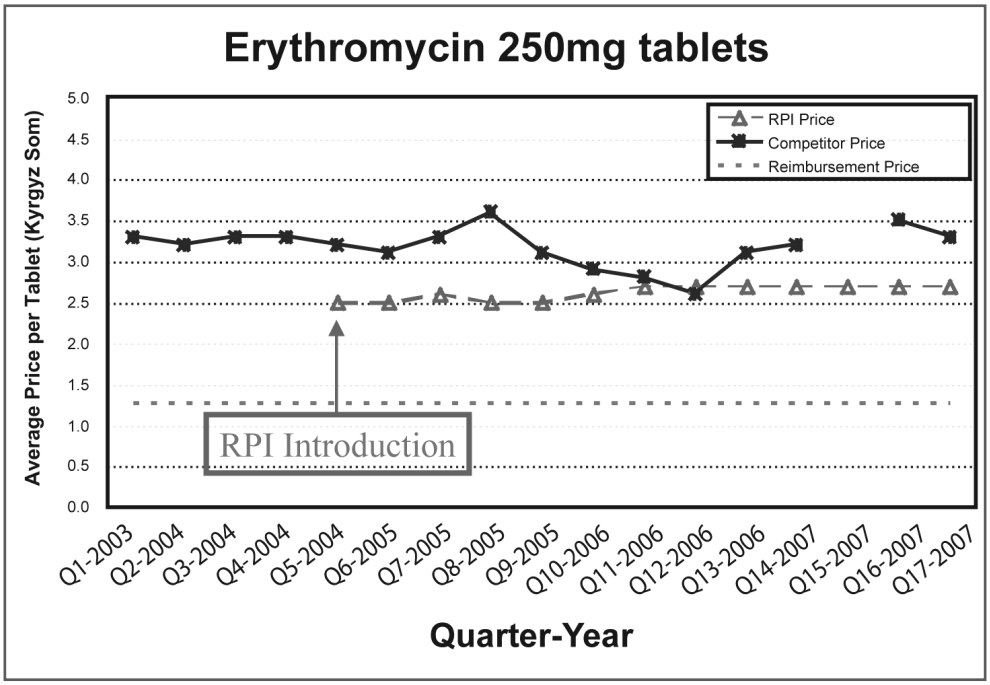

Figure 6. Price changes for erythromycin 250mg tablets

Multivariate analysis revealed fourteen of nineteen (74%) competitor medicines with significant price changes from the quarter before RPI introduction to the quarter after RPI introduction (Table 3, Column B). Nine of the nineteen (47%) medicines revealed price decreases, which ranged from ranged from 0.35-4.85 Kyrgyz Som per unit, while five of the nineteen (26%) revealed price increases, ranging from 0.06-1.96 Kyrgyz Som per unit.

Interestingly, among medicines with differences in price trends before and after the RPI introduction, 6 of 6 (100%) revealed downward price trends before the RPI (Table 3, Column C). All six of these medicines revealed significant price decreases immediately after RPI introduction (Table 3, Column B) with long term prices remaining relatively unchanged (Table 3, Column D).

Mixed results are noted among thirteen medicines with no differences in price trends before and after RPI introduction. Seven of these 13 (54%) medicines showed downward price trends, while prices for 3 of the 13 (23%) trended upward (Table 3, Column E). For most of these medicines, the changes in price trends over time (Table 3, Column E) are far less than those observed immediately after the introduction of the RPI (Table 3, Column B).

Discussion

This study confirms the success of the RPI as an innovative, not-for-profit option for promoting medicine price competition in Kyrgyzstan, and ultimately increasing access to medicines. The RPI not only addressed geographic access by enabling rural residents to buy medicines in their own villages, it also spurred dramatic price competition in private pharmacies located in the district center. Thus, the RPI's impact was far greater than anticipated as the new pharmacies managed also to increase access to medicines in other villages through the competitive price reductions they engendered.The ultimate result was more affordable medicine for both villagers and residents of the district center. It is worth noting, however, that for some medicines, when the RPI introduced prices higher than competitor prices, the competitor increased their prices to match those of the RPI. In this regard, the RPI demonstrates power to drive markets both downward and upward in price.

We do not believe the RPI resulted in the institution of a rural market. Instead, we believe the market already existed in Jumgal prior to the RPI and that the entry of the not-for-profit RPI spurred a more competitive market. Indeed, demand for medicines was already documented before the RPI when villagers identified access to medicines as their number one health concern. On the supply side, medicines were available in the rayon center, but not in the villages themselves. Prior to the establishment of the RPI, villagers either hired a taxi to deliver medicines from existing pharmacies to their homes or they secured some means of transport to travel outside the village to the nearest pharmacy. The establishment of the RPI, therefore, took business away from the existing pharmacies despite being located far away. The emergence of the RPI pharmacies also seems to have stimulated expansion of the private sector into new villages. Owners of pharmacies in the rayon center opened two branch pharmacies in two of the larger villages, perhaps in an attempt to minimize loss of business in the rayon center.

While we have no means to assess price collusion, we suspect that some degree of collusion existed among the private pharmacies that were established prior to the RPI. We therefore suspect the introduction of the RPI disrupted any existing price collusion in the region. Given that our study tracks prices for three years after the establishment of the RPI, we suspect the competitors' price reactions are sustained and not a one-off reaction to the RPI.

When the competitors change prices to mimic RPI medicine prices, their prices are often near identical to the RPI prices. We were unable to fully ascertain how the competitors gained market intelligence on RPI medicine prices. Upon establishment of the RPIs, the RPI nurses were instructed to display all medicines with price tags affixed to their packages. When interviewed a few months later, the nurses told investigators that they

no longer displayed medicine prices because employees from competitor pharmacies would visit RPI pharmacies and record medicine prices. The RPI nurses, management, and others were greatly concerned about predatory pricing by competitor pharmacies. The RPI was quite fragile when first established and many feared the existing private sector pharmacies would intentionally undercut RPI prices in order to drive them out of business. Our results suggest that competitors are still obtaining price information from RPI pharmacies even though price tags are no longer affixed.

While our study provides compelling results, it has limitations. First, we were only able to access prices for those medicines covered by the Health Insurance Fund. The sale of all medicines covered by the Health Insurance Fund, however, accounted for 51% of total RPI revenue in the fourth quarter of 2007 [41]. Because these pharmacies serve sparsely-populated rural regions, small sample sizes limited us to analyzing only 19 of the 30 top-selling medicines with multivariate methods. Some medicines that passed our sample size criteria for multivariate analysis had limited insurance claims prior to or after RPI introduction. We utilized a linear model that assumes a relatively constant quarter-on-quarter price change. Given that we only observed seventeen quarters of data, we believe the linear assumption is reasonable. Model-checking diagnostics, such as test for residual autocorrelation, showed that our model is adequate for our purposes.

Furthermore, we note that to make optimum use of space, we provided price trends in graphic form for only four of the thirty medicines studied, however a full set of figures is provided in Additional File 1. Figures provided in this paper depict the three types of competitor price changes observed after the introduction of the RPI-price decreases, price increases, and no price changes-and are representative of the medicines in each price change category. We had no means to determine why some medicines exhibited dramatic price changes and others remained unchanged. While we had no data on the quality of medicines, we do not believe that quality confounded our price findings. For branded generic medicines, we assume the quality of medicines to be identical in RPI and non-RPI pharmacies. Because the RPI and non-RPI pharmacies purchase medicines from the same wholesalers in Bishkek, we assume quality of non-branded generic medicines is comparable. We have no evidence of pharmacies over-charging insurers, however we expect it happens to some degree. Over-charging is less likely to happen within the RPI because it is supervised by staff from the Mandatory Health Insurance Fund.

While research on market impact is typically complicated due to many concurrent interventions and changing market conditions, we are confident that the market in Jumgal is truly local and has no other large-scale interventions that might be responsible for our findings. Indeed, even an annual inflation of 10% [42] did not seem to

affect medicine prices in this region over the study period. We decided to use current medicine prices in lieu of adjusting prices for inflation after noting that most medicine prices trended downward or remained unchanged over the 4 years and did not seem to follow the national inflation rate. We are not sure why medicine price trends are inconsistent with national inflation trends. We suspect that medicine prices were already priced at the highest prices the market could bear or that national inflation rates simply do not represent the price trends in rural medicine markets. Lastly, we have no means of determining if the market existing prior to the RPI was competitive or collusive with regards to price setting.

Our study was designed only to assess whether the RPI induced regional price competition and not to evaluate rational use of medicines in RPI pharmacies. Others have shown that perverse incentives to misuse medicines may result when prescribers benefit from medicine sales [43]. In this study, we note that ampicillin injection has the highest sales volume and the largest number of insurance claims (Table 2), suggesting overuse of both antibiotics and injections. Additional research is needed to assess the impact of the RPI on rational use of medicines.

Similarly, our study does not aim to explain why the RPI has been successful or how the RPI has been sustainable amidst other documented failures to increase access to medicines in rural regions. The RPI may offer a model that can be scaled up across many more regions and in other parts of Central Asia, but it is important to first determine the most critical elements that led to its success. While we cannot pinpoint theses critical components, we note the key characteristics of the RPI, including the role of highly trained and motivated players who genuinely wanted to develop and test new ways to increase access to essential medicines in rural areas. These staff devoted a great deal of their personal time and energy to seeing the project through, and it would be a mistake to overlook or underestimate the value of this social capital, especially in post- Soviet Central Asia. From a social and political stand- point, the climate of Kyrgyzstan is recognized as being more conducive to civil society than that of any of its neighbors in Central Asia. However, with the exception of a few very strong professional organizations, the country's health sector NGOs tend to be less evolved than the NGO managing the RPI. In addition, the NGOs tend to be rather fractured, often working from outside the government rather than in collaboration with it. We therefore see a need for donors, international organizations, and governments to assist in reorganizing and building the capacity of existing NGOs to refocus their social capital towards more concrete activities, such as establishing and overseeing the RPIs.

Understanding that the majority of people in developing countries still seek care from pharmacies rather than public sector health facilities, many donors have been ea-

ger to develop private sector interventions but have been wary of engaging directly with the private sector. At the same time, donors are eager to establish and promote community-based programs and civil society. The non-profit nature and involvement of civil society organizations in the rural pharmacy initiative model could provide donors with an opportunity to accomplish multiple goals without compromising their non-profit missions.

Lastly, the study reveals the utility of data on medicines that are routinely collected through mechanisms such as insurance schemes. These types of data sources are rich and should be used to build a solid body of evidence to guide policy on access to medicines for the poor. Research on interventions to increases access to medicines must include assessment of potential impact on both formal and informal markets. More work is needed to identify incentives for NGOs and other non-profits to engage in the establishment and management of rural pharmacies that can compete with existing private pharmacies. This should include determination of the operating costs to establish and maintain rural pharmacies and the minimum mark-ups needed to sustain these pharmacies, as well as pricing policies that promote rational use of medicines. Additional research is also needed to examine policies and programs that promote and impede competition in the pharmaceutical sector, including description of market size and structure, presence or absence of competition laws, price regulation, barriers to market entry, and marketing.

Conclusion

Initiatives designed to increase equitable access to medicines in rural regions of developing and transitional countries should consider the potential to leverage medicine price competition as a means of achieving their goal. The inclusion of civil-society organizations and non-governmental organizations in the design and management of these initiatives, in collaboration with governments and international organizations, provides opportunities for capacity building, health sector development, and business development in rural regions that are often neglected.

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Key Feature	Description
Buy-in and Support	Popular consensus that access to medicines is the number one health determinant in communities
	Involvement of Village Health Committees in the design of the RPI and refurbishment of pharmacy outlets
	Political will of the Kyrgyz authorities, and support from international organizations and the Mandatory Health Insurance Fund
Cost Savings and Income	Co-location of RPI outlets in existing government-owned health clinics, resulting in free rent and utilities
	Co-location of the RPI headquarters in government offices in the capital city, resulting in free rent and utilities
	Revenue stream assured by contractual arrangement between RPI pharmacies and the Mandatory Health Insurance Fund for administration of state-funded medicines benefit
Human Resources and Oversight	Contractual arrangements with existing nurses, paying them a modest bonus for their part-time pharmacy activities
	Availability of a highly-qualified pharmacist to manage the central RPI warehouse
	NGO managers' exceptional technical capacity in pharmaceutical management and their contributions of a great deal of personal time to support the RPI

Table 1. Key features of the Rural Pharmacy Initiative

Volume Rank*	Total # Claims (RPI and Competitor)		Generic Medicine Name (Brand Name)	Average Initial Price per Unit (SD) in Kyrgyz Som		Average Final Price per Unit (SD) in Kyrgyz Som		Competitor Price Change after RPI Introduction**
	Before RPI Intro-duction	After RPI Intro-duction		Comp-etitor	RPI	Comp-etitor	RPI	
1*	630	1,923	ampicillin 500mg injection	7.6 (0.6)	6.0 (0.0)	7.7 (0.5)	6.0 (0.1)	+1.3%
2	0	494	amoxicillin 250mg capsules	3.0*** (0.0)	2.5 (0.0)	3.0 (0.0)	2.5 (0.0)	0%
3*	467	1,138	benzylpenicillin 1g injection	5.0 (0.0)	4.8 (0.2)	5.0 (0.0)	5.0 (0.2)	0%
4*	67	680	erythromycin 250mg tablets	3.3 (0.2)	2.5 (0.0)	3.3 (0.4)	2.7 (0.0)	0%
5*	130	870	amoxicillin 250mg tablets	3.0 (0.7)	2.6 (0.2)	2.8 (0.8)	2.5 (0.0)	-6.7%
6*	342	779	atenolol 50mg tablets	1.6 (0.1)	1.1 (0.0)	0.9 (0.1)	0.9 (0.0)	-43.8%
7*	3	544	ciprofloxacin 250mg tablets	4.3 (0.5)	2.4 (0.5)	3.5 (0.8)	2.8 (0.2)	-18.6%
8*	130	1,036	enalapril 20mg tablets (Ednyt®)	10.5 (1.0)	5.4 (0.0)	8.1 (0.5)	8.1 (1.0)	-22.9%
9*	515	760	metronidazole 250m tablets	1.0 (0.2)	0.8 (0.0)	0.9 (0.0)	0.6 (0.1)	-10%
10*	5	226	ferrous sulfate+folic acid+ascorbic acid tablets (Gyno-Tardyferon®)	3.8 (1.6	8.2 (0.0)	8.2 (0.8)	8.2 (0.0)	+115.8%
11*	12	214	carbamazepine 200mg tablets	1.9 (0.6)	2.0 (0.0)	1.5 (0.1)	1.4 (0.0)	-21.1%
12*	3	268	ferrous sulfate+ascorbic acid tablets (Taryferon®)	2.7 (0.0)	7.3 (0.0)	8.7 (1.2)	7.3 (0.0)	+222.2%
13	43	314	enalapril 10mg tablets (Ednyt®)	6.9 (1.2)	5.1 (0.2)	5.0 (0.6)	5.2 (0.0)	-27.5%
14	150	429	co-trimoxazole 480mg tablets	2.6 (0.3)	1.8 (0.0)	2.7 (0.3)	1.9 (0.0)	+3.8%
15	0	187	iron combination tablets (Ferum Lek®)	6.4** (1.0)	10.0 (0.0)	7.5 (1.9)	10.3 (1.3)	+17.2%
16*	53	209	nifedipine 20mg retard tablets (Corinafar Retard®)	3.3 (0.9)	3.6 (0.3)	3.7 (0.7)	5.0 (0.0)	+12.1%
17*	7	49	Prednisolone 5mg tablets	1.1 (0.1)	1.3 (0.4)	0.5 (0.0)	0.9 (0.5)	-54.5%
18*	138	193	diclofenac 25mg tablets (Ortophen®)	0.7 (0.2)	0.4 (0.0)	0.6 (0.1)	0.6 (0.1)	-14.3%
19	114	197	ampicillin 250mg tablets	1.9 (0.1)	1.4 (0.0)	1.5 (0.0)	1.6 (0.0)	-21.1%
20	484	395	co-trimoxazole 480mg tablets (Biseptol®)	4.0 (0.0)	2.2 (0.0)	3.5 (0.0)	3.8 (0.0)	-12.50%

Volume Rank*	Total # Claims (RPI and Competitor)		Generic Medicine Name (Brand Name)	Average Initial Price per Unit (SD) in Kyrgyz Som		Average Final Price per Unit (SD) in Kyrgyz Som		Competitor Price Change after RPI Introduction**
	Before RPI Intro-duction	After RPI Intro-duction		Comp-etitor	RPI	Comp-etitor	RPI	
21	43	74	drotaverine 40mg tablets (No-Spa®)	2.4 (0.2)	2.3 (0.0)	2.5 (0.0)	2.6 (0.0)	+4.2%
22	28	110	metronidazole 250mg tablets (Trichopol®)	3.5 (0.4)	2.1 (0.0)	3.5 (0.0)	3.5 (0.0)	0%
23*	73	548	metronidazole 500mg vaginal suppositories	11.9 (5.3)	5.2 (0.0)	6.5 (0.8)	6.0 (0.0)	-45.4%
24	13	60	ferrous sulfate+ascorbic acid drag (Ferroplek®)	1.5 (0.5)	0.8 (0.0)	1.5 (0.0)	1.6 (0.0)	0%
25*	445	927	diclofenac 75mg injection	8.1 (1.0)	3.9 (0.4)	6.0 (0.2)	5.3 (0.3)	-25.9%
26	140	226	bromhexine 8mg tablets	0.5 (0.1)	0.3 (0.0)	0.4 (0.1)	0.6 (0.3)	-20%
27*	64	336	omeprazole 20mg capsules	5.9 (0.5)	5.1 (0.6)	3.4 (1.0)	2.7 (0.0)	-42.4%
28*	70	113	ketotifen tablets	1.4 (0.3)	0.8 (0.0)	0.8 (0.0)	0.8 (0.0)	-42.9%
29*	269	216	doxycycline 100mg capsules	2.8 (0.0)	1.3 (0.2)	1.0 (0.0)	1.5 (0.0)	-64.3%
30	3	56	verapamil 80mg tablets	2.2 (0.5)	1.2 (0.0)	1.6 (0.0)	1.7 (0.0)	-27.3%

Table 2. Descriptive results of RPI and competitor prices for the 30 highest volume insurance medicines before and after RPI introduction

**Used in time-series analyses*

***Difference in competitors' price from the quarter before the RPI was introduced to the end of the study period*

****No price for quarter before RPI intro; this price from quarter where RPI price first appears*

		Price Trends Before RPI are NOT Equal to Price Trends After RPI		Price Trends Before RPI are Equal to Price Trends After RPI
A Medicine	B Immediate price effect of RPI§	C Quarterly price trends before RPI	D Quarterly price trends after RPI	E Quarterly price trends before and after RPI
ampicillin 500mg injection	-1.19**	-0.27**	0.01	
atenolol 50mg tablets	-0.52**	-0.14*	-0.05	
metronidazole 250mg tablets	-0.35**	-0.03**	0.01	
carbamazepine 200mg tablets	-1.04*	-0.22*	-0.02	
diclofenac 75mg injection	-2.33**	-0.34**	-0.07	
doxycycline 100mg capsules	-1.19**	-0.08**	-0.03	
benzylpenicillin 1g injection	0.06*			-0.02**
erythromycin 250mg tablets	-0.07			-0.01
amoxicillin 250mg tablets	0.20*			-0.05**
ciprofloxacin 250mg tablets	-0.73*			-0.01
enalapril 20mg tablets (Ednyt®)	-0.18			-0.21**
ferrous sulfate+folic acid+ascorbic acid tablets (Gyno-Tardyferon®)	1.96*			0.26**
ferrous sulfate+ascorbic acid tablets (Taryferon®)	1.40			0.29**
nifedipine 20mg retard tablets (Corinafar Retard®)	0.93*			-0.06
prednisolone 5mg tablets	0.38			-0.10*
diclofenac 25mg tablets (Ortophen®)	-0.05			-0.01*
metronidazole 500mg vaginal suppositories	-4.85**			-0.27**
omeprazole 20mg capsules	0.75*			-0.30**
ketotifen tablets	0.18			-0.08**

Table 3. Multivariate results of competitor price trends for 19 medicines before and after RPI introduction

§ *Difference in competitor price from the quarter before to the quarter after the RPI was introduced*
**p≤0.05, **p<0.0001*

Chapter 2.2

Balancing medicine prices and business sustainability; analyses of pharmacy costs, revenues and profit shed light on retail medicine mark-ups in rural Kyrgyzstan

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Abstract

Background

Numerous not-for-profit pharmacies have been created to improve access to medicines for the poor, but many have failed due to insufficient financial planning and management. These pharmacies are not well described in health services literature despite strong demand from policy makers, implementers, and researchers. Surveys reporting unaffordable medicine prices and high mark-ups have spurred efforts to reduce medicine prices, but price reduction goals are arbitrary in the absence of information on pharmacy costs, revenues, and profit structures. Health services research is needed to develop sustainable and "reasonable" medicine price goals and strategic initiatives to reach them.

Methods

We utilized cost accounting methods on inventory and financial information obtained from a not-for-profit rural pharmacy network in mountainous Kyrgyzstan to quantify costs, revenues, profits and medicine mark-ups during establishment and maintenance periods (October 2004-December 2007).

Results

Twelve pharmacies and one warehouse were established in remote Kyrgyzstan with < US $25,000 due to governmental resource-sharing. The network operated at break-even profit, leaving little room to lower medicine prices and mark-ups. Medicine mark-ups needed for sustainability were greater than originally envisioned by network administration. In 2005, 55%, 35%, and 10% of the network's top 50 products revealed mark-ups of < 50%, 50-99% and> 100%, respectively. Annual mark-ups increased dramatically each year to cover increasing recurrent costs, and by 2007, only 19% and 46% of products revealed mark-ups of < 50% and 50-99%, respectively; while 35% of products revealed mark-ups > 100%. 2007 medicine mark-ups varied substantially across these products, ranging from 32% to 244%. Mark-ups needed to sustain private pharmacies would be even higher in the absence of government subsidies.

Conclusions

Pharmacy networks can be established in hard-to-reach regions with little funding using public-private partnership, resource-sharing models. Medicine prices and mark-ups must be interpreted with consideration for regional costs of business. Mark-ups vary dramatically across medicines. Some mark-ups appear "excessive" but are likely necessary for pharmacy viability. Pharmacy financial data is available in remote settings and

can be used towards determination of "reasonable" medicine price goals. Health systems researchers must document the positive and negative financial experiences of pharmacy initiatives to inform future projects and advance access to medicines goals.

Background

Much of the developing world still lacks access to essential medicines. Most people in developing countries seek care and medicines from private sector pharmacies, even before seeking care at a clinic or hospital [1]. Health systems research must include assessment of pharmacy interventions designed to increase access to medicines given the dominant role pharmacies play in health service delivery.

Access to essential medicines in low-resource settings is hindered by high and unaffordable medicine prices [2-7], and global calls to make medicines more affordable have increased in recent years. The Millennium Development Goals include a target that aims "in cooperation with pharmaceutical companies, [to] provide access to affordable essential drugs in developing countries" [8]. The Millennium Development Task Force specifically recommends that countries "seek ways to reduce the trade and distribution mark-ups on prices of essential medicines and to ensure availability of essential medicines in public health care facilities" [8]. The Working Group on Access to Essential Medicines established by the United Nations Millennium Project suggested that generic competition, price negotiation, differential pricing, and effective procurement are the four strongest levers to reduce medicine prices [9].

The World Health Organization (WHO) and Health Action International (HAI) recently released a methodology to measure medicine price components along the supply chain [10,-11]. The new module is designed to identify where "add-on" prices are applied throughout the supply chain from manufacturer to patient, including duties, taxes, tariffs, and mark-ups [11]. A recent synthesis of WHO/HAI medicine price surveys revealed average retail mark-ups on medicines ranging up to 552% [3], while another summary reported excessive mark-ups specifically in the private sector [11]. These results are compelling and useful for advocates who pressure policy makers to intervene to bring about lower prices. But when confronted with survey results, Ministers of Health inevitably ask: "What is a reasonable mark-up for medicines?" This question has yet to be answered. Indeed, the authors of the WHO/HAI synthesis themselves note that additional research is required to determine appropriate medicine mark-ups that are not only reasonable, i.e. as affordable to the consumer as possible, but also ensure the economic viability of the supply chain [3]. This paper is the first publication to respond to this call.

Medicine prices and mark-ups will be difficult to interpret without some basic understanding of the cost, revenue, and profit structures of pharmacy businesses. To remain viable, a pharmacy must be able to recoup its costs and make some minimal profit. While numerous small- and large-scale pharmacies and pharmacy networks have been created to improve access to medicines for the poor [12-32], many have failed due to non-existent or poor quality business plans and financial planning [29]. Health services research, however has failed to provide details of how and why these pharmacy initiatives failed. Organizations and governments will continue to open pharmacies as a means of increasing access to medicines. But, until the financial and managerial success and failures of these initiatives are documented, lessons learned from previous experiences will be lost, the same mistakes will be repeated, and pharmacies will continue to fail.

Health services research is also needed to determine medicine prices that not only advance access goals through affordability but also provide incentives for ownership and management of pharmaceutical enterprises. While affordability is a key determinant of access to medicines, downward pressure on prices to unsustainable levels can actually threaten access by removing incentives for entrepreneurs to own and operate pharmacies, therefore making pharmacies less geographically accessible to consumers. Striking a balance between the availability of medicines and the sustainability of pharmacies is critical, given that the majority of people in developing countries rely on the private sector for essential medicines [1]. This balance becomes even more tenuous in rural regions where population densities are low, pharmacies are scarce or nonexistent, residents have little money, and the few available medicines are expensive. In Kyrgyzstan, more than 80% of the country is covered by mountains and 64% of people live in rural regions [33].

The purpose of this study is to quantify the cost and revenue structures for establishing and maintaining rural pharmacies in Kyrgyzstan and to examine medicine mark-ups to determine if they can be further reduced without jeopardizing the sustainability of these enterprises. In so doing, we provide the first example of how cost accounting methods can be applied to pharmacy financial data to ascertain "reasonable" medicine prices and mark-ups. Given the demand for this type of information by researchers [3] and national policy makers, we provide guidance on expanding and replicating this research to advance and support future access to medicines initiatives.

Methods

For this case study, we applied cost accounting methods to information obtained from a not-for-profit rural pharmacy network to quantify cost, revenue, profit and medicine

mark-ups from 2004 to 2007. The retail network is located in Jumgal District of Naryn Province in Kyrgyzstan. Jumgal, like most of Kyrgyzstan, is mountainous, but one of the most accessible mountainous region to the capital city of Bishkek. The retail network, comprising 12 pharmacies and one warehouse, is managed by a local non-governmental organization (NGO) and operated under a revolving medicine fund mechanism. Established in late 2004 in collaboration with the Kyrgyzstani government, the network was designed specifically to increase access to high quality, affordable medicines in rural villages lacking access to pharmacy outlets. The network is described in detail elsewhere [34].

Pharmacy network costs

We estimated start-up costs (expenses incurred in establishing the network) and recurrent costs (ongoing costs associated with maintaining the network). We distinguish between fixed recurrent costs - costs that are independent of business volume - and variable recurrent costs - costs that fluctuate depending upon business volume. Examples of fixed recurrent costs include salaries, insurance payments, utilities, and travel from the central office to the region for medicine deliveries. Variable recurrent costs included office supplies, repairs, taxes, nurse-dispenser bonuses, and travel between the warehouse and pharmacies. Cost information was obtained from documents such as purchase receipts, payment invoices, and inventory reports.

While non-product costs to support the central office, warehouse, and each pharmacy could be easily tracked, costs for product purchases were only available for the network as a whole and could not be allocated directly to individual pharmacies.

Pharmacy network revenues

Pharmacy revenues are limited to income from the sale of products, namely medicines and sundries. Monthly revenue reports for individual pharmacies were provided by the central NGO administration. While inventory information was available on medicine flow through the central office, warehouse, and individual pharmacies, the pharmacies did not keep detailed sales records.

Pharmacy network profit

Profit is presented for both the network as a whole and for individual pharmacies within it. Network profit is calculated on a monthly basis as follows:

$$profit_{network} = revenues_{network} - costs_{network}$$

Individual pharmacy profit is estimated on a monthly basis as follows:

$$profit_{\text{pharmacy } i} = revenue_{\text{pharmacy } i} - costs_{\text{pharmacy } i}$$

where $costs_{\text{pharmacy } i} =$

$$non\text{-}product\ costs_{\text{pharmacy } i} + \frac{non\text{-product } costs_{\text{office and warehouse}}}{12} + product\ costs_{\text{network}} \times \frac{revenue_{\text{pharmacy } i}}{revenues_{\text{network}}}$$

This estimation assigns the costs to maintain the central office and warehouse equally across each of the 12 pharmacies. In the absence of pharmacy-specific product purchase and sales records, it also estimates pharmacy-specific monthly product costs as a function of individual pharmacy revenue.

Medicine mark-ups

The pharmacy network was established in September 2004 and it took a few months to build up sufficient inventory to meet local demand. We, therefore, selected the 50 most profitable products over the 2005-2007 time period. We then calculated mark-ups for these top 50 products in each of the study years (2004, 2005, 2006, 2007). Mark-ups for these products were calculated by year as follows:

$$retail\ mark\text{-}up = \frac{retail\ price\ of\ product\ procured - wholesale\ price\ of\ products\ procured}{wholesale\ price\ of\ products\ procured}$$

Calculations for medicine mark-ups utilize warehouse level records for products distributed to pharmacies in a given month. All cost and revenue estimates are provided in Kyrgyz Som (KGS), although start-up costs are converted to United States (US) dollars to provide value context using a conversion factor of 40 KGS per one US dollar.

Results

Pharmacy network start-up costs

The costs to establish the pharmacy network in late 2004 totaled 866,665 KGS (US $21,667), split almost equally across medicine and non-medicine costs (Figure 1). Building pharmacies and training staff accounted for 39% and 25% of non-medicine costs, respectively, while establishing the warehouse and central office each accounted for 18%.

In-kind donations from local Village Health Committees [35] and the Kyrgyz-Swiss Health Reform Support Project also helped establish the network. Such donations included materials and labour to refurbish the pharmacies and warehouse, and some pharmacy furniture (additional file 1).

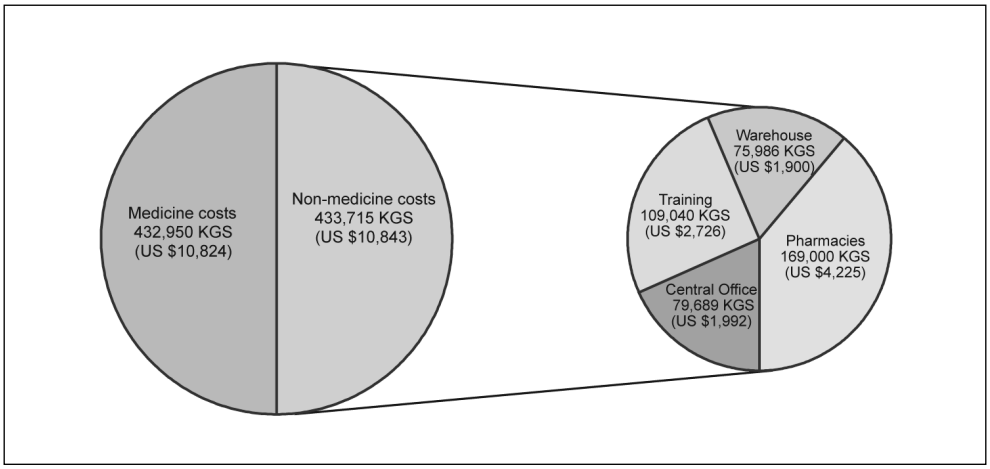

Figure 1. Start-up costs to esatablish the pharmacy network

Pharmacy network recurrent costs

Costs for wholesale product purchases vary according to sales volumes in pharmacies. The more products sold by pharmacies each month, the more products the central staff need to purchase from wholesalers to replenish pharmacy stock. As expected, product purchases comprise the largest portion of the variable recurrent costs across all years (Figure 2). All non-product costs increased annually as the newly formed business steadily grew. Non-product variable costs increased 40% from 2005 to 2007, while fixed costs increased 54% from 2005 to 2007, largely due to increased salary expenses for central administrative staff whose contributions were provided in-kind in the first year only. Recurrent cost estimates for 2007 are the most accurate, reflecting the realities of a "mature" network. In 2007, product variable costs, non-product variable costs, and non-product fixed costs comprise 70%, 12%, and 18% of total costs, respectively.

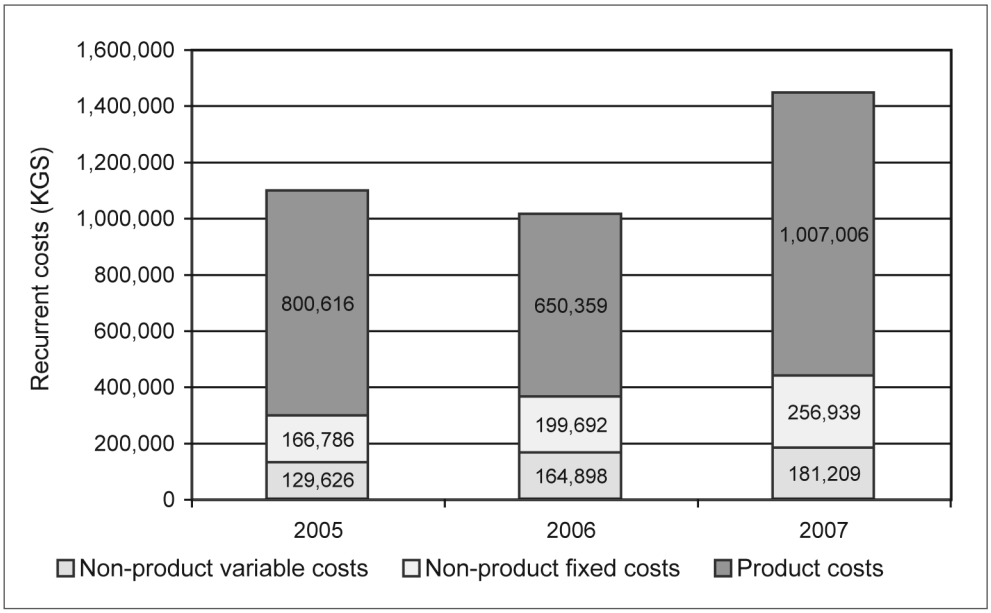

Figure 2. Overview of recurrent costs (KGS) for pharmacy network

Salaries for central office and warehouse staff represent the greatest portion of non-medicine fixed costs. In 2007, salaries and social insurance payments for employees accounted for 58% and 24% of these costs, respectively (table 1). Travel from Bishkek, the capital city and headquarters, accounted for 17% of fixed costs, and included trips to the warehouse and to the pharmacies for medicine deliveries. The supervisory trips from headquarters were always combined with medicine deliveries to avoid additional travel costs.

	2005	2006	2007
Non-product fixed costs			
Central office salaries (supervisors)	44,400	93,600	110,500
Warehouse salaries	39,710	35,835	38,582
Social insurance	45,602	54,557	61,856
Utilities	6,997	2,764	3,413
Travel from central office to region	30,077	12,936	42,588
Non-product variable costs			
Office supplies, repair, other	16,230	4,917	15,271
Taxes	4,736	8,159	2,854
Nurse-dispenser bonuses	91,229	125,092	135,694
Travel between warehouse and pharmacies	17,431	26,730	27,390

Table 1. Detailed non-product recurrent costs (KGS) for pharmacy network

Nurse-dispenser bonuses, determined by product sales volume, are the largest portion of non-product variable costs, representing 75% of these costs in 2007 (table 1) and averaging 634, 869, and 942 KGS per nurse per month for 2005, 2006, and 2007, respectively. Transport for travel between the warehouse and pharmacies, which includes product deliveries, accounts for 15% of variable costs in 2007.

Cost-sharing arrangements with the Kyrgyzstani Ministry of Health (MOH) allow for very low operating costs. The MOH donated space within primary care clinics to house the pharmacies, on hospital premises to establish the warehouse, and in a Bishkek government building to house the central office. Co-location of the pharmacy network within government facilities means the pharmacy network operates without paying rent or utilities, with the exception of a very modest share of utilities in its central office. In addition, the MOH pays the regular salaries of the nurse-dispensers - who work principally as practicing nurses in the co-located primary care clinics - while the NGO pays the nurses a bonus for taking on the additional task of operating the pharmacies. Whereas the nurses' regular salaries are fixed and subsidized by the Kyrgyz government, the bonuses paid by the NGO are variable, based on pharmacy sales volume.

Pharmacy network revenues

Average monthly revenues increased from 82,837 KGS in 2005 to 121,438 KGS in 2007 (Figure 3). Monthly revenues were highly erratic in the first two years of operation, likely due to inconsistent delivery of stock replenishment to network pharmacies and seasonal variation of medicine use. By, 2007, however, deliveries and revenues had become more stable.

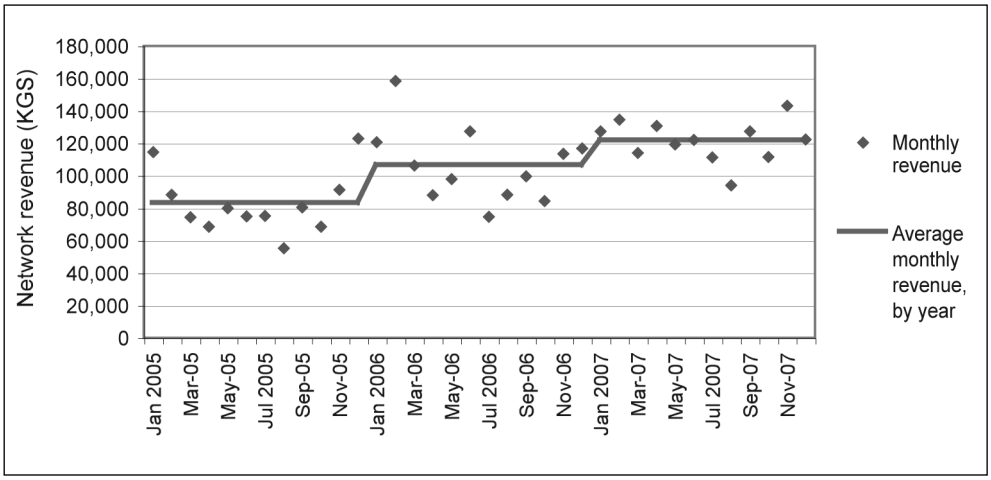

Figure 3. Monthly revenue and average monthly revenue by year of pharmacy network (KGS)

Pharmacy network profit

Analyses reveal pharmacy network profits at approximately break-even levels over the entire study period. After operating slightly below break-even levels in 2005, the network averaged small positive profits in 2006 and break-even profit levels in 2007 (Figure 4). Like monthly revenues, monthly expenditures on products and monthly profits were erratic.

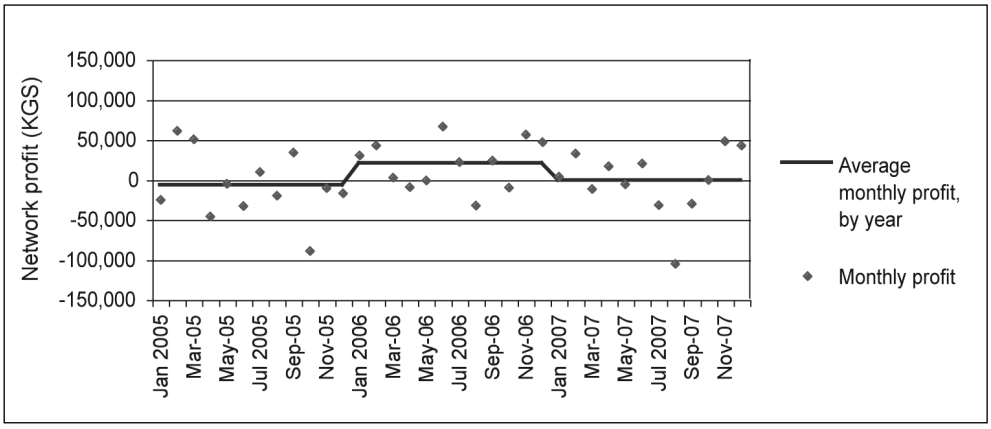

Figure 4. Pharmacy network monthly profit and average monthly profit by year (KGS)

Retail product mark-ups

Mark-ups vary substantially across the network's top 50 products (which account for >50% of network profits), ranging from 32% to 244% in 2007. Those above 150% that might be considered "excessive" cross-subsidize lower mark-ups applied to other medicines. Upward trends in retail mark-ups are noted for nearly all 50 top-selling medicines and health products from 2004 to 2007. Initial mark-ups were low in 2005, the first full year of operation, with 27 (55%) and 17 (35%) products revealing mark-ups of < 50% and 50-99%, respectively (Table 2). Only five (10%) products had a mark-up greater than 100% in 2005. Mark-ups steadily increased from 2005 to 2007 as the NGO was unable to cover its operating costs with the initial mark-ups. By 2007, only nine (19%) and 22 (46%) products revealed mark-ups of < 50% and 50-99%, respectively; while 17 (35%) products showed mark-ups greater than 100%. Mark-up trends for these specific medicines and health products are provided in additional file 2.

	# of products per mark-up category			
	<50% n (%)	**50-99% n (%)**	**100-200% n (%)**	**>200% n (%)**
2004	26 (74)	5 (14)	2 (6)	2 (6)
2005	27 (55)	17 (35)	3 (6)	2 (4)
2006	14 (29)	21 (44)	12 (25)	1 (2)
2007	9 (19)	22 (46)	15 (31)	2 (4)

Table 2. Retail mark-up trends for the 50 top-selling products*, 2004-2007

**50 most profitable products 2005-2007. Not all products sold in all years.*

Discussion

This study demonstrates the utility of analyzing financial data obtained from pharmacies to predict costs of establishing new pharmacy businesses and determine reasonable medicine prices and mark-ups that are affordable but still ensure pharmacy viability. Information gained from this type of research can empower policy makers and advocates to develop strategic, evidence-based interventions appropriate for their local context, without jeopardizing sustainability of pharmacy enterprises and availability of medicines.

Medicine mark-ups needed to ensure non-profit viability were higher than expected and might be considered "excessive" when interpreted without consideration for the cost of business

The level of medicine mark-up needed to sustain the pharmacies was much greater than expected in the planning phase of the project. While the majority of medicines revealed mark-ups of less than 50% upon the initial establishment of the network, mark-ups increased steadily year after year, with few medicines marked-up below 50% and the vast majority marked-up well above 50% and 100% by the end of 2007.

High mark-ups were necessary even given the network's reliance on government subsidies for rent, overhead, and nurses' salaries, as well the in-kind contributions of others. The network's high operating costs for salaries and travel/transport, together with low inventory turnover, translated into high carrying costs for the pharmacy network. This is likely the case in many other rural regions.

The pharmacy network has few options to lower medicine prices without jeopardizing availability

In order to lower some mark-ups that may be considered "excessive" (e.g. >150%), the management would need to increase mark-ups on other medicines. The NGO could leverage medicine prices and mark-ups in an effort to drive demand of specific products. Mark-ups could be redistributed, applying low mark-ups to encourage the use of key essential medicines and high mark-ups to discourage the use of non-essential medicines. Similarly, the NGO should increase mark-ups on sundries (e.g. creams, shampoos, etc.) to maximize revenues and cross-subsidize lower mark-ups on medicines. The NGO could also conduct market surveys to identify additional sundries held in high demand by the local community.

While we have not presented the analysis in this paper, we found that profit at the individual pharmacy level varied, with some pharmacies performing better than others [36]. Not surprisingly, pharmacies located in villages with larger populations enjoyed greater profits than those in less-populated villages. Distance from the warehouse in the district center was more closely related to profit, with the most remote pharmacies operating at a slight loss. In this mountainous region, remote pharmacies are located 45-66 kilometers (28-41 miles) from the warehouse. Roads to many of these villages are unpaved and in disrepair, making travel time-consuming and costly, especially during the region's long winters.

It is certainly possible to increase the operational efficiency of these pharmacies, but potential gains would be marginal and insufficient to reduce current medicine prices and mark-ups. Closing pharmacies or reducing the number and type of medicines stocked

in villages operating at a loss would increase overall network profit, but at the expense of decreasing access to medicines in the villages most in need. This option would directly contradict the original intention of establishing the network to meet the needs of the least served. Nurse dispenser bonuses should be re-evaluated. Current compensation is based upon sales volume and creates perverse incentives for over-prescribing. These nurse dispenser bonuses account for costs nearly equal to product costs and could be reduced by revising compensation policies.

Results from analyses of not-for-profit pharmacies can be used to guide policy decisions in for-profit pharmacies

Medicine prices and mark-ups revealed in this study can be used as reliable benchmarks to assess those applied to medicines in for-profit pharmacies in similar regions of Kyrgyzstan. Private sector pharmacies in this region would need to apply even higher retail medicine mark-ups in order to remain profitable in the absence of subsidies. Private pharmacies need to recoup the costs of rent, utilities, and salaries in addition to the costs we included in our analysis of the subsidized, not-for-profit pharmacy network. In addition, the start-up costs in the Kyrgyz pharmacy network were paid up-front by others, and therefore, no amortization of these costs was needed; however, private pharmacies would need to amortize these up-front costs over several years. After accounting for these additional costs, advocates can provide policy makers with realistic, evidence-based goals for medicine price determination that ensure the viability and sustainability of pharmacy businesses.

Medicine markets in rural regions are local, requiring additional localized research with improved methods to better inform decision makers

While these results can be extrapolated to similar rural regions in Kyrgyzstan, they cannot be extrapolated to large cities or more remote regions in Kyrgyzstan or to other low-resource countries. The supply and demand sides of pharmaceutical markets, as well as the business structures of pharmacies, vary dramatically within and across countries. Sound policy decisions can only be made after understanding the unique characteristics of local markets and pharmacy businesses. For example, a WHO/HAI survey in Syria reports a fixed price system whereby retail pharmacies apply maximum medicine mark-ups of 8% for more expensive medicines to 30% for less expensive medicines [37]. If this pricing system was adopted by Kyrgyzstan, the rural pharmacies would fail to thrive and there would be no incentive to open new pharmacies in regions without them. Price controls are often a knee-jerk governmental reaction to high and unaffordable medicine prices; but without understanding local cost of business, imposing arbitrary price and

mark-up limitations could jeopardize the availability of medicines and market growth, especially in rural regions.

Our study also revealed the importance of using sampling methods based upon local medicine use patterns. We based our selection of medicines in this study upon sales volume, rather than a predetermined basket of medicines, to ensure we are measuring prices and mark- ups for medicines that are actually used in the local context. While several hundred items were purchased by the network over the study period, we chose the top selling 50 products because their sales represent more than 50% of all revenues. The top-selling 50 products in terms of profit and volume of sales are similar and represent those products in regular demand while the remaining products are typically purchased only a few times over the entire period. Researchers might consider replicating studies such as ours using volume-based sampling and the local not for profit prices as reference prices.

Research on medicine mark-ups often uses summary measures (such as the average mark-up) across all or a select basket of medicines. Our study found higher mark-ups applied to the more commonly purchased medicines, underscoring the importance of selecting medicines based upon local demand. In addition, we revealed dramatic and unpredictable variation in mark-ups applied across the top selling products, illustrating the limited utility of summary measures and the need to provide detailed results for the entire distribution of medicine mark-ups.

We recognize that it is difficult to obtain financial data on cost of doing business, given the proprietary nature of this information. But we believe this information is avail- able, since most countries have pharmacy networks owned and operated by NGOs or other non-profit entities. Typically, these organizations are in the pharmacy business in order to provide quality and affordable medicines to the poor and would likely share their financial information in the interest of national efforts to increase access to medicines. Projects such as the Medicines Transparency Alliance are in a good position to obtain and use this type of information to inform policy, given their multi-stakeholder and country-led approaches [38].

Study limitations

Our study contributes to the growing body of literature on medicine prices, but it has limitations. We had full access to all financial data but expect we missed some un-accounted costs, such as “informal payments” to inspectors, as well as other undocumented revenues. We measure mark-ups at retail level only. The determination of cost of business and mark-up at manufacturer and wholesale level would provide a more comprehensive view of the market, but we had no access to such data.

Because pharmacies did not record medicine-specific sales or information on product losses (e.g., unpaid customer bills, theft, expiration, etc.), we were unable to assess product-specific revenues and costs associated with low turnover. In the absence of pharmacy-specific purchase information, we were unable to measure directly recurrent medicine costs at the pharmacy level. Instead, we estimated these costs as a function of individual pharmacy revenue.

There is no evidence to suggest wholesalers engaged in rebate and bundling practices that are common in developed countries [39,40]. Finally, we present current medicine prices in lieu of adjusting prices for inflation after noting that most medicine prices outside the pharmacy network trended downward or remained unchanged over the four years [34,36] and did not seem to follow the overall national inflation rate of 10% [41].

Conclusion

Running pharmacy businesses in rural regions is costly, requiring high medicine mark-ups to recoup operating costs and maintain inventory with low turnover. Our study revealed high medicine mark-ups were needed to sustain not-for-profit pharmacies even in the presence of government subsidies and cost-sharing arrangements. Few options to lower medicine prices are available when pharmacies are operating at break-even or low profit levels, but might include interventions to increase operational efficiency; decrease stock levels in low-volume outlets; and redistribute low mark-ups to encourage the use of key essential medicines and high mark-ups to discourage the use of non-essential medicines.

Survey results detailing medicine prices and mark-ups have limited utility without an understanding of regional pharmacy cost, revenue, and profit structures such as those we observed in this study. Policy makers and advocates need this context to set realistic and non-arbitrary goals to reduce medicine prices and mark-ups.

Because medicine prices and mark-ups are locally determined, this type of analysis will need to be replicated in other regions to better inform local and national policies and strategies aimed to increase access to medicines. Interventions must be designed and evaluated to carefully balance medicine prices with pharmacy business sustainability to ensure the availability of medicines in rural regions.

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Chapter 3

Innovative Approaches To Examine Medicine Prices And Their Relationships To Policies At Global Level

Chapter 3.1

Temporal trends in generic and brand prices of antiretroviral medicines procured with donor funds in developing countries

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Abstract

Pharmaceutical markets in low-resource settings are imperfect. Suppliers provide information on 'suggested' medicine prices, but actual purchase prices vary substantially across purchasers and these prices paid are typically unavailable. Public procurement databases now, however, provide timely market intelligence on prices for antiretroviral (ARV) medicines purchased with donor funds, allowing for careful examination of market trends. We used data posted by the World Health Organization to create a longitudinal database of 15,111 ARV procurements from 2002–2008. We noted dramatic price reductions for ARVs over this 6-year time period. Most generic ARVs were cheaper than branded counterparts, with the exception of protease inhibitors (PIs) in which some generic versions were more expensive than branded counterparts. Less price variation was noted for ARVs in low-income countries than middle-income countries where price variations of threefold or greater were noted in five of 28 (18 percent) generic and 15 of 25 (60 percent) brand dosage forms. In order to meet global goals of universal access to HIV/AIDS treatment, further price reductions are needed for abacavir, tenofovir and PIs. New approaches are needed to create incentives for generic manufacturers of these ARVs to enter the market and create price competition with these medicines.

Introduction

Pharmaceutical markets are typically imperfect, characterized by monopolistic or oligopolistic practices whereby a small number of producers exert control over supply and prices [1]. Factors that contribute to supplier-controlled market power include market exclusivity due to patents and data exclusivity, limited supply of active principle ingredients, drug registration barriers, and price-undercutting strategies of sellers. Information asymmetries exist whereby suppliers have full access to market intelligence on medicine prices while purchasers often lack such information. Information imbalances put suppliers at an obvious advantage over purchasers during contract negotiations. Likewise, the quality of pharmaceuticals on the market can vary tremendously [2-3] leaving countries with limited quality assurance capacity vulnerable to purchase of substandard and counterfeit medicines. Pharmaceutical markets in many low resource settings are often further constrained by insufficient financing for medicines, inadequate administrative structures and procurement systems, and varying abilities to adequately regulate medicines [4-5].

The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) and the World Health Organization (WHO), in particular, have been proactive in implementing poli-

cies and procedures that address some of the problems that arise from market imperfections and pharmaceutical management constraints in low resource settings. To address information asymmetry in prices paid for medicines used to treat HIV/AIDS, tuberculosis and malaria, the GFATM requires principal recipients to submit prices paid for medicines, which are then posted on publicly available websites [6-9]. The Board of the GFATM recognized that public disclosure of ARV prices 'would contribute to processes leading to lower prices over time [7] and would provide a 'foundation of sound market dynamic and procurement practices' [8].

Shortly after the establishment of the GFATM public procurement database, the WHO followed suit with the establishment of the Global Price Reporting Mechanism (GPRM), a web-based database that serves as the global repository for medicines procured for HIV/AIDS, tuberculosis and malaria [10]. The WHO GPRM uploads data from the GFATM procurement database and also collects procurements reported outside the GFATM from many other sources [11]. The GPRM mostly contains national procurements made with external donor funding and does not typically contain procurements from countries that are self-funding HIV/AIDS treatment.

Efforts to promote medicine price transparency have evolved partly owing to extreme price variation noted for similar essential medicines purchased within and across low- and middle-income countries. A comparison of international reference prices to prices paid by 30 countries for 14 essential medicines used to treat chronic diseases revealed dramatic variation among national procurement systems, public pharmacies and private pharmacies [12]. Prices paid for antihypertensive medicines in the private sector varied from less than half the international reference price to more than 58 times the international reference price [12]. Similar price variations were noted in public pharmacies and in procurements made at the national level [12]. Using the same methodology, research in Malaysia revealed large variations in medicine prices across four geographical areas within the country[13].

More than 50 studies have been conducted in low resource settings to assess price variations for a core set of essential medicines [14] purchased outside of donor initiatives. Systematic, comprehensive research describing price variations and temporal price trends for antiretroviral (ARV) medicines purchased with donor funds is rare. Still, many organizations have published information from various sources for more than a decade. Médicins sans Frontières has regularly published extensive information on ARV prices, including survey results of ARV prices reported by producers [15]. Price information on essential medicines has also been reliably provided by Management Sciences for Health in the International Drug Price Indicator Guide for more than two decades [16]; however, fewer than 10 countries typically report actual prices paid for a given ARV.

The availability of new procurement databases hosted by GFATM and WHO allows for careful examination of actual prices paid for ARVs over the past 6 years across more than 100 countries. The WHO uses these databases to prepare quarterly and summary reports of select ARV prices and regimens [11, 17-18]. In the early days of the GFATM, these procurement data were used to describe the relationships between ARV prices reported by manufacturers and ARV prices paid at country level [19]. More recently, these data were used to compare volumes of generic and brand ARVs procured in Sub-Saharan Africa [20], to compare ARV prices in Brazil to prices in other low- and middle-income countries [21], and to provide supporting data for analyses of 'conditional scholarships' for health workers [22].

In this article, we utilize existing ARV procurement data to describe annual changes in ARV prices and comparisons of brand and generic ARV prices from 2002 to 2008, as well as variability in prices paid for equivalent ARVs over a 1-year time period, July 2007 – June 2008.

Methods

We downloaded ARV procurement transactions reported to the WHO GPRM from July 2002 to June 2008 [10]. Procurement records with a purchase price of zero (US$0) were removed from the database. The resulting analytic data set contained 19,432 ARV procurements representing 18 unique ARV medicines in 74 different dosage forms purchased by 113 countries totaling approximately $1.06 billion. For this article, we restricted procurements to medicines supplied in solid dosage forms (for example, tablets, capsules and caplets) that were purchased at least 95 times from known manufacturers over the 6-year period. This selection process resulted in 15,111 ARV procurements comprised of 32 ARV dosage forms.

All prices are reported by the WHO in US dollars. We report prices in constant dollars, after adjusting for inflation to the July 2007 – June 2008 time period using the United States Consumer Price Index [23]. ARV prices are described as annual prices per person for individual products (adjusted price per tablet/capsule × defined daily dose × 365 days), using doses recommended by the WHO for adults [24-25] weighing >60 kg and for children weighing 10 kg [26-27]. We present prices without adjusting for the impact of add-on costs due to shipping, insurance and other charges, which has been estimated to add 15 percent to the total cost [16, 28].

To compare price differences between brand and generic versions of ARVs, we divided the annual median price per person for the brand version of an ARV by the annual median price per person for the corresponding generic version. We then grouped ARVs according to classes (nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside

reverse transcriptase inhibitors (NNRTI), 2NNRTI + NRTI fixed-dose combination (FDC) and protease inhibitors (PI)), and determined the median brand:generic price ratio for each ARV class across all years (Figure 1).

To assess variability in prices paid, we present ratios of highest price:lowest price for each brand and generic ARV dosage form in the most current year, July 2007 – June 2008 (Figure 2). To do this, we stratify countries into low- or middle-income categories [29]. We next identify and remove extreme low and high price outliers using a three-step process.

First, we identify those ARVs with a high:low price ratio greater than three. Second, we determine the price difference between the outlier price and the next closest price paid for that ARV. If the price difference between the presumed outlier and the next closest price is less than or equal to threefold, we do not remove the outlier. Third, for price differences between the presumed outlier and the next closest price that are greater than threefold, we note the country that purchased the 'outlying' ARV and compare that price to other procurements in that same country for the same ARV. If the price difference is greater than three-fold, we remove the price outlier. High:low price ratios calculated after this outlier removal procedure are depicted in bar graphs with actual high:low price ratios calculated before outlier removal provided in text boxes with an asterisk (Figures 3 and 4). All analyses were done using SAS version 9.1 (SAS Institute, Cary NC).

Results

Overview

Applying the above-mentioned selection criteria for solid dosage forms purchased most frequently, we analyzed data from 15,111 ARV procurements representing 14 unique ARV medicines available in 32 dosage forms and purchased by 112 countries. Details of data contents are provided in Tables 1 and 2. The total value of ARV procurements is approximately $1 billion. The number of ARV procurements reported has increased annually. The decrease in total number of procurements in the last year, July 2007 – June 2008, is because of a time delay between the date ARVs are procured and the date ARV procurements are actually reported. Over the entire time period, 66 percent of these ARV procurement transactions were for generic forms. Low- and middle-income countries accounted for 65 percent and 33 percent of total procurement transactions and 52 percent and 48 percent of total procurement value, respectively.

Trends in annual ARV prices, 2002–2008

Nearly all ARV dosage forms experienced a downward trend in median price over the 6-year observation period (Appendix). Price trends are described in this section using the year July 2003 – June 2004 as the baseline, as this year provides substantially more data than the first year represented in the database, July 2002 – June 2003. For adult NRTI, generic median prices per person per year decreased from $49–$1117 in July 2003 – June 2004 to $11–$372 in July 2007 – June 2008, while brand NRTIs decreased from $58–$2044 to $73–$635 over this time period. Despite price decreases over time, tenofovir, abacavir and didanosine remained expensive at the end of this time period, with generic versions priced at $168, $372 and $172–$270, respectively, and brand versions priced at $223, $635 and $223–438, respectively.

For adult NNRTI, prices for generic nevirapine and efavirenz decreased from $91 and $536, respectively, to $44 and $172, respectively, while brand nevirapine and efavirenz decreased from $494 and $391, respectively, to $248 and $274, respectively, over this time period. Three adult generic FDC products contained both NRTI and NNRTI medicines. These products decreased in price from $181–$338 to $95–$175 over this time period.

Generally, PIs were the most expensive class of ARVs. Excluding ritonavir, generic PIs ranged in price from $445–2575 at baseline to $350–2803 at the end of the time period, while brand PIs decreased from $462–5093 to $438–1332. At the end of this time period, generic versions of ritonavir, saquinavir and lopinavir/ritonavir 133/33, and lopinavir/ritonavir 200/50 remained more expensive than branded versions. Caution must be used, however, in interpreting these findings owing to the small number of procurements for generic PIs.

Pediatric ARV dosage forms generally followed downward trends similar to adult dosage forms, with generic versions substantially less expensive than brand versions at the end of this time period. Although prices for nearly all ARVs decreased considerably over the 2002–2008 time period (Table A1), the inter-annual percentage changes in annual median prices [(YearB -YearA)/YearA] × 100] outlined in Table 3 reveal a complex picture. Many year-to-year price decreases are often substantial, in the order of 20–30 percent or more. Among generic and brand ARV dosage forms, 41 percent (12/29) and 44 percent (12/27), respectively, show consistent year-to-year decreases in price.

The remainder, however, show one or two inter-annual price increases in which the global median price has jumped from one year to the next. These price increases are given in bold in Table 3 and are interspersed among the overall decreases in price. There

is no consistent pattern to these price increases. Among generic ARVs, interannual price increases ranged from 1 to 10 percent (9/20), 11 to 30 percent (4/20) and greater than 30 percent (7/20). Among brand ARVs, these interannual price increases were 1–10 percent (12/21), 11–30 percent (5/21) and greater than 30 percent (4/21).

Trends in brand and generic ARV price comparisons, 2002–2008

Figure 1 depicts the ratio of the global median brand price to the global median generic price for equivalent ARV dosage forms over time when both generic and branded prices were available. Generic NRTIs and NNRTIs were less expensive than their branded counterparts, evidenced by a brand:generic price ratio consistently greater than 1. The brand:generic price ratios for PIs, however, were different. For many observations, the brand:generic price ratio is less than 1 for many years, indicating that generic prices were actually higher than brand prices for PIs in these years.

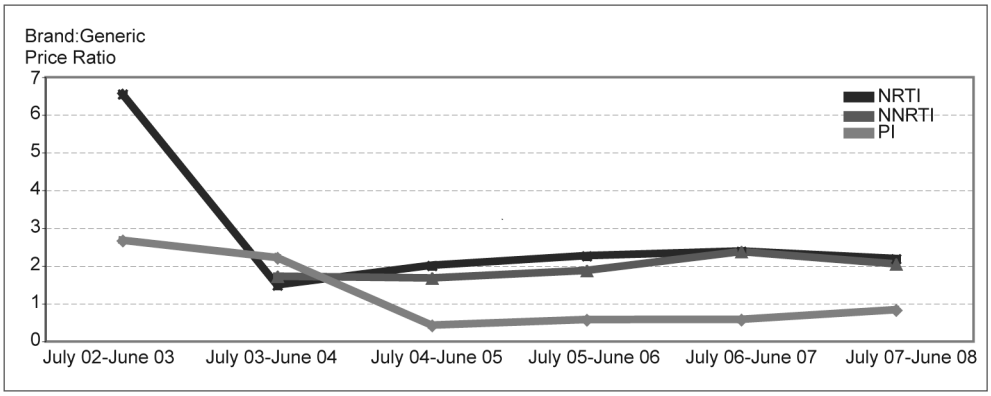

Figure 1. Brand:Generic Median Price Ratios for ARV Classes, 2002-2008

Trends in prices of brand and generic ARV classes

All brand and generic ARV classes showed continuous price decreases, albeit at different rates. Generic NRTIs, NNRTIs and 2NNRTI + NRTI FDC all showed dramatic cumulative price reductions of 62 percent, 72 percent and 58 percent, respectively, while generic PIs showed a 37 percent price reduction over this entire time period (Figure 2). Branded NRTIs and NNRTIs revealed only 12 percent and 29 percent price reductions; however, brand PIs showed a 80 percent price reduction over this time period.

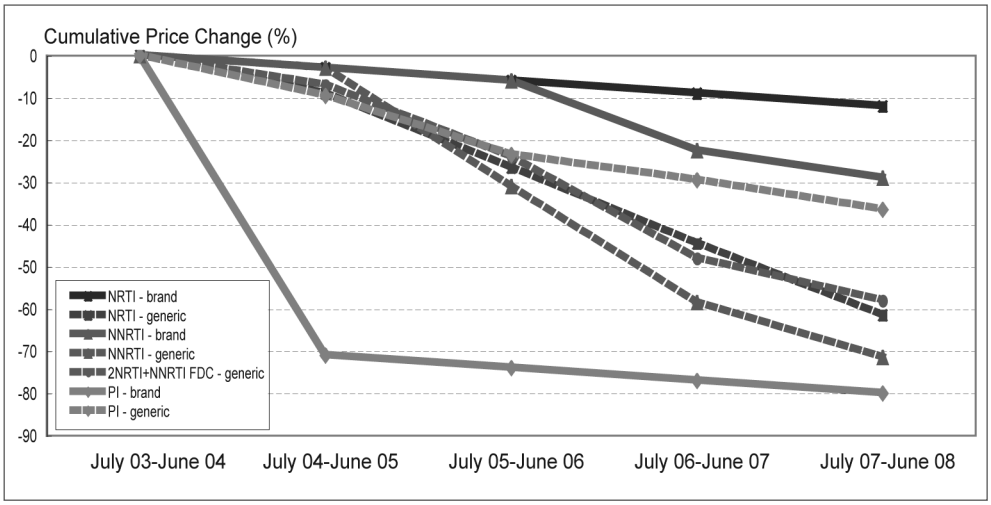

Figure 2. Median Price Changes for ARV Classes, 2003-2008

Variability in prices paid for ARVs, July 2007 – June 2008

Price variations in low-income countries ranged up to 10-fold for generic and up to 20-fold for brand ARV dosage forms. Price variations of threefold or greater were noted in five of 26 (19 percent) generic dosage forms and four of 22 (20 percent) brand dosage forms in low-income countries, while two generic and two brand ARV dosage forms revealed price variations of fivefold or more (Figure 3).

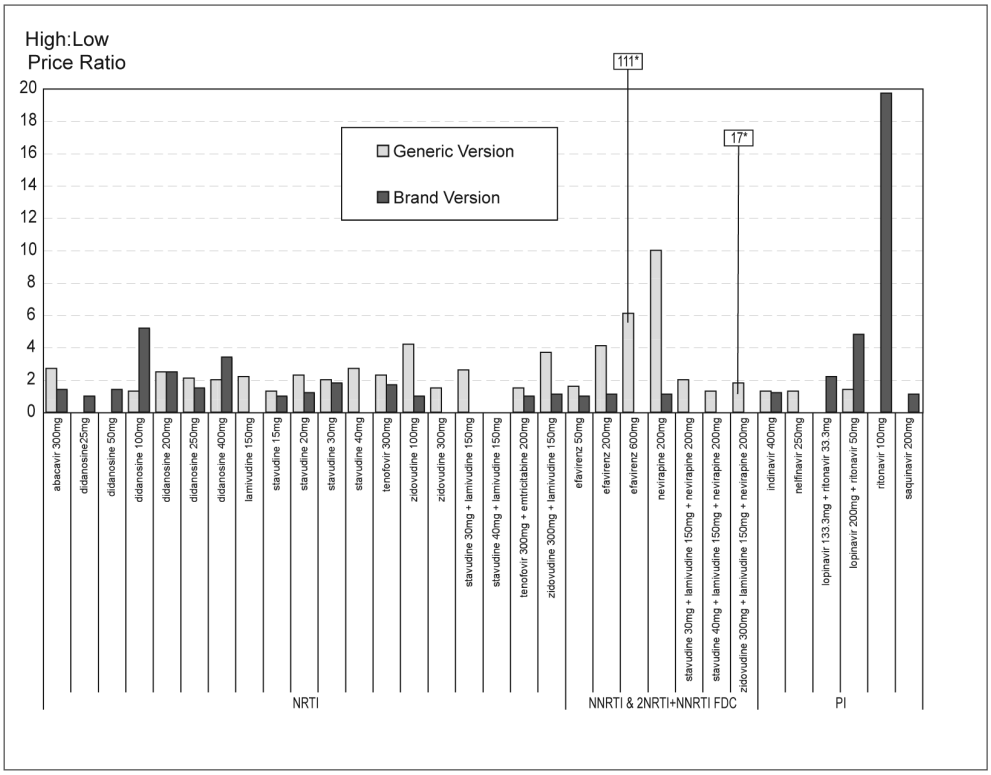

Figure 3. Highest Price to Lowest Price Ratio, July 2007-June 2008, Low Income Countries

**High:low price ratio before removing extreme price outliers*

Price variations in middle-income countries ranged up to nine-fold for generic and up to 16-fold for brand ARV dosage forms. Price variations of threefold or greater were noted in five of 28 (18 percent) generic and 15 of 25 (60 percent) brand dosage forms in middle-income countries, while one generic and 10 brand ARV dosage forms revealed price variations of fivefold or more (Figure 4).

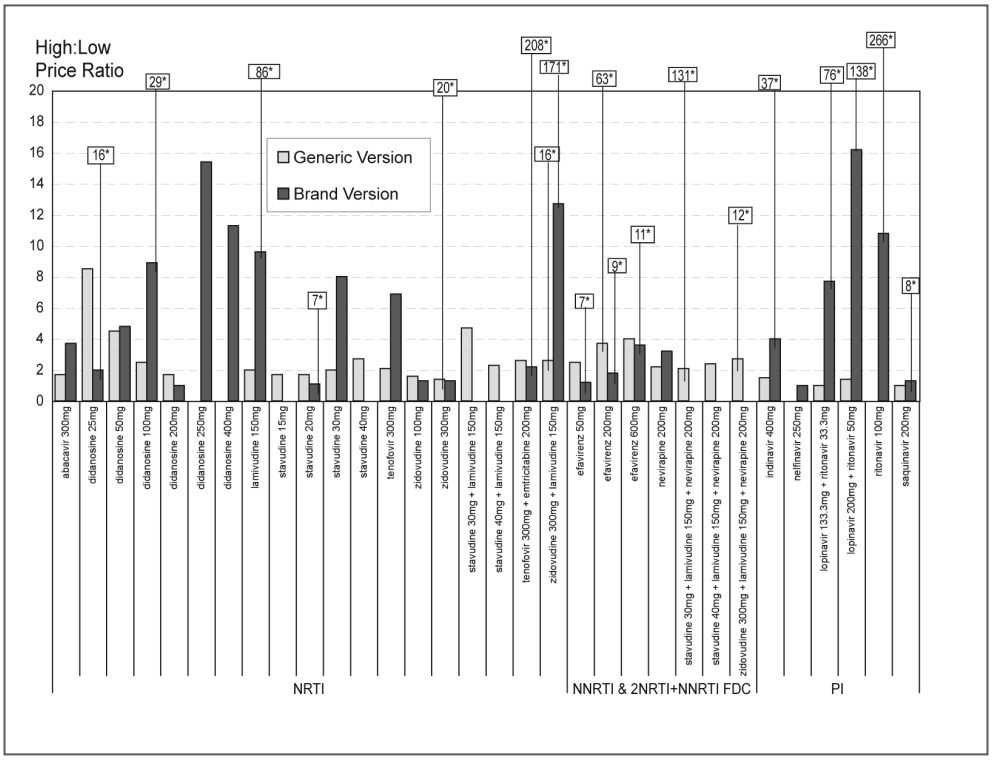

Figure 4. Ratio of Highest Price Paid to Lowest Price Paid, July 2007 - June 2008 in Middle Income Countries

** High:low price ratio before removing extreme price outliers*

Discussion

Substantial price reductions for commonly used ARVs have been achieved over the past 6 years. These price reductions are likely owing to many factors, some of which include willingness of brand ARV producers to decrease prices and waive patents in low-income countries, unprecedented global funding, emergence of a generic ARV market, constant pressure from HIV/AIDS activists, policies of donors and international organizations that address market imperfections, creation and use of standard treatment guidelines, pricing and other interventions made by the Clinton HIV/AIDS Initiative, ARV price publications by Médicins sans Frontières and others, and government will to provide treatment.

Although the overall trend for ARV prices is downwards, a more detailed analysis of inter-annual price changes (Table 3) shows that some generic and brand ARVs have sporadically experienced very large inter-annual price increases across some years, especially since 2005. These observations warrant close monitoring.

Notwithstanding these sporadic interannual increases in price, comparisons of brand and generic ARV prices over the past 6 years show that the majority of generic ARVs have become less expensive than branded ARVs. PIs, the most expensive class of ARVs, are the significant exception, whereby generic PIs have historically been more expensive than their branded counterparts. This trend is beginning to change, however, with the availability of some generic PIs that are less expensive than their branded counterparts (Table A1 and Figures 3 and 4). Some generic PIs are more competitively priced than others. More research is needed to better understand how generic PIs can best compete with branded PIs, and what interventions are needed to further decrease PI prices overall. Indeed, the low global demand for PIs combined with the diversity of PIs available to these countries (currently lopinavir + ritonavir, indinavir, fosamprenavir, nelfinavir, atazanavir, saquinavir) may actually contribute to high PI prices. Given the increasing number of people in need of second-line treatment, incentives should be created to encourage generic manufacturers to enter the PI market. Perhaps increasing generic competition, consolidating global PI demand around a smaller number of PIs, improving forecasts for PIs, and investing in technology transfers to generic producers would help stabilize and drive down prices. Similar approaches are also needed to further reduce prices of abacavir and tenofovir, which have become commonly used ARVs in first-line regimens, as recommended by the WHO[25].

Generic ARVs in low- and middle-income countries had similar high:low price variation (Figures 3 and 4). For branded medicines, however, such price variations across middle-income countries (Figure 4) were substantially greater than those observed across low-income countries, with threefold or greater price variations noted for 60 percent of ARVs in middle-income countries (Figure 3). It is therefore critical to understand the reasons for the lowest and highest prices among similar countries for the same ARV. Low prices should be identified and investigated by donors to inform best procurement practices. While domestic patent laws may be playing a role in maintaining high ARV prices, there are many other possible reasons worth exploring, including inadequate administrative structures, lack of information about 'fair' market prices, difficulties in estimating the amount of ARVs needed, insufficient lag times between ordering and receiving ARVs, late payments to suppliers, in-country tariffs, in-country middleman mark-ups and barriers to product entry. Interventions to address high prices can only be implemented if they are identified and investigated.

Our analysis has some limitations. First, it is estimated that the WHO GPRM currently captures approximately 50 percent of global ARV procurements made with donor funds [11, 17]. We cannot estimate how under-reporting of procurements may affect results. Second, we present median ARV prices without adjusting for the impact of added costs due to shipping, insurance, taxes, duties and the like; however, these add-on costs may be no more than 15 percent [16, 28]. Although the implications of these add-on costs are not fully understood, we are confident that these additional costs do not account for the dramatic price variations observed for equivalent ARVs in this study. Third, given this is secondary data analysis, we cannot guarantee the quality of procurement data reported and suspect that some erroneous prices have been reported. We attempted to address quality concerns by removing extreme low and high price outliers that we deemed most likely to be erroneous reports. Our method to remove outliers should not affect interquartile prices reported in this article. Because our removal of outliers did affect price variation results, we chose to present these results before and after the removal of outliers (Figures 3 and 4). We also note that analyses of some generic PIs and other select ARVs are based on rather small numbers of procurements (Table A1).

In this article, we have demonstrated the utility of public disclosure of ARV procurement data and quantified the remarkable decrease in most ARV prices over the past 6 years. We have also confirmed prior research that generic ARVs are less expensive than branded ARVs, with the important exception of some PIs that form the basis of many second-line ARV regimens [24-25]. As more people transition onto second-line regimens containing PIs as well as first-line regimens containing abacavir and tenofovir, it is imperative to develop new approaches to create incentives for generic manufacturers to produce less expensive versions of these medicines. New approaches to promote price reduction of patented ARVs might include compulsory licensing, parallel import of generic ARVs and the creation of a patent pool for these ARVs.

The momentum for global medicine price transparency is building upon strong foundations previously laid by Management Sciences for Health, Médicins sans Frontières, Health Action International and others. The GFATM, WHO and others who share procurement data have changed the landscape around medicine prices by publicly posting this information. These organizations, along with other initiatives such as the Medicines Transparency Alliance Project [31], believe that improving transparency of information on medicine prices, policies and quality will ultimately improve access to essential medicines in low resource settings. We encourage all relevant governments, donors, non-governmental organizations and other stakeholders to find consensus on mandatory reporting of a standardized set of key price and procurement indicators for medicines to treat HIV/AIDS, tuberculosis and malaria.

In principle, a comprehensive and reliable set of data could address information asymmetries typically inherent in pharmaceutical markets and empower purchasers to enter into negotiations with the vital information in hand needed to obtain lower prices. But medicine price information needs to be accurate and reliable. As noted in Figures 3 and 4, the publicly available data required substantial cleaning in order to create this analytic data set. Quality assurance procedures must be implemented by donors and international organizations collecting and posting these data to ensure validity and reliability of data.

This information must also be provided using a mechanism that is convenient and accessible to users in low resource settings. Once accurate information is provided in a user-friendly manner, the use of such information must be incorporated into procurement policies and systems at donor and country levels. We also suggest that these procurement databases be expanded to provide additional information relevant to medicines (for example timeliness of payments, intellectual property status and registration status in country, add-on costs, lead times and so on). Some of this information exists separately in other databases, but could be directly incorporated into these public procurement databases. A comprehensive and accurate medicines database would facilitate the creation of a solid evidence base and would eliminate reliance on untested assumptions to guide policy and program decisions.

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	All ARVs Reported to WHO *GPRM*	Subset of 32 Oral Solid Antiretroviral Dosage Forms Used in this Analysis						
Dates	**July 2002 – June 2008**	**July 2002- June 2003**	**July 2003- June 2004**	**July 2004- June 2005**	**July 2005- June 2006**	**July 2006- June 2007**	**July 2007- June 2008**	**Total**
Total # Procurements	19,432	52	784	2,568	4,072	4,767	2,868	15,111
Total # Countries	113	7	45	73	88	85	86	112
Total # ARVs	18	8	13	14	14	14	14	14
Total # Dosage Forms	74	12	29	31	32	32	32	32
Total # Manufacturers	31	3	11	18	16	16	16	19
% Generic Procurements (Value in USD)	63% (750,651,590)	92% ($353,051)	69% ($19,823,973)	48% ($82,703,618)	64% ($112,956,241)	74% ($339,549,739)	69% ($166,793,842)	66% ($722,180,464)

Table1. Characteristics of analytic data set for antiretrovirals purchased July 2002-June 2008

	All ARVs Reported to WHO *GPRM*	Subset of 32 Oral Solid Antiretroviral Dosage Forms Used in this Analysis						
	# Procurements (Value in USD)	Total # of Procurements (Value in USD)						
	July 2002 – June 2008	July 2002- June 2003	July 2003- June 2004	July 2004- June 2005	July 2005- June 2006	July 2006- June 2007	July 2007- June 2008	Total
All regions	19,432 ($1,064,015,550)	52 ($409,082)	784 ($35,798,293)	2,568 ($142,612,032)	4,072 ($198,738,835)	4,767 ($407,186,802)	2,868 ($219,190,769)	15,111 $1,003,935,813)
Africa region*	13,534 ($568,755,189)	19 ($85,026)	228 ($6,971,819)	1,722 ($86,319,952)	2,757 ($119,617,581)	3,779 ($143,628,265)	2,053 ($172,905,551)	10,558 ($529,528,194)
Americas region*	2,596 ($109,205,300)	30 ($268,640)	368 ($12,294,885)	308 ($12,957,735)	614 ($25,319,196)	394 ($22,087,146)	325 ($26,599,789)	2,039 ($99,527,391)
Eastern Mediterranean region*	356 ($5,630,054)		1 ($57,201)	62 ($1,426,452)	76 ($1,686,267)	25 ($514,489)	79 ($1,358,563)	243 ($5,042,972)
Europe region*	1,328 ($82,363,201)	3 ($55,416)	62 ($7,818,330)	147 ($5,850,407)	329 ($23,762,180)	235 ($29,311,304)	184 ($11,380,233)	960 ($78,177,870)
Southeast Asia region*	707 ($262,219,947)		98 ($8,343,962)	184 ($28,990,767)	71 ($12,313,542)	120 ($204,705,854)	108 ($2,871,834)	581 ($257,225,959)
Western Pacific region*	911 ($35,841,859)		27 ($312,096)	145 ($7,066,719)	225 ($16,040,069)	214 ($6,939,744)	119 ($4,074,799)	730 ($34,433,427)
Low Income Countries**	12,233 ($549,744,973)	13 ($56,622)	257 ($7,693,448)	1,425 ($84,519,914)	2,711 ($124,836,457)	3,455 ($129,786,164)	1,895 ($170,345,957)	9,756 ($517,238,562)
Middle Income Countries**	6,872 ($508,542,476)	8 ($71,278)	474 ($27,710,133)	1,117 ($57,389,828)	1,309 ($73,583,776)	1,243 ($275,260,754)	904 ($46,997,668)	5,055 ($481,013,437)
High Income Countries**	327 ($5,728,101)	31 ($281,182)	53 ($394,712)	26 ($702,290)	52 ($318,602)	69 ($2,139,884)	69 ($1,847,144)	300 ($5,683,814)

Table 2. Total number and value of ARV procurements by WHO region and World Bank Classification, July 2002-June 2008

**Regions according to WHO classification [30]; ** Income level according to World Bank classification [29]*

	Jul 02-Jun 03 to Jul 03-Jun 04		July03-Jun 04 to Jul 04-Jun 05		Jul 04-Jun 05 to Jul 05-Jun 06		Jul 05-Jun 06 to Jul 06-Jun 07		Jul 06-Jun 07 to Jul 07-Jun 08	
	Percent Change		Percent Change		Percent Change		Percent Change		Percent Change	
	Generic	Brand	Generic	Brand	Generic	Brand	Generic	Brand	Generic	Brand
Nucleoside Reverse Transcriptase Inhibitors (NRTI)										
abacavir 300mg			-19*	-3**	-28*	-3**	-28*	-30**	-20*	-3**
didanosine 25mg†			63*	-3*	-6*	-3*	-21*	-3*	-73*	-3*
didanosine 50mg†	-28*		25*	-3*	-9*	-3*	-17*	-3*	-20*	-3*
didanosine 100mg†			8*	-36**	2*	-3**	-26*	-3**	-15*	20**
didanosine 200mg	-39*		-9*	-3*	-23*	-3*	6*	-3*	19*	35*
didanosine 250mg††				-70*		15*		-7*		-3*
didanosine 400mg				-3*		-84*		-8*		-3*
lamivudine 150mg	-46*		-13*	-3**	-14*	-3**	-15*	-3**	-17*	-3**
stavudine 15mg				2*	-19*	-18*	-42*	-3*	-3*	-3*
stavudine 20mg†				-3*	-3**	-3*	-42**	-3*	-3**	7*
stavudine 30mg	-16*		-19*	-3*	-3*	-3*	-22*	39*	-3*	6*
stavudine 40mg	-22*		13*	-3**	-17*	-3**	-19*	22**	-23*	369*
tenofovir 300mg					-27*	-14**	-3*	-24**	-22*	3**
tenofovir 300mg + emtricitabine 200mg						-14*		-3*	35*	-3*
zidovudine 100mg†	6*		-15*	-25*	-26*	-9*	-15*	-3*	-17*	-3*
zidovudine 300mg	37*		-8*	-3*	2*	-3*	-8*	11*	-25*	-3*
stavudine 30mg + lamivudine 150mg			-7		-19		-3		-23	
stavudine 40mg + lamivudine 150mg			-22**		-19**		-3**		35*	
zidovudine 300mg + lamivudine 150mg	-34*	-69*	-10*	-3*	-18*	-3*	-19*	3*	-13*	2*
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI) and 2NRTI+NNRTI FDC										
efavirenz 50mg †				-10*		-3*	-35*	-11*	9*	5*
efavirenz 200mg†			-3**	-3**	-28**	-3**	-36**	-24**	-3**	-3**
efavirenz 600mg	-5*		-23*	-3**	-33*	3**	-20*	-22**	-23*	-10**
nevirapine 200mg	-64*		-3*	-3	-21*	-3	-13*	-3	-27*	-45
stavudine 30mg + lamivudine 150mg + nevirapine 200mg			-7		-17		-24		-10	
stavudine 40mg + lamivudine 150mg + nevirapine 200mg			-7**		-21**		-24**		4**	
zidovudine 300mg + lamivudine 150mg + nevirapine 200mg			-24*		15*		-13*		-32*	
Protease Inhibitors (PI)										
indinavir 400mg	-6*		1*	1*	-14*	-3*	-3*	8*	-7*	-9*
nelfinavir 250mg	-53*	-32*	-12*	-71*	-25*	4*	-14*	-3*	2*	18*
ritonavir 100mg			-59*	-88**	51*	-3**	42*	-9**	-43*	-7**
saquinavir 200mg			-7*	-25*	0*	-42*	-6*	-3*	-7*	-3*
lopinavir 133.3mg + ritonavir 33.3mg				-87**	-55*	-3**	-39*	3**	103*	53**
lopinavir 200mg + ritonavir 50mg								-28*		-3*

Table 3: Annual percent change in brand and generic ARV prices, 2002-2008

**procurements with sample sizes less than 10 for one year time period; **Procurements with sample sizes 10-29 for one year time period; †ARV prices calculated using doses for children weighing 10kg; ††ARV prices calculated using doses for adults weighing <60kg*

Appendix Table S1: Median and interquartile ARV prices, per person per year, for brand and generic versions

	July 02-June 03		July 03-June 04		July 04-June 05		July 05-June 06		July 06-June 07		July 07-June 08	
	Median Price (25th, 75th percentiles)		Median Price (25th, 75th percentiles)		Median Price (25th, 75th percentiles)		Median Price (25th, 75th percentiles)		Median Price (25th, 75th percentiles)		Median Price (25th, 75th percentiles)	
	Generic	Brand	Generic	Brand	Generic	Brand	Generic	Brand	Generic	Brand	Generic	Brand
Nucleoside Reverse Transcriptase Inhibitors (NRTI)												
abacavir 300mg			1117* (478,1434)	1005** (1005,1005)	904* (872,976)	976 (976,1048)	650** (612,798)	945 (945,1014)	468 (423,559)	657** (604,702)	372 (343,402)	635** (562,679)
didanosine 25mg†			227* (227,227)	247* (247,247)	370* (360,520)	240** (240,240)	348 (348,348)	232** (232,232)	274 (264,283)	226 (226,245)	73* (37,274)	219 (219,219)
didanosine 50mg†	201* (201,201)		144* (124,155)	165* (165,227)	180** (170,270)	160** (150,170)	165* (155,174)	155** (155,165)	137* (132,146)	151 (151,160)	110* (55,164)	146 (146,146)
didanosine 100mg†			111* (111,142)	198** (130,247)	120** (108,180)	126 (126,228)	122** (70,122)	122 (122,163)	91** (74,102)	119 (91,153)	77 (77,88)	142 (115,214)
didanosine 200mg	431* (431,431)		264** (264,264)	354* (354,354)	240** (208,320)	344** (344,360)	186** (178,186)	333 (333,348)	196** (143,257)	325 (234,325)	234** (212,256)	438** (314,504)
didanosine 250mg††				719* (49,1389)		216** (200,1348)		248 (236,767)		230 (230,525)	172* (157,172)	223 (223,285)
didanosine 400mg			412* (412,470)	2044* (2044,2044)		1984** (290,2128)		325 (306,538)		298 (287,525)	270* (252,270)	288 (288,369)
lamivudine 150mg	152* (110,152)		82 (66,82)	82** (82,91)	72 (72,88)	80 (80,88)	62 (62,70)	77 (77,85)	53 (38,60)	75 (75,83)	44 (37,44)	73** (73,80)
stavudine 15mg				148* (132,165)	96* (96,96)	152** (144,160)	77* (77,77)	124** (124,147)	45 (45,60)	121 (121,121)	44 (44,44)	117* (117,117)
stavudine 20mg†				37* (37,462)	20** (20,28)	36 (36,40)	19** (19,19)	35 (35,35)	11 (11,15)	34** (34,38)	11 (11,11)	37** (33,40)
stavudine 30mg	59* (59,59)		49** (33,58)	58* (58,58)	40 (40,56)	56 (56,64)	39 (39,46)	54 (54,62)	30 (23,38)	75** (60,521)	29 (22,29)	80** (80,540)
stavudine 40mg	63* (59,76)		49 (49,58)	66** (66,354)	56 (48,64)	64 (64,64)	46 (39,46)	62 (62,85)	38 (23,38)	75** (68,664)	29** (29,44)	354* (66,642)
tenofovir 300mg					302* (248,356)	328** (240,352)	221* (147,387)	283 (232,329)	215** (159,238)	215 (215,234)	168 (168,208)	223 (208,270)
tenofovir 300mg + emtricitabine 200mg						396* (396,396)		341* (337,341)	238* (238,332)	332** (332,351)	321 (252,321)	321** (321,356)
zidovudine 100mg†	93* (93,93)		99* (66,99)	181* (181,181)	84** (64,88)	136 (128,144)	62 (54,70)	124** (124,132)	53 (45,60)	121** (121,121)	44 (44,44)	117* (102,117)
zidovudine 300mg	114* (17,211)		157 (148,165)	239* (239,239)	144 (144,168)	232 (232,240)	147 (139,170)	225** (225,240)	136 (106,151)	249** (219,249)	102 (102,110)	241* (234,241)
stavudine 30mg + lamivudine 150mg			103 (99,115)		96 (88,96)		77 (77,93)		75 (45,75)		58 (51,66)	

Appendix Table S1: Median and interquartile ARV prices, per person per year, for brand and generic versions (cont.)

	July 02-June 03		July 03-June 04		July 04-June 05		July 05-June 06		July 06-June 07		July 07-June 08	
	Median Price (25th, 75th percentiles)		Median Price (25th, 75th percentiles)		Median Price (25th, 75th percentiles)		Median Price (25th, 75th percentiles)		Median Price (25th, 75th percentiles)		Median Price (25th, 75th percentiles)	
	Generic	Brand	Generic	Brand	Generic	Brand	Generic	Brand	Generic	Brand	Generic	Brand
Nucleoside Reverse Transcriptase Inhibitors (NRTI)												
stavudine 40mg + lamivudine 150mg			124** (115,124)		96 (96,104)		77 (77,101)		75 (53,83)		102* (58,102)	
zidovudine 300mg + lamivudine 150mg	363* (321,380)	870* (431,1039)	239 (214,247)	272** (272,288)	216 (208,232)	264 (264,272)	178 (155,209)	256 (256,287)	143 (125,174)	264 (249,1004)	124 (117,131)	270** (241,621)
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI) and 2NRTI+NNRTI FDC												
efavirenz 50mg†				214* (198,214)		192 (192,208)	186* (186,186)	186 (170,201)	121** (121,121)	166 (166,181)	131 (131,146)	175** (175,175)
efavirenz 200mg†			177** (177,218)	190** (190,206)	172** (148,196)	184 (184,196)	124 (108,155)	178 (124,190)	79 (75,83)	136 (136,174)	77 (66,77)	131** (131,157)
efavirenz 600mg	566* (566,570)		536* (420,536)	391** (391,433)	414 (382,462)	380 (380,400)	279 (259,333)	391 (368,676)	223 (162,253)	306 (283,393)	172 (150,192)	274** (245,657)
nevirapine 200mg	253* (25,253)		91 (16,115)	494 (494,494)	88 (72,104)	480 (480,520)	70 (70,77)	465 (465,527)	60 (45,68)	453** (385,513)	44 (44,51)	248** (248,285)
stavudine 30mg + lamivudine 150mg + nevirapine 200mg			181 (107,202)		168 (160,224)		139 (108,170)		106 (91,106)		95 (88,110)	
stavudine 40mg + lamivudine 150mg + nevirapine 200mg			190** (190,198)		176 (168,208)		139 (108,170)		106 (83,113)		110** (95,110)	
zidovudine 300mg + lamivudine 150mg + nevirapine 200mg			338** (338,346)		256* (256,280)		294** (163,317)		257 (211,340)		175 (161,219)	
Protease Inhibitors (PI)												
indinavir 400mg	473* (473,541)		445** (445,445)	462* (462,775)	448** (400,480)	464 (448,768)	387** (356,403)	449 (434,472)	377** (332,393)	483 (423,725)	350** (336,453)	438 (409,701)
nelfinavir 250mg	3843* (3843,3843)	5743* (5743,5743)	1813** (1813,1854)	3915** (1277,3915)	1600** (1320,1760)	1120 (1080,1560)	1200 (1084,1704)	1162 (968,2246)	1038** (906,1472)	1132 (944,1472)	1059* (986,1132)	1332* (1314,1351)
ritonavir 100mg			618* (618,618)	898** (503,898)	256* (120,584)	112** (96,696)	387 (108,581)	108 (85,403)	551* (106,551)	98 (83,785)	314* (314,314)	91 (80,566)
saquinavir 200mg			2575* (2472,2678)	2678** (1813,2678)	2400* (2400,2400)	2000* (1160,3380)	2400* (2400,2400)	1162 (1045,2575)	2265* (2189,2340)	1132** (1095,2303)	2117* (2117,2117)	1095** (1059,2409)
lopinavir 133.3mg + ritonavir 33.3mg				5093** (5093,5093)	5039* (5039,5039)	660 (600,4511)	2277** (2067,2369)	639 (546,4739)	1382** (1212,3295)	657 (566,2265)	2803* (2070,2825)	1007 (504,1128)
lopinavir 200mg + ritonavir 50mg								712* (712,712)		513 (513,528)	774 (774,774)	496 (496,511)

**Procurements with sample sizes less than 10 for one year time period; **Procurements with sample sizes 10-29 for one year time period*

†ARV prices calculated using doses for children weighing 10kg;; ††ARV prices calculated for adults weighing <60kg

Chapter 3.2

Global strategies to reduce the price of antiretroviral medicines: evidence from transactional databases

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Abstract

Objective

To estimate the impact of global strategies, such as pooled procurement arrangements, third-party price negotiation and differential pricing, on reducing the price of antiretrovirals (ARVs), which currently hinders universal access to HIV/AIDS treatment.

Methods

We estimated the impact of global strategies to reduce ARV prices using data on 7253 procurement transactions (July 2002–October 2007) from databases hosted by WHO and the Global Fund to Fight AIDS, Tuberculosis and Malaria.

Findings

For 19 of 24 ARV dosage forms, we detected no association between price and volume purchased. For the other five ARVs, high-volume purchases were 4–21% less expensive than medium- or low-volume purchases. Nine of 13 generic ARVs were priced 6–36% lower when purchased under the Clinton Foundation HIV/AIDS Initiative (CHAI). Fifteen of 18 branded ARVs were priced 23–498% higher for differentially priced purchases compared with non-CHAI generic purchases. However, two branded, differentially priced ARVs were priced 63% and 73% lower, respectively, than generic non-CHAI equivalents.

Conclusion

Large purchase volumes did not necessarily result in lower ARV prices. Although current plans for pooled procurement will further increase purchase volumes, savings are uncertain and should be balanced against programmatic costs. Third-party negotiation by CHAI resulted in lower generic ARV prices. Generics were less expensive than differentially priced branded ARVs, except where little generic competition exists. Alternative strategies for reducing ARV prices, such as streamlining financial management systems, improving demand forecasting and removing barriers to generics, should be explored.

Introduction

New goals on providing universal access to HIV/AIDS services by 2010 were announced in 2007 by WHO, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the United Nations Children's Fund (UNICEF) [1]. The need for life-long HIV/AIDS

treatment and the high cost of anti- retroviral (ARV) agents present challenges to achieving and sustaining universal access targets. During the past decade, various large-scale strategies have been used to reduce ARV prices in low- and middle-income countries. This paper focuses on three price-reduction strategies: procurement arrangements designed to increase purchase volumes, third-party price negotiation for generic ARVs and differential pricing for branded ARVs.

The first strategy, procurement arrangements to increase purchase volumes, often involves pooled procurement schemes that group multiple purchasers into a single purchasing unit in the hope that economies of scale will lead to lower prices. A pooled procurement mechanism is currently being developed at the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) [2-3].

The second large-scale strategy involves third-party consultation and price negotiation with generic ARV suppliers, a practice introduced by the Clinton Foundation HIV/AIDS Initiative (CHAI) in 2003 [5]. In practice, CHAI attempts to make ARVs more affordable by negotiating price ceilings that reflect suppliers' costs plus reasonable and sustainable profit margins [4]. Moreover, CHAI furthers this strategy by providing direct technical assistance to some suppliers to help lower their production costs [4]. The resulting ceiling prices are made available to all members of the CHAI procurement consortium [4]. Countries that wish to become part of the consortium sign a memorandum of understanding with CHAI and manufacturers are required to offer ARVs to these countries at prices equal to or less than CHAI-negotiated ceiling prices [4].

The third strategy involves differential pricing, sometimes referred to as price discrimination or tiered pricing. In 2000, the Accelerating Access Initiative, a collaborative endeavor of multiple international agencies and pharmaceutical manufacturers, first launched such a strategy for ARVs [5]. Whereas CHAI price negotiation deals exclusively with generic ARVs, differential pricing pertains to branded ARVs and was introduced at a time when generic ARVs were not yet available. Under differential-pricing schemes, each manufacturer selects certain branded ARVs to be sold to low- and middle-income countries at prices lower than those charged in high-income countries [5]. Each manufacturer determines which countries are eligible to purchase ARVs under their differential-pricing scheme, with eligibility typically being based on the country's income level and prevalence of HIV infection.

Data on transactions involving the procurement of ARVs with donor funds are made public by the Global Fund and WHO [6-7]. The Global Fund and WHO databases can be used to monitor and examine the global ARV marketplace. Although some analyses of these databases have been carried out [8-11], none has examined price-reduction strategies mentioned above. We used the Global Fund and WHO databases to test the

following hypotheses on three different ARV price-reduction strategies: prices for high-volume ARV purchases are less than for low-volume purchases; prices for generic ARVs purchased within the CHAI consortium are less than for generic ARVs purchased outside the consortium; and prices for branded ARVs purchased under differential-pricing schemes are equal to or less than those for generic ARVs.

Methods

Data sources

We used data on ARV procurement transactions from the Global Fund Price Reporting Mechanism and the WHO Global Price Reporting Mechanism (GPRM) for the period between July 2002 and October 2007 [6-7]. The Global Fund posts details of ARV procurements reported by their international aid recipients on the web-based Price Reporting Mechanism [6]. In addition, procurement data from the Global Fund as well as procurement data provided by WHO country offices, international organizations, procurement agencies and others are posted by WHO on the web-based GPRM, which serves as the global repository for data on ARV procurement [7,12].

As shown in Figure 1, data from these two sources were combined in a way that allowed us to remove any overlap in procurement data either within or between data sources. We also made sure that the data concerned valid transactions by removing incomplete records, erroneous reports (e.g., the wrong manufacturer) and suspect data entries with extremely low or high prices. Suspect data entries were identified using standard box-plot equation intervals.

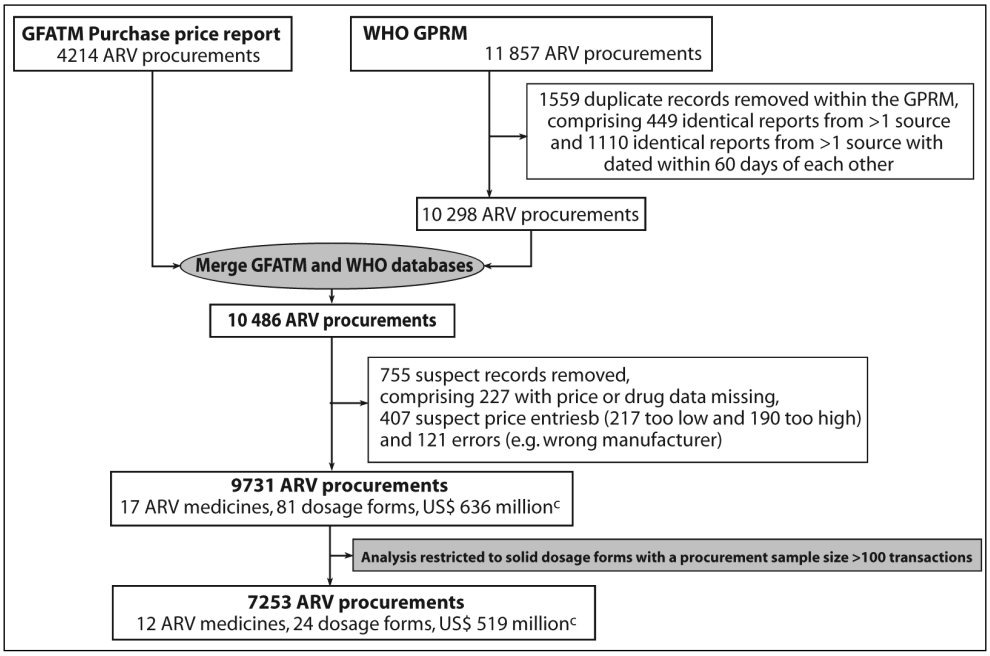

Figure 1. Flow chart illustrating the removal of duplicate, erroneous and suspect records from combined data[a] on the procurement of ARVs in solid form between July 2002 and October 2007[a]

ARV, antiretroviral; GFATM, Global Fund to Fight AIDS, Tuberculosis and Malaria; GPRM, Global Price Reporting Mechanism; US$, United States dollar.

a Data sources were the GFATM Purchase price report and WHO's GPRM.

b A price was regarded as a low price outlier if it was < Q1 - 3 × IQR and as a high price outlier if it was > Q3 + 3 × IQR, where Q1 was the 25th percentile of price, Q3 was the 75th percentile of price and IQR was the width of the interquartile range.

c The value of procurements before adjustment based on the United States annual consumer price index.

For the current analysis, we restricted our data set to ARV products supplied in a solid form, such as tablets, capsules and caplets. To focus on the more commonly used ARVs and to ensure reasonable sample sizes for regression models, we chose ARVs with procurement sample sizes of 100 or more (i.e., the ARV was purchased at least 100 times between July 2002 and October 2007). As a result, the analysis included 7,253 procurement transactions for 24 ARV dosage forms. These 24 dosage forms provide the basis for the regimens commonly used for the prevention of mother-to-child transmission of HIV as well as for first- and second-line treatment of HIV/AIDS. They belong to three major classes of ARV: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors. We adjusted all prices, which were reported by the Global Fund and WHO in United States dollars

(US$), to the July 2006–June 2007 time period using the United States annual consumer price index [13].

The public data sources provided basic transaction information; however, to examine determinants of price, we created additional independent variables, namely, differential price-eligibility, CHAI-eligibility, volume and quality. Whether or not a branded ARV purchase was eligible for differential pricing was determined using information obtained from the 2001 to 2008 editions of *Untangling the web of price reductions*, published by Médecins Sans Frontières [14]. Whether or not a generic ARV purchase was classified as a CHAI or a non-CHAI purchase was determined from information provided by CHAI on when countries joined the consortium and from CHAI ARV price lists, which indicated the manufacturers and products subject to agreements over the previous 5 years (conversation and material provided by D Ellis, CHAI, December 2007). Relevant ARV purchases were considered eligible for CHAI or differential pricing 6 months after the announcement of new prices offered via CHAI or differential-pricing schemes. This was done to account for the likely scenario that a country may have been locked into a previously negotiated price for an annual procurement cycle and may, therefore, have been unable to access newly announced prices.

Volume was categorized as low, medium or high on the basis of thirds of the specific volume distribution for each ARV dosage form. The quality variable indicated whether an ARV was approved or not by a universally accepted, stringent regulatory body. Approved ARVs were those classified as prequalified by WHO or those approved or tentatively approved by the United States Food and Drug Administration (FDA) [15-16]. A summary of the number and total value of purchases of individual ARVs and their corresponding volume categories is provided in Table 1.

Analytic approach

We used existing and newly created variables to examine determinants of the price of ARVs. We devised separate regression models for each of the 24 ARV dosage forms by using generalized estimating equation linear regression to take account of the correlated nature of the data. Price, our dependent variable, was non-normally distributed; therefore, we adopted the natural log of the price per tablet or capsule as our outcome measure. Data were clustered by country and year of purchase to take into account potential correlations in price within these variables. Candidate predictor variables were: the International Chamber of Commerce standard trade definition (Incoterm) [17], the World Bank Country Income Classification,18 eligibility for CHAI or differential pricing [14] (D Ellis, CHAI, personal communication, 2007), FDA-approved or WHO-prequalified ARV [15-16], purchase volume third, and analytic year of purchase. For

each predictor variable we calculated the percentage change in price for each one-unit increase in the predictor variable by exponentiating the βcoefficients from the regression equations and subtracting 1. Multivariate analysis was used to determine the effect of purchase volume, eligibility for CHAI and eligibility for differential pricing on ARV price. The results of the multivariate analysis are presented as percentage price differences between categories, with a negative percentage difference indicating that the ARV price in the comparator group is less than that in the reference category and a positive percentage difference indicating the opposite. Price differences with p-values ≤ 0.05 were considered statistically significant and are highlighted in boldfaced type in Table 2 and Table 3.

To provide a context for interpreting the findings of the regression analysis, Table 2 also lists raw, unadjusted ARV prices for July 2006–June 2007 together with the results of the regression analysis. These raw prices are described in terms of the median annual price per person of individual products (i.e., median price per tablet or capsule × daily dose × 365 days). For ARVs for adults, we used doses for individuals weighing ≥ 60 kg; for paediatric ARVs, we used doses for children weighing 10 kg, as recommended by WHO [19-21].

Results

Effect of purchase volume

We detected no statistically significant association between purchase volume and price at the country level for 19 of the 24 (79%) dosage forms after adjusting for other variables in the regression model (Table 2). For two of the five dosage forms for which there was a significant association between volume and price, the prices for high-volume purchases were 7% and 21% less, respectively, than for low-volume purchases. For two other dosage forms, the prices for high-volume purchases were less than for both medium- and low-volume purchases, with differences being 4% and 5% less, respectively, for one ARV and 11% and 16% less, respectively, for the other. The other dosage form was 6% less expensive for high-volume purchases than for medium-volume purchases.

Generic prices for CHAI and non-CHAI purchases

We identified 13 generic ARV products for which CHAI had negotiated price ceilings with manufacturers on behalf of CHAI country consortium members. We compared the actual prices paid for generic ARVs by CHAI and non-CHAI countries and found that the price of 9 of 13 (69%) dosage forms was significantly lower for CHAI purchases

than non-CHAI purchases (Table 3, columns A, B and C). Overall, CHAI prices were less than non-CHAI prices by 6–36% (Table 3, column C).

Generic and differentially priced branded prices

Of the 24 (79%) solid ARV dosage forms analysed, 19 were available to some countries through differential-pricing schemes provided by the brand- name manufacturer (Table 3, column D). Of these 19 (95%) differentially priced branded products, 18 could be compared in price with non-CHAI generics (Table 3, column E). For 15 of these 18 (83%) dosage forms, purchases made under differential-pricing schemes were significantly more expensive than non-CHAI generic purchases, with price differences ranging from 23–498% (Table 3, column E). For two of the 18 (11%) ARV dosage forms, prices for differentially priced branded ARVs were 63% and 73% lower, respectively, than prices for non-CHAI generic ARVs. The price difference between the differentially priced branded product and the non-CHAI generic version was significant for all 18 ARV dosage forms, apart from ritonavir 100 mg.

Discussion

We combined data from medicine procurement databases made public by the Global Fund and WHO with information from other sources to evaluate price-reduction strategies for ARVs for the first time and found some surprising results. The most counterintuitive finding is the absence of an association between purchase volume and price at the country level for 19 of the 24 ARV dosage forms (see Table 2). Although conventional business practice suggests that making a large-volume purchase at the country level will result in a discounted price, this appears not to be the case for these medicines.

The Global Fund has recommended the facilitation of voluntary pooled procurement as a means of increasing procurement efficiency [2,3]. Pooled procurement of ARVs will result in much larger purchase volumes than those explored in our study, but it remains difficult to quantify exactly how much money could be saved by pooling purchase orders. Any estimate of potential savings resulting from pooled procurement must be balanced against the programmatic costs of establishing and managing the procurement systems required. While some surveys and desk reviews have described potential pooled procurement mechanisms in developing countries [22,23], insufficient empirical research has been carried out to validate pooled procurement and identify the conditions under which it can operate most efficiently. Pooled procurement may certainly offer other potential supply chain efficiencies beyond increased purchase volumes, but it should be carefully monitored to ensure such efficiencies are achieved.

While interventions for improving procurement efficiency are certainly desirable, they should be designed to develop and increase the technical capability for managing these procurement systems in the countries concerned. New procurement arrangements, whereby donors and international organizations act on behalf of countries for selected diseases, may fail to help strengthen those countries' health systems. Lastly, pooled purchase arrangements will reduce the number of purchasers and could, therefore, result in a dramatic restructuring of the current global ARV market. Econometric modeling should be used to predict the potential impact of pooled procurement on the global ARV market and the findings should be used to inform the design of these schemes.

Third-party price negotiation by CHAI shows promise. Overall, the price of generic ARVs was less for CHAI purchases than for non-CHAI purchases. However, price differences between CHAI and non-CHAI purchases varied widely across ARVs. While price differences were as high as 27–36% for some ARVs, for others they were less than 10%. The most dramatic price differences between CHAI and non-CHAI generic ARVs were typically observed in the 1 to 2 years immediately following negotiations with suppliers. We recommend, therefore, that additional time-series research be carried out to explore the reasons why these price differences diminish over time and their potential impact on the overall ARV market.

Traditional approaches using differential-pricing schemes have not decreased the prices of branded ARVs to levels that can make these drugs compete with generic ARVs in most scenarios, which suggests that differential pricing alone is insufficient for achieving and sustaining universal access to HIV/AIDS treatment. In this study, nearly all the branded ARVs offered under differential pricing schemes were more expensive than the equivalent generics. There were a few exceptions where generic competition was lacking and differential pricing schemes for branded ARVs offered substantial cost savings over generic ARVs. The most notable exception was for lopinavir 133.3mg plus ritonavir 33.3mg, a branded combination purchased under a differential pricing scheme; it was 73% less expensive than its non-CHAI generic equivalent. Likewise, there may be country scenarios in which generics cannot be purchased because of patent protection or other intellectual property barriers, and differential pricing may, therefore, offer substantial cost savings. Clearly, differential pricing of ARVs coexists in an environment that now includes large-scale financing of HIV/AIDS treatment and the maturation of generic ARV markets, two forces that did not exist when the Accelerating Access Initiative began. Additional work is needed to better explain the particular role of differential pricing in providing treatment for HIV/AIDS in today's global ARV market, with special attention paid to the impact of differential pricing on the price of first-entry generic competitors.

While this research has provided some important findings, our analysis has limitations. Because we were dealing with pre-existing data, we used a standard method to remove outliers that may have come from erroneous reports. However, we repeated our analysis with the outliers included and the results did not differ from those presented in this paper. We also repeated our regression analyses using volume fourths instead of volume thirds and found the same results. Our study examined price–volume relationships at the level of individual purchases and did not consider total volume–price relationships at the level of tender arrangements, as these data were unavailable. Indeed, countries usually tender once or twice a year for larger volumes that are delivered in the multiple smaller purchase volumes reported in the databases. Still, larger tenders are likely to involve larger individual purchase volumes, so an analysis at the tender level would probably reveal similar results. It is notable that an association between volume and price was found for 5 of the 24 ARV dosage forms. This suggests that more work is needed to better understand the exceptional conditions under which the volume purchased at the country level may determine the ARV price.

Our regression models contained many candidate variables thought to be associated with price; however, we lacked access to information on additional factors that may have an influence, such as the timeliness of payment, the lead time between when an ARV is ordered and when it is needed, the presence or absence of drug registration, and intellectual property regulation. While many pricing studies must consider purchase incentives such as bundling, rebates and discounts, we doubt that such purchase arrangements played a major role in our study of donor-funded national ARV procurements. Lastly, our study focused on ARV prices only; other programmatic costs associated with the treatment of HIV/AIDS were not considered.

The quality of medicines on the market varies within and between low-resource countries, which means that previous price research compared medicines of unequal quality. For ARVs purchased with donor funds, however, the policies of the Global Fund and the United States President's Emergency Plan for AIDS Relief mandate that the purchase of ARVs is approved by the WHO Prequalification Programme, the United States FDA or other stringent regulatory authorities. The WHO Prequalification Programme in particular has increased the availability of lower-priced, high-quality generic ARVs and this has enabled us to compare the prices of ARVs of equal quality.

Alternative strategies for reducing ARV prices should be explored. For instance, financial management systems in donor and country programmes could be improved and generic competition could be promoted by removing barriers to generic entry. Improved forecasting of future demand for ARVs may result in lower prices by preventing or minimizing the need for costly emergency shipments. For ARVs such as protease inhibitors

that are expensive to make and are used less often, efforts could be made to consolidate global demand by reaching a consensus on the use of one or two key compounds. Alternatively, interventions aimed at transferring technology to generic producers may result in more timely generic competition for protease inhibitors and subsequent price reductions. Lastly, existing publicly available procurement databases should be expanded and used to guide future policies aimed at increasing access to essential ARV therapies.

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Antiretroviral	Total number of purchases	Total value of all purchases (US $)[a]	Volume of ARV doses purchased[b]		
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)			**Low (lowest third)**	**Medium (middle third)**	**High (highest third)**
abacavir 300mg	247	9,612,930	300–6,120	6,240–37,140	39,000–781,200
didanosine 100mg	172	1,854,615	60–3,600	3,720–29,880	30,000–324,480
didanosine 200mg	115	1,693,087	240–3,960	4,020–27,000	28,680–343,260
didanosine 400mg	126	4,648,567	90–2,310	2,400–15,390	15,540–332,340
lamivudine 150mg	580	15,911,293	120–28,080	28,320–179,160	180,000–5,904,000
stavudine 20mg	113	461,819	56–10,800	12,000–48,600	51,600–840,000
stavudine 30mg	389	4,018,395	60–11,880	12,000–120,000	121,440–5,790,000
stavudine 40mg	382	5,745,885	120–9,600	9,900–94,696	95,200–4,373,100
stavudine 30mg+lamivudine150mg	257	43,916,698	240–6,900	7,200–48,000	51,000–401,346,960
stavudine 40mg+lamivudine150mg	206	1,389,119	27–4,020	4,080–24,120	24,180–1,500,000
tenofovir 300mg	137	8,800,097	89–9,000	10,140–45,600	45,900–1,440,000
zidovudine 100mg	232	2,734,390	200–7,400	7,500–42,800	43,200–3,550,000
zidovudine 300mg	311	6,016,544	120–11,580	12,000–47,280	48,000–1,600,020
zidovudine 300mg+lamivudine 150mg	691	79,642,912	120–30,000	32,040–230,040	231,000–137,648,400
Non–Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)					
efavirenz 50mg	170	801,118	90–5,400	5,700–31,500	34,500–454,500
efavirenz 200mg	350	13,661,610	90–9,000	9,270–45,630	45,720–2,563,200
efavirenz 600mg	616	73,531,130	60–12,990	13,020–110,970	112,440–6,693,480
nevirapine 200mg	727	32,204,756	60–19,020	19,500–120,000	120,120–12,534,000
Fixed Dose Combination (FDC) of NRTIs and NNRTI					
stavudine 30mg+lamivudine 150mg + nevirapine 200mg	392	145,267,223	420–25,620	27,000–262,200	282,000–486,404,460
stavudine 40mg+lamivudine 150mg + nevirapine 200mg	335	17, 617,177	360–18,960	19,080–92,520	92,760–3,957,093
Protease Inhibitors (PIs)					
indinavir 400mg	164	7,573,719	540–27,000	27,900–112,680	115,200–1,602,000
lopinavir 133mg + ritonavir 33mg	217	18,281,938	138–19,440	21,600–88,200	90,000–2,640,780
nelfinavir 250mg	214	21,941,575	540–33,750	34,290–167,400	175,500–4,185,000
ritonavir 100mg	110	1,908,638	336–6,720	7,140–45,360	47,040–360,024

Table 1. Number and total value of individual ARV purchases between July 2002 and October 2007

ARV, antiretroviral, US$, United States dollar.

[a] Value before adjustment based on the United States annual consumer price index

[b] The purchase volume was categorized as low, medium, or high using thirds for the specific purchase volume distribution for each ARV dosage form

Antiretroviral	Median unadjusted annual price per person[a]			Price difference from regression analysis[b] (%)	
	High-volume purchases (US$)	Medium-volume purchases (US$)	Low-volume purchases (US$)	High-volume vs medium-volume purchases	High-volume vs low-volume purchases
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)					
abacavir 300mg	438	453	540	3	–1
didanosine 100mg[c]	115	115	88	4	–2
didanosine 200mg	314	241	226	4	–3
didanosine 400mg	303	434	288	–12	–4
lamivudine 150mg	51	51	58	2	–2
stavudine 20mg[c]	15	15	33	–2	–2
stavudine 30mg	29	29	37	6	–5
stavudine 40mg	37	37	37	4	12
stavudine 30mg+lamivudine150mg	66	73	66	0.7	5
stavudine 40mg+lamivudine150mg	80	73	66	–2	6
tenofovir 300mg	208	208	226	7	–7
zidovudine 100mg[c]	51	55	58	3	3
zidovudine 300mg	124	117	146	**–4**	**–5**
zidovudine 300mg+lamivudine 150mg	139	168	139	–1	–7
Non–Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)					
efavirenz 50mg[c]	161	161	161	1	3
efavirenz 200mg[c]	111	131	77	–7	–6
efavirenz 600mg	234	245	245	–4	–7
nevirapine 200mg	58	55	58	–3	–3
Fixed Dose Combination (FDC) of NRTIs and NNRTI					
stavudine 30mg+lamivudine 150mg + nevirapine 200mg	95	102	102	–5	–5
stavudine 40mg+lamivudine 150mg + nevirapine 200mg	131	102	102	**–11**	**–16**
Protease Inhibitors (PIs)					
indinavir 400mg	394	511	496	**–6**	–7
lopinavir 133mg + ritonavir 33mg	920	1007	591	–13	**–21**
nelfinavir 250mg	1059	1113	1059	–4	3
ritonavir 100mg	80	88	91	–8	6

Table 2. Effect of purchase volume, divided into thirds, on the price of individual ARVs as determined by regression analysis. The median unadjusted annual price per person of individual products during July 2006–June 2007 is shown for reference

ARV, antiretroviral, US$, United States dollar. [a] Median price per person per year during July 2006-June 2007. [b] Statistically significant differences (p<0.05) are shown in ***boldface type****. [c] Paediatric dose for children weighing 10 kg.*

Antiretroviral	Median Annual Price per Person[a] (unadjusted)		Price difference from Regression[b] (%)	Median Annual Price per Person[a] (unadjusted)	Price difference from Regression[b] (%)
	A	B	C	D	E
	Non-CHAI Generic (US$)	CHAI Generic (US$)	CHAI *vs* non-CHAI generic ARVs	Differentially priced Brand (US$)	Differentially priced branded product *vs* non-CHAI generic product
Nucleoside reverse transcriptase inhibitors (NRTIs)					
Abacavir 300 mg	515	358	**-15****	635	**60****
Didanosine 100 mg[c]	293	NA	NA	115	**30***
Didanosine 200 mg	190	NA	NA	NA	NA
Didanosine 400 mg	176[d]	NA	NA	288	**-63***
Lamivudine 150 mg	51	44	-5	73	**51****
Stavudine 20 mg[c]	15	11	**-36****	33	**137****
Stavudine 30 mg	37	22	**-18***	73	**100****
Stavudine 40 mg	37	22	-9	73	**98****
Stavudine 30 mg plus lamivudine 150 mg	73	NA	NA	NA	NA
Stavudine 40 mg plus lamivudine 150 mg	73	NA	NA	NA	NA
Tenofovir 300 mg	NA	NA	NA	208	NA
Zidovudine 100 mg[c]	58	37	**-18***	117	**112****
Zidovudine 300 mg	131	110	**-6***	226	**43****
Zidovudine 300 mg plus lamivudine 150 mg	139	124	**-13****	241	**44****
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)					
Efavirenz 50 mg[c]	117	NA	NA	161	**48****
Efavirenz 200 mg[c]	77	77	-3	131	**47****
Efavirenz 600 mg	245	150	**-27***	296	**23***
Nevirapine 200 mg	66	44	**-9***	438	**498****

Antiretroviral	Median Annual Price per Person[a] (unadjusted)		Price difference from Regression[b] (%)	Median Annual Price per Person[a] (unadjusted)	Price difference from Regression[b] (%)
	A	B	C	D	E
	Non-CHAI Generic (US$)	CHAI Generic (US$)	CHAI *vs* non-CHAI generic ARVs	Differentially priced Brand (US$)	Differentially priced branded product *vs* non-CHAI generic product
Fixed-dose combination of NRTIs and an NNRTI					
Stavudine 30 mg plus lamivudine 150 mg plus nevirapine 200 mg	102	95	**-11***	NA	NA
Stavudine 40 mg plus lamivudine 150 mg plus nevirapine 200 mg	102	80	-11	NA	NA
Protease inhibitors					
Indinavir 400 mg	380	NA	NA	467	**29***
Lopinavir 133.3 mg plus ritonavir 33.3 mg	4358	NA	NA	591	**-73****
Nelfinavir 250 mg	931	NA	NA	1095	**44****
Ritonavir 100 mg	102	NA	NA	80	-35

Table 3. Differences between the prices of generic ARVs purchased under CHAI, generic ARVs not purchased under CHAI and differentially priced branded ARVs

**P_≤_0.05; **P_≤_0.0001 (Generalized estimating equation linear regression).*
ARV, antiretroviral; CHAI, Clinton Foundation HIV/AIDS Initiative; NA, not applicable; US$, United States dollar.
[a] *Median price per person per year during July 2006–June 2007.*
[b] *Statistically significant differences are shown in boldface type.*
[c] *Paediatric dose for children weighing 10 kg.*
[d] *Adjusted median price per person per year based on price during July 2005–June 2006.*

Chapter 4

Moving The Access To Medicines Dialogue Beyond Price: Policy Impacts On Pharmaceutical Market Evolution

Chapter 4.1

Intervening in global markets to improve access to HIV/AIDS treatment: an analysis of international policies and the dynamics of global antiretroviral medicines markets

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Abstract

Background

Universal access to antiretroviral therapy (ART) in low- and middle-income countries faces numerous challenges: increasing numbers of people needing ART, new guidelines recommending more expensive antiretroviral (ARV) medicines, limited financing, and few fixed-dose combination (FDC) products. Global initiatives aim to promote efficient global ARV markets, yet little is known about market dynamics and the impact of global policy interventions.

Methods

We utilize several data sources, including 12,958 donor-funded, adult first-line ARV purchase transactions, to describe the market from 2002-2008. We examine relationships between market trends and: World Health Organization (WHO) HIV/AIDS treatment guidelines; WHO Prequalification Programme (WHO Prequal) and United States (US) Food and Drug Administration (FDA) approvals; and procurement policies of the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM), US President's Emergency Plan for AIDS Relief (PEPFAR) and UNITAID.

Results

WHO recommended 7, 4, 24, and 6 first-line regimens in 2002, 2003, 2006 and 2009 guidelines, respectively. 2009 guidelines replaced a stavudine-based regimen ($88/person/year) with more expensive zidovudine- ($154-260/person/year) or tenofovir-based ($244-465/person/year) regimens. Purchase volumes for ARVs newly-recommended in 2006 (emtricitabine, tenofovir) increased >15-fold from 2006 to 2008. Twenty-four generic FDCs were quality-approved for older regimens but only four for newer regimens. Generic FDCs were available to GFATM recipients in 2004 but to PEPFAR recipients only after FDA approval in 2006. Price trends for single-component generic medicines mirrored generic FDC prices. Two large-scale purchasers, PEPFAR and UNITAID, together accounted for 53%, 84%, and 77% of market volume for abacavir, emtricitabine, and tenofovir, respectively, in 2008. PEPFAR and UNITAID purchases were often split across two manufacturers.

Conclusions

Global initiatives facilitated the creation of fairly efficient markets for older ARVs, but markets for newer ARVs are less competitive and slower to evolve. WHO guidelines shape demand, and their complexity may help or hinder achievement of economies of

scale in pharmaceutical manufacturing. Certification programs assure ARV quality but can delay uptake of new formulations. Large-scale procurement policies may decrease the numbers of buyers and sellers, rendering the market less competitive in the longer-term. Global policies must be developed with consideration for their short- and long-term impact on market dynamics.

Background

Although much progress has been achieved in scaling-up access to HIV/AIDS treatment in low and middle-income countries, the 4 million people who had received antiretroviral therapy (ART) by the end of 2008 still represent only a small fraction of the 22 million estimated to need treatment by 2015 [1]. Donors provided $10 billion in 2007, but an estimated $50 billion will be required to cover all HIV/AIDS program costs in 2015 [1]. At the same time, new World Health Organization (WHO) guidelines recommend not only using better, more expensive medicine, but also starting ART earlier, implying immediate increases in the numbers of people eligible for treatment [2]. As costs and needs escalate, however, international organizations are facing serious financing shortfalls. For example, in late 2008 the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM) asked principal recipients to decrease eighth-round budgets by10% [3]. The fallout from the current world economic crisis, meanwhile, is still uncertain. With this "perfect storm" of converging dynamics, policy makers urgently need to understand all factors affecting our ability to meet universal access goals. Market factors, in particular, add even more complexities to the situation.

By intervening in global antiretroviral (ARV) markets serving low- and middle-income countries, the GFATM [4], the Clinton Health Access Initiative (CHAI) [5], the US President's Emergency Plan for AIDS Relief (PEPFAR) [6] and UNITAID [7], among other international organizations, are working to narrow the gap between the funding available and the amounts necessary to achieve universal access. Their interventions aim to provide safe, acceptable and good quality diagnostics and medicines for HIV/AIDS treatment and care, and to promote competition among suppliers. The organizations, however, currently confront daunting challenges and a very different marketplace compared to ART scale-up conditions of the past. Recently available data enable us to describe and assess these changing conditions.

Of pressing concern is the shifting demand for antiretrovirals as countries adopt the newer, more expensive first-line regimens recommended by WHO [2,8]. Some key ARVs in newer regimens are widely patented, while patents for older ARVs were largely absent in the countries that produced and exported them, namely India, Brazil, and

Thailand [9]. These and other developing countries now must provide patent protection for more recently-developed medicines as they implement the World Trade Organization (WTO) Agreement on Trade Related Aspects of Intellectual Property Rights [10]. Patent-related barriers for newer regimens result in a less competitive and more fragmented generic market; they also hamper development of improved formulations such as fixed-dose combination (FDC) products, in which two or more medicines are combined into a single tablet. WHO strongly recommends the use of FDCs [8] because of their numerous advantages over single component medicines, most notably simplified prescribing, improved patient adherence, reduced risk of resistance and easier supply chain management [11-15]. Yet far fewer FDCs are available for newer than for older first- line regimens.

Quality assurance and procurement issues also factor into the complex market equation. Initiatives such as the WHO Prequalification Programme (WHO Prequal) [16] and the tentative approval system of the United States (US) Food and Drug Administration (FDA) [17,18] not only ensure that ARVs procured with donor funds meet international quality standards, but also influence the rate and extent of ARV dispersion across low- and middle- income countries. The establishment of large-scale purchasers such as PEPFAR, UNITAID, and the Voluntary Pooled Procurement program of the GFATM, which relieves individual countries of their procurement responsibilities, is rapidly consolidating the number of buyers in the market.

Research to date on ARV markets has focused largely on the evolution of ARV prices [19-23]. Other elements of the "perfect storm" -- in particular the interconnectedness of decisions made by international organizations and their relationships to ARV market dynamics -- have not been well described. Yet understanding these relationships is critical to support future policy making.

To further such understanding, this paper describes the most salient supply- and demand-side characteristics of the market for first-line, adult ARVs in low- and middle-income countries and illustrates relationships between market evolution and the policies of international organizations. We examine ARV market trends in relation to three areas of intervention: WHO HIV/AIDS treatment guidelines; certification decisions of WHO Prequal and FDA; and pooled procurement policies of GFATM, PEPFAR and UNITAID. Since these three factors play out in markets simultaneously, we believe that examining them in relation to one another will provide policy makers and academicians with a more useful analysis than focusing on any one of them in isolation.

Methods

Using several data sources, we created a dataset of market intelligence information for ARVs that includes purchases made with donor funds in low- and middle-income countries. Information on approvals of quality-assured FDC ARVs was obtained from WHO Prequal [16] and the US FDA [17,18] and added to an analytic dataset that contains ARV product information (manufacturer, strength, dosage form, and price when available) obtained from MSF Untangling the Web of Price Reductions [24], CHAI consortium ARV price lists [25], and various manufacturer and national drug regulatory authority websites.

All of this information was used to systematically validate ARV products and prices for ARV purchase transactions obtained from the WHO Global Price Reporting Mechanism [26] and the GFATM Price Quality Report [27] from 2002-2008, after merging and removal of duplicates.

In addition, we included information from the World Bank on country income classifications [28], the International Monetary Fund on annual inflation [29], and WHO on recommended first-line regimens in all editions of WHO adult treatment guidelines for HIV/AIDS[2,8,30,31]. We restricted our analytic dataset to solid dosage forms (tablets, capsules) of adult ARVs used for first-line treatment of HIV/AIDS, namely abacavir (ABC), efavirenz (EFV), emtricitabine (FTC), lamivudine (3TC), nevirapine (NVP), stavudine (d4T), tenofovir (TDF), and zidovudine (ZDV). A detailed process of the creation of the analytic data set is provided in Figure 1.

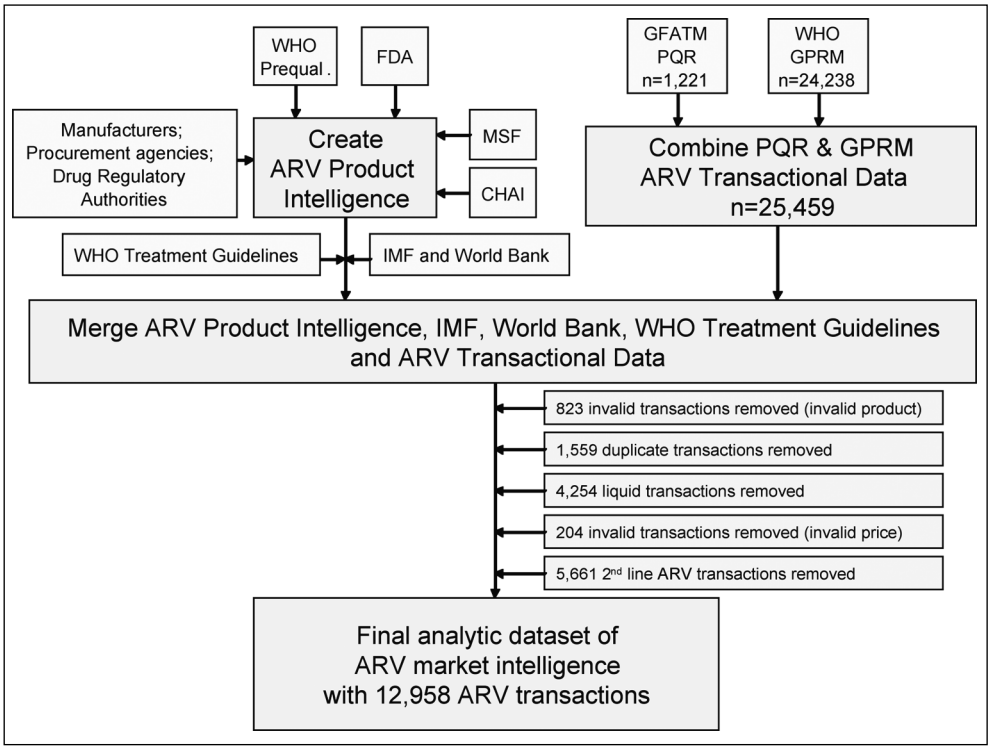


Figure 1. Description of analytic data set

We adjusted all prices, provided by GFATM and WHO in US Dollars, to the January-December 2008 time period using the annual US Consumer Price Index [29]. We then conducted a descriptive and comprehensive case study on the global market for adult first-line ARVs in low- and middle-income countries.

We present trends from 2002-2009 in the number of first-line regimens recommended by WHO by showing the main regimens that appear in key tables and figures of WHO HIV/AIDS treatment guidelines [2,8,30-32]. We do not include regimens recommended in specific situations as noted throughout the text and footnotes of guidelines. For the purpose of this paper, "older" regimens are defined as those recommended in 2003 WHO Guidelines and "newer" regimens are those in 2006 WHO Guidelines.

Antiretroviral demand is estimated by volumes purchased and presented in person-years whereby:

Annual volume (in person-years) = (total number of tablets purchased per year)/ (daily dose x 365 days).

When estimating volume of ARVs purchased, we include all products (FDCs, co-packaged products, and individual medicines) that contain the ARV of interest in calculating volumes purchased. For example, the total volume purchased for tenofovir would include TDF, 3TC/ TDF, FTC/TDF, and EFV/FTC/TDF.

Antiretroviral prices are calculated using adult dosages for persons weighing greater than sixty kilograms [8], whereby:

ARV regimen price (in US Dollars) = (price / tablet) x (defined daily dose) x (365 days).

Median prices plus 25th and 75th percentile prices are provided for the most commonly used first-line ARV regimens [33] and calculated using the least expensive ARVs to create each regimen. For example, the stavudine (d4T) 30, lamivudine (3TC) 150, nevirapine (NVP) 200 regimen price is based upon the price of the generic fixed-dose combination product, whereas the tenofovir (TDF) 300, emtricitabine (FTC) 200, NVP200 regimen is based upon generic prices of TDF300/FTC200 fixed-dose product and NVP200 tablet.

For three-in-one FDCs, we plot timelines of products and manufacturers approved by the FDA approval, FDA tentative approval, and WHO Prequalification systems from 2000-2009 [16-18].

In depicting FDC market dynamics, for each year we present the number of manufacturers reported in transactional purchase data, the total number of manufacturers who have been approved by either WHO Prequal or US FDA to date, and the number of countries who purchased the FDC.

We describe FDC products using a "/" between ARVs included in a given FDC. We use a "+" to depict regimens comprised of two or three distinct tablets. For example, for the regimen of 3TC150, NVP200, and ZDV300, the format 3TC150/NVP200/ZDV300 reflects the FDC version, whereas 3TC150+NVP200+ZDV300 reflects three individual tablets, and 3TC150/ZDV300 + NVP200 reflects a FDC plus an individual NVP200 tablet.

We present trends in market share by volume for the most commonly used three-in-one FDCs by plotting the annual volume (in person-years) bought by each purchaser. The purchaser is defined as the organization providing funds to buy ARVs and includes four categories: GFATM, PEPFAR, UNITAID and miscellaneous. The PEPFAR purchases are actually purchases made by the Supply Chain Management System (SCMS), a consortium organization that purchases ARVs on behalf of PEPFAR. In our data sources, no PEPFAR purchases were recorded outside of SCMS. The manufacturer split across each purchaser is also depicted.

2008 market share is calculated across purchasers according to both the value (in US Dollars) and the volume (in person-years) of ARVs purchased. Analyses of 2008 market share include all products (FDCs, co-packaged medicines, and individual medicines) that contain the ARV of interest.

$$\text{2008 percent market share for purchasers by value} = (\text{value in USD}_{\text{purchaser}} / \text{value in USD}_{\text{total}}) * 100$$

$$\text{2008 percent market share for purchasers by volume} = (\text{volume in person-years}_{\text{purchaser}} / \text{volume in person-years}_{\text{total}}) * 100$$

Results

Relationships between WHO treatment guidelines and demand

Figure 2 shows the composition of WHO treatment guidelines from 2002-2009. The number of first-line regimens and their components varied significantly, with corresponding swings in purchase volumes, as described below in more detail.

The first WHO HIV/AIDS treatment guidelines for adults and adolescents were released in 2002. They recommended seven regimens comprised of ten ARVs, including the relatively costly protease inhibitors (Figure 2) [30]. One year later, WHO issued revised guidelines that included only four key first-line regimens [31] comprised of five different ARVs, namely EFV, 3TC, NVP, d4T and ZDV; these guidelines excluded protease inhibitors altogether [31].

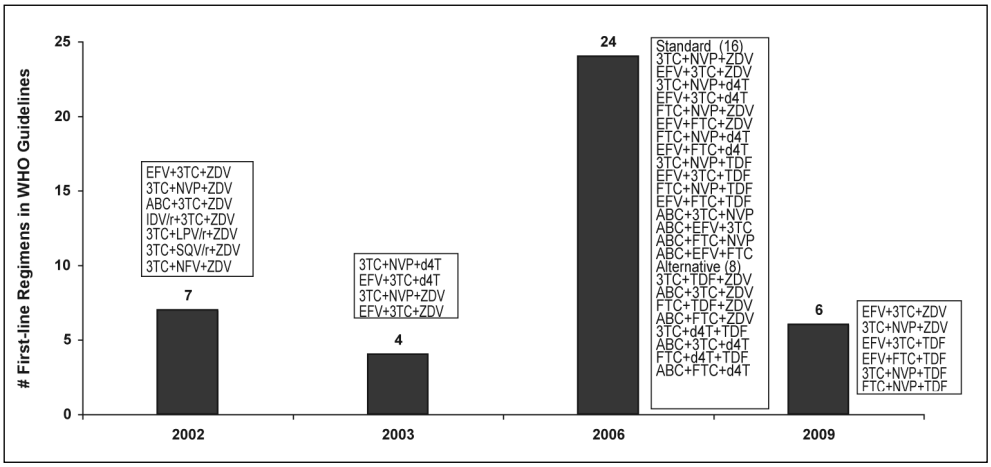


Figure 2. Trends in numbers of first-line ARV regimens in WHO treatment guidelines

In 2006, WHO released a second revision of HIV/AIDS treatment guidelines [8] with an increase to 24 recommended first-line regimens (16 regimens characterized as "standard" and eight characterized as "alternative") [8]. The revision offered much more flexibility in terms of clinical options for prescribers. To the five ARVs in the 2003 guidelines, the 2006 revision added three more, namely ABC, FTC, and TDF. The 2006 guidelines also suggested that practitioners start planning to move away from d4T-based regimens due to related toxicities [8]. In May 2007, WHO issued an addendum recommendation to dose d4T at 30 mg twice daily for all adults regardless of weight, replacing the previous dosing of 40 mg twice daily for patients weighing more than 60 kilograms [32].

The latest WHO revisions, announced in November 2009 and to be officially released in 2010 [2], recommend only six key first-line regimens comprised of six ARVs for treatment-naïve individuals [2]. Each of these regimens contains ZDV or TDF plus 3TC or FTC plus EFV or NVP [2]. The 2009 regimens do not introduce new ARVs or regimens, but prioritize regimens listed in the 2006 guidelines. The newest guidelines no longer recommend the use of d4T because of its side effects and toxicities.

Examination of purchase trends for first-line ARVs strongly suggests that the WHO guideline recommendations play an important role in driving ARV demand. The five ARVs listed in the 2003 WHO treatment guidelines accounted for more than 98% of ARVs purchased in 2004-2006 (Figure 3). Shortly after the addition of TDF and FTC to WHO first-line treatment guidelines in 2006, TDF purchase volumes increased more than 15-fold, from 16,000 person-years in 2006 to 240,000 person-years in 2008, while FTC purchase volumes increased more than 20-fold over the same period, with 162,000 person-years of purchase volume noted in 2008.

Similarly, purchase patterns appear to reflect 2006 WHO guidance away from d4T-containing regimens [8]. From 2006 to 2008, demand for d4T increased less than two-fold from 515,000 person-years to 895,000 person- years, while demand for ZDV (the lowest-cost substitute for d4T) grew more than five-fold, from 139,000 person- years to more 733,000 person-years over the same time period.

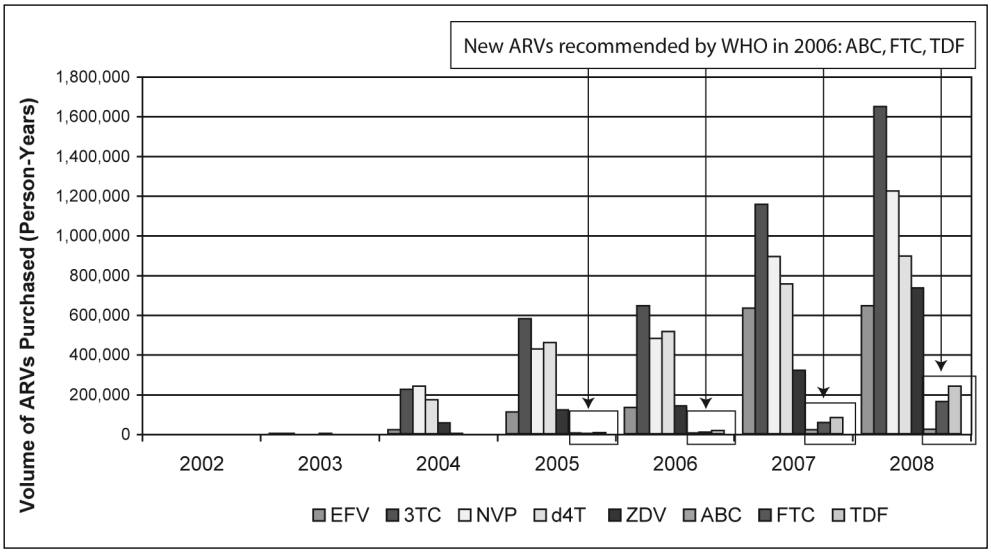


Figure 3. Consumption trends of WHO-recommended first-line ARVs (2002-2008)

Price implications of new WHO Guidelines

Prices for newer first-line regimens (those more recently recommended by WHO) are considerably higher than prices for older regimens. In 2008, the most commonly used older regimen (3TC+NVP+d4T) was $88/person/year in low-income countries. As countries adopt new 2009 WHO recommendations to phase out d4T use, they are likely to instead use ZDV-based regimens priced 1.8-3 times higher at $154 (3TC/NVP/ZDV) and $260 (EFV+3TC/ZDV) or a TDF-based regimen (TDF+3TC+NVP), priced 2.8 times higher at $244/person/year in low income countries (Table 1).

	Median (25th, 75th percentile) Regimen Prices* in USD		
	Low Income	**Lower-Middle Income**	**Lower-Middle Income**
Old First-Line Regimens from 2003 WHO Guidelines:			
3TC/NVP/d4T30	88 (83, 90)	87 (80, 151)	110 (84, 222)
EFV+3TC/d4T30	198 (183, 223)	147 (52, 253)	211 (172, 235)
3TC/NVP/ZDV**	154 (144, 162)	172 (154, 259)	161 (161, 189)
EFV+3TC/ZDV**	260 (246, 286)	216 (118, 298)	326 (260, 370)
New First-Line Regimens from 2006, 2009 WHO Guidelines:			
3TC+NVP+TDF**	244 (226, 278)	256 (244, 288)	387 (311, 591)
EFV+3TC+TDF**	349 (321, 399)	301 (207, 392)	477 (404, 527)
FTC/TDF+NVP**	361 (325, 366)	399 (292, 427)	525 (368, 726)
EFV+FTC/TDF**	465 (419, 487)	443 (256, 531)	616 (461, 663)
ABC+3TC+NVP	398 (361, 450)	418 (392, 457)	491 (443, 705)
ABC+EFV+3TC	503 (455, 571)	463 (355, 561)	581 (536, 641)
ABC+FTC+NVP	n/a§	n/a§	n/a§
ABC+EFV+FTC	n/a§	n/a§	n/a§

Table 1. 2008 Prices for most-commonly used first-line ARV regimens

**price/person/year calculated using the least expensive ARVs to create each regimen (see methods section)*
***first-line regimens recommended in 2009 WHO guidelines*
§price data unavailable; less than 5 purchases for at least one ARV in regimen

Relationships between regulatory bodies and availability of ARV FDCs across donor programs

WHO established WHO Prequal in 2001 to ensure that medicines purchased with funds from United Nations organizations met international quality standards [16]. In most cases, principal recipients of GFATM funds are required to purchase medicines pre-qualified by WHO Prequal or strict regulatory authorities such as the US FDA, the European Medicines Agency, or Health Canada.

The US FDA established the tentative approval system in May 2004 to enable PEPFAR recipients to access generic versions of products still under patent protection or other forms of market exclusivity in the US and to expedite approval of ARVs [17]. Antiretroviral medicines purchased with PEPFAR funds must be approved by either the standard or the tentative FDA approval process [17].

Figure 4 illustrates the timing of regulatory approval for different WHO-recommended FDCs. By the end of 2009, 19 three-in-one FDCs had been approved through WHO

Prequal and 15 FDCs through the FDA tentative process. The first generic FDC (3TC/NVP/d4t40) was prequalified by WHO in 2003 (Figure 4), the same year WHO released guidelines recommending use of the FDC as one of four regimens. By 2006, six d4T-based FDCs and two ZDV-based FDCs were WHO-prequalified. In contrast, the FDA first approved a generic FDC (3TC/NVP/ZDV) in mid-2006 (thereby allowing PEPFAR programs to purchase them), approximately three years after the release of 2003 WHO Guidelines. The FDA first approved d4T- based FDCs in November 2006, approximately three years after the first approval by WHO (Figure 4). In short, the FDA approved FDCs for older regimens several years after WHO, which was reflected in delayed market demand from PEPFAR recipients for these products.

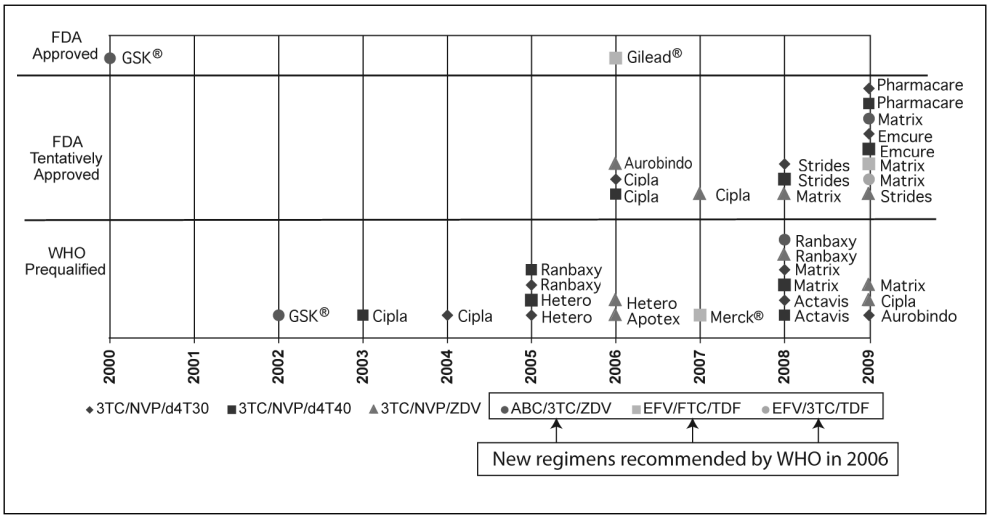


Figure 4. Timeline of WHO Prequalification Programme and US FDA approvals of first-line fixed-dose combination ARVs

Quality-assured generic FDC ARVs used in newer regimens are appearing at a much slower rate than that observed with older regimens. While 24 generic FDCs have been approved by either FDA or WHO to support older regimens recommended in 2003, only four generic FDCs have been approved to support new regimens recommended by WHO in 2006: two ABC-based FDCs no longer prioritized on 2009 WHO guidelines, and two TDF-based FDCs. Three of these were approved through the tentative FDA process and only one through WHO Prequal.

Relationships between prices of three-in-one FDC ARVs and their component medicines

Prices for older ARV regimens have decreased dramatically over the past seven years. For the 3TC, NVP, and d4T30 regimen, the median price when purchasing three generic, single-ingredient ARVs was $484/person/year in 2002 and decreased 82% by 2008 to $88/person/year when purchasing the generic FDC (Figure 5a). The ZDV-based regimen of 3TC, NVP, and ZDV exhibited the same trends with the median price for three generic, single- ingredient ARVs decreasing 71% from 564/person/year for the three generic, single-ingredient ARVs in 2003 to $161/person/year in 2008 for the generic FDC (Figure 5b).

Figure 5. Price trends for three-in-one FDCs and their component medicines.

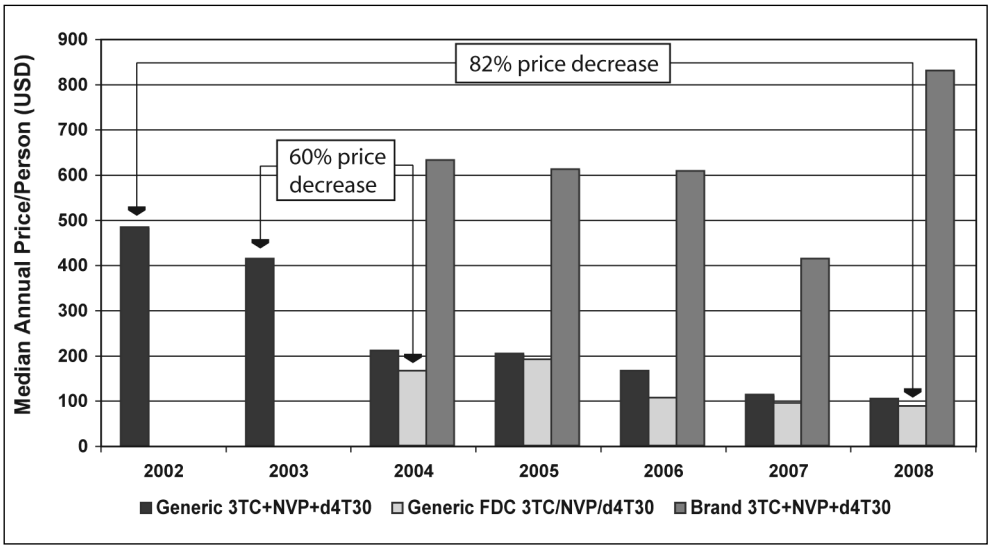
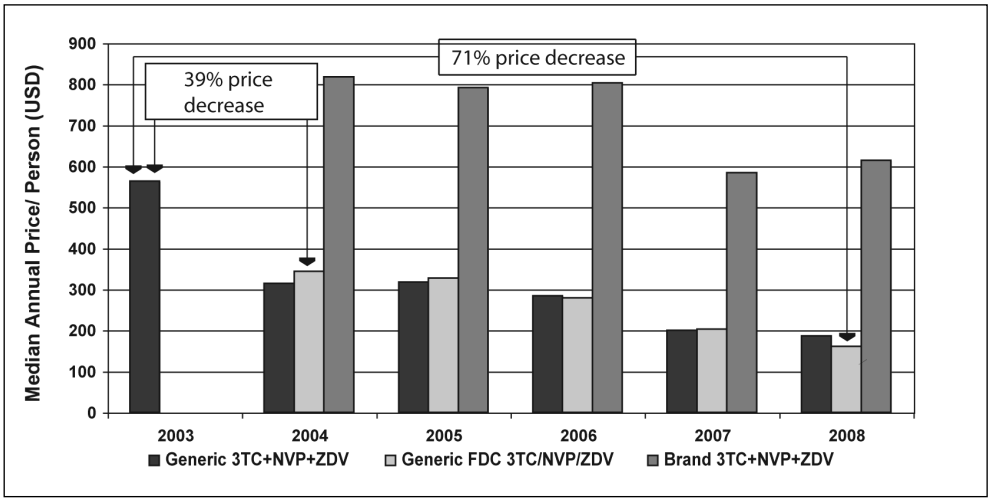


Figure 5a. Price trends for 3TC, NVP, and d4T30



5b. Price trends for 3TC, NVP, and ZDV

All regimens, including those provided through single ingredient medicines, co-packaged medicines, and FDCs, exhibit steep price reductions upon market entry of the generic FDC. Price reductions of 60%, 66% and, 39% are noted when the FDC version first appear compared to prices for three single-ingredient ARVs in the previous year for d4T-30, d4T-40, and ZDV-based regimens, respectively (Figure 5a and Table 2).

	Median Price/Person/year (25th , 75th Percentile) in USD						
	2002	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**
3TC, NVP, d4T40							
Generic NVP+3TC+d4T40	490 (486, 496)	418 (245, 489)	212 (184, 249)	209 (183, 255)	169 (150, 172)	114 (108, 130)	107 (97, 149)
Brand NVP+3TC+d4T40			640 (640, 648)	619 (619, 707)	618 (597, 746)	637 (370, 954)	897 (601, 1,219)
Generic FDC		165*	180 (143, 193)	180 (163, 214)	112 (112, 129)	83 (83, 102)	104 (80, 151)
ABC, 3TC, ZDV							
Generic ABC+3TC+ZDV			1,083 (510, 1591)	1,101 (1,039, 1,212)	794 (744, 813)	568 (525, 626)	475 (436, 587)
Brand ABC+3TC+ZDV		1,669*	1,329 (1,329, 1,363)	1,286 (1,285, 1,387)	1,282 (978, 1,354)	984 (938, 991)	702 (681, 1,064)
Brand FDC		1,652*	1,483*	1,366 (1,366, 1,489)	1,363*	883 (883, 989)	
EFV, FTC, TDF							
Generic EFV + FTC/TDF						516 (417, 536)	464 (441, 487)
Brand EFV + FTC/TDF				781*	678 (636, 769)	593 (579, 624)	619 (573, 834)
Generic FDC							485*
Brand FDC						712*	613*

Table 2 . Price trends for first-line, three-in-one FDCs and their component ARVs

**25th and 75th percentiles not calculated because n<5 purchases*

Generic prices for the three single ingredients mirror prices of FDCs after their launch. Whereas d4T-based FDCs offer consistent price discounts compared to their components, the ZDV-based FDC entered at a slightly higher price than its components but by 2008 offered savings. Prices for single-ingredient, branded ARVs consistently ranged from 2.4-9.5 times higher than prices for generic FDCs for both d4T- and ZDV-based regimens.

For newer regimens recommended by WHO in 2006, only two FDCs were purchased: ABC/3TC/ZDV and EFV/FTC/TDF. No generic version of the ABC-based FDC was purchased and prices for the branded FDC were consistently higher compared to prices for the three generic ARVs (Table 2). Similarly, the branded TDF- based FDC with EFV offers no price savings over purchasing three generic ARVs (Table 2). A generic EFV- based FDC was first reported in 2008 and its price is similar to the price of three generic ingredients.

Market dynamics for three-in-one FDC ARVs

The market dynamics of FDC versions of ARVs are indicative of market efficiency over the past several years, at least using typical measures of competition. First, there has been a large increase in the number of manufacturers. In addition, the number of purchasers and total volume purchased increased. A reduction in the market power of suppliers has likely contributed to the reduction in price, while at the same time the increases in demand have attracted new entry by generics producers.

For the 3TC/NVP/d4T30 FDC, the number of manufacturers approved by WHO or FDA increased from one to six from 2004 to 2008, while the number of manufacturers who sold this FDC to recipient countries increased from four to seven over the same time period (Figure 6a). By 2008, 55 countries were purchasing this FDC. An increase in purchase volume makes entry more attractive to new suppliers and may also facilitate economies of scale in production. Purchase volume rose dramatically from 2004 to 2008, from 89,221 to 623,336 person-years. Notable increases in purchase volume occurred for this FDC following the first FDA approval in December 2006. More striking, though, is the immediate reaction to the WHO recommendation to reduce d4T dosing from 40mg to 30mg in May 2007. Purchase volumes for the 40mg d4T-based FDC immediately dropped off (Table 3), while purchase volumes for the 30mg d4T-based FDC sharply increased (Figure 6a). As purchase volumes increased for 3TC/NVP/d4T30 FDC, the global median price decreased from $166/person/year in 2004 to $88/person/year in 2008.

Market dynamics around the 3TC/NVP/ZDV FDC are similar. From 2004 to 2008, the number of manufacturers approved by WHO or FDA increased from zero to six, while the number of manufacturers who sold the medicine to recipient countries increased from two to six (Figure 6b). Similar purchase volume increases were noted for the ZDV-based FDC which is often used in place of d4T (Figure 6b) immediately after the 2007 WHO guidance to reduce d4T dosing.

Figure 6. Market dynamics for three-in-one FDCs

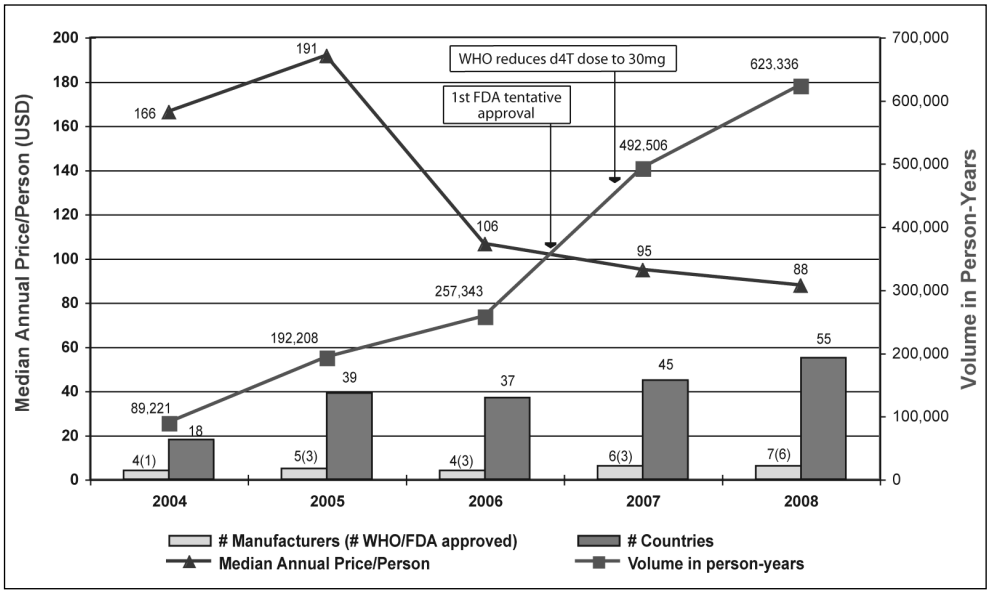
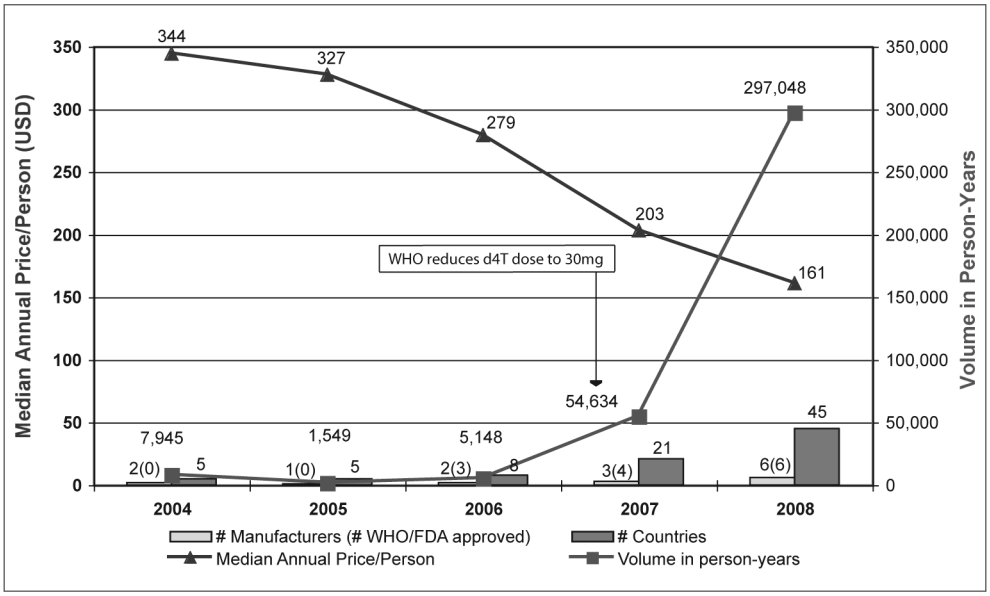


Figure 6a. Market dynamics for lamivudine/nevirapine/stavudine30 FDC



6b. Market dynamics for lamivudine/nevirapine/zidovudine FDC

Market dynamics for 3TC/NVP/d4T40 were similar to those already described except for dramatic decreases in purchase volume noted after WHO issued guidance recommending lower doses of d4t. While purchase volumes had grown to more than 100,000 person-years in 2007, they decreased to fewer than 15,000 person-years in 2008 (Table 3).

Analysis of FDC market dynamics for newer regimens reveals relatively low purchase volumes and higher prices as compared to FDCs used in older regimens. While the branded ABC/3TC/ZDV FDC was FDA-approved in 2000 (Figure 4), demand for this product has been low, peaking at fewer than 500 person-years of volume in 2007 but dropping dramatically thereafter (Table 3). The branded EFV/FTC/TDF was FDA-approved in 2006 (Figure 4), but demand for the FDC has only just started to grow, reaching 3,720 person-years of volume in 2008.

	2004	2005	2006	2007	2008
3TC/NVP/d4T40:					
# Manufacturers *	2	5	3	4	3
# Approved Manufacturers (WHO & FDA)	1	3	3	3	6
# Countries	21	38	32	21	7
Volume in person-years	55,758	126,005	114,178	103,690	14,810
Median annual price/person, USD (generic)	180	180	112	83	104
ABC/3TC/ZDV:					
# Manufacturers*	3	2	1	1	3
# Approved Manufacturers (WHO & FDA)	1	1	1	1	2
# Countries	3	6	2	3	2
Volume in person-years	61	250	106	479	129
Median annual price/person, USD (brand)	1,483	1,366	1,363	883	3,257
EFV/FTC/TDF:					
# Manufacturers*				1	3
# Approved Manufacturers (WHO & FDA)			1	2	2
# Countries				1	7
Volume in person-years				335	3,720
Median annual price/person, USD (brand)				712	613

Table 3. Market dynamics for FDC versions of 3TC/NVP/d4T40, ABC/3TC/ZDV and EFV/FTC/TDF

** # of manufacturers refers to the number of manufacturers who sold ARVs to donor recipients in a given year, as reported to either GFATM or WHO; this is NOT the total # of manufacturers in the market*

Trends in FDC market share across purchasers and manufacturers

Analysis of market share by both purchasers and the manufacturers that supply them reflects the dominant role large-scale buyers are beginning to play in the global market. PEPFAR was the first large-scale purchaser and it changed the market structure for first-line FDCs. The first FDC version of 3TC/NVP/d4T30 was only approved by the FDA tentative approval system in November 2006 (Figure 4), allowing PEPFAR to begin purchasing in 2007. For 2004-2006, therefore, GFATM was the major purchaser and the market was split across the various manufacturers chosen by the principal recipients of GFATM funds. By 2008, however, PEPFAR, represented 40% of the total market for this FDC, with purchases split across only two manufacturers (Figure 7a).

The same general trends are observed with the FDC version of 3TC/NVP/ZDV. By 2008, PEPFAR accounted for 28% of market volume for this product, with purchases split across three manufacturers, one of which accounted for 94% of PEPFAR purchases (Figure 7b). In contrast, the GFATM's disaggregated purchases for both these FDCs are split across 4-5 different manufacturers.

Figure 7. FDC Annual market trends by purchaser and manufacturer

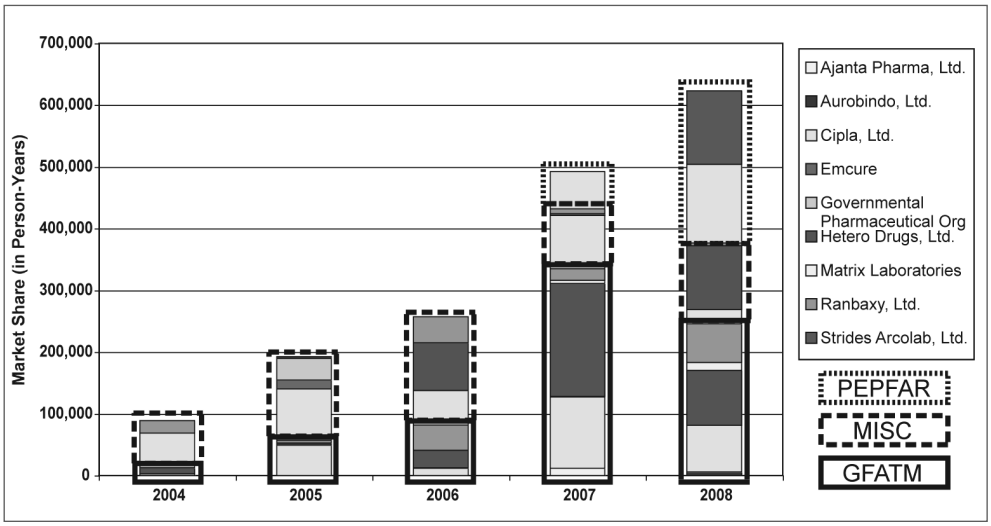


Figure 7a. Market trends for 3TC/NVP/d4T30 by purchaser and manufacturer

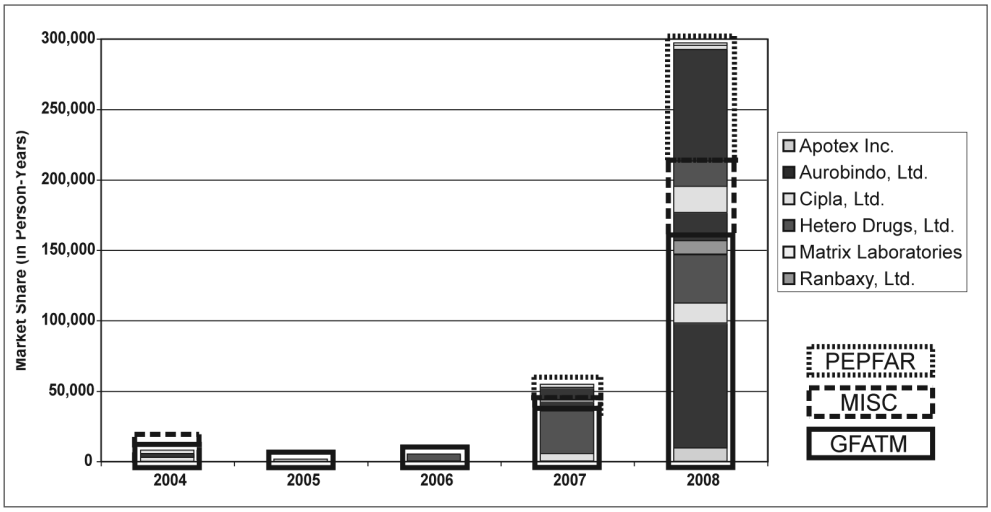


Figure 7b. Market trends for 3TC/NVP/ZDV by purchaser and manufacturer

Cross-section of 2008 market share by purchaser for all ARVs containing first-line medicines

The impact of large-scale purchasing organizations on market dynamics --both market value and market volume-- is even more pronounced in analyses on all ARVs (single-ingredient, co-packaged medicines, and FDCs) containing first-line medicines.

For newer first-line ARVs recommended by WHO (ABC, FTC and TDF), PEPFAR accounts for 9%, 42%, and 33% of market value, respectively, while UNITAID accounts for 35%, 38%, and 42%, respectively (Figure 8a). Indeed, PEPFAR and UNITAID together account for 44%, 80% and 75% of the global market for ABC, FTC and TDF, respectively, while the GFATM accounts for 41%, 8%, and 13% (Figure 8a).

Examination of purchaser market share by volume reveals similar results. For older first-line ARVs (EFV, 3TC, NVP, d4T, and ZDV), PEPFAR accounts for 27-34% of the market by volume, while the GFATM accounts for 47-57% (Figure 8b).

Figure 8. 2008 Market share across purchasers

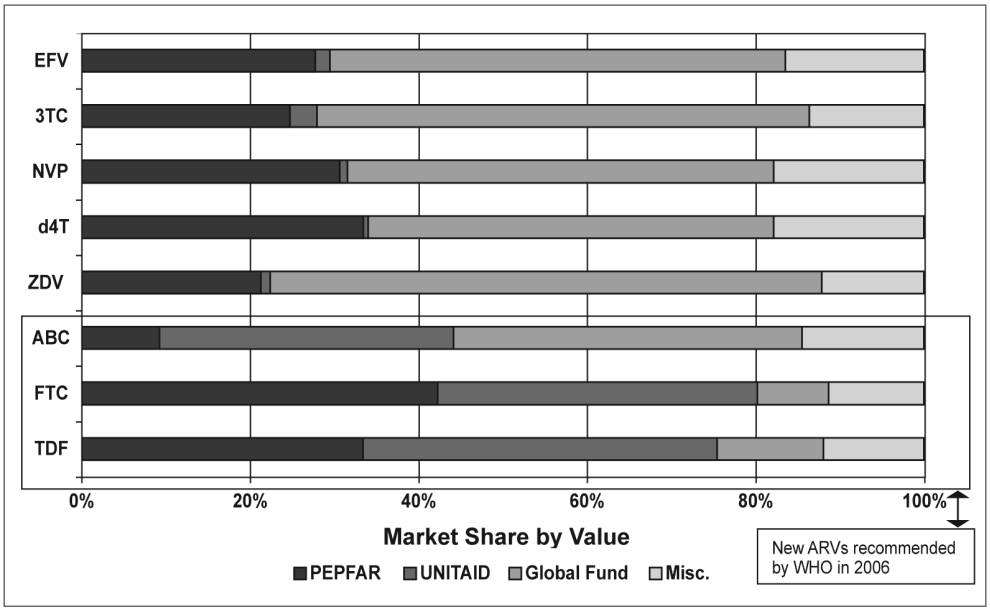


Figure 8a. 2008 Market share by value across purchasers

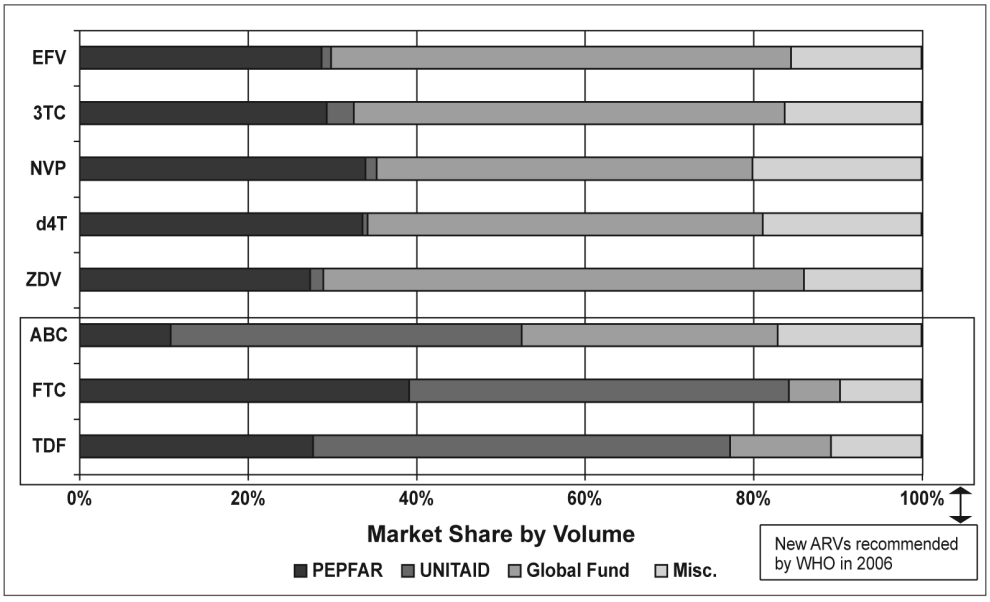


Figure 8b. 2008 Market share by volume across purchasers

For the newer first-line ARVs (ABC, FTC, and TDF), PEPFAR accounts for 11%, 39%, and 28% of market volume, respectively, while UNITAID accounts for 42%, 45%, and 49%, respectively (Figure 8b). Again, PEPFAR and UNITAID together account for 53%, 84% and 77% of the global market for ABC, FTC, and TDF, respectively, while the GFATM accounts for only 30%, 6%, and 12%, respectively (Figure 8b). It is worth noting that many of these ARVs can be used in both first- and second line regimens and that the majority of UNITAID purchases are likely used in second-line treatment. Regardless of whether these ARVs are used for first- or second-line treatment, PEPFAR and UNITAID clearly dominate the market for these products.

Discussion

Relationships between interventions and markets

The data presented here strongly suggest that the policies of donors and international organizations bear directly on the evolution of antiretroviral medicines markets in low- and middle-income countries. A number of highlights emerge in our analyses.

1. Remarkably efficient ARV markets evolved shortly after the 2002 establishment of the GFATM for the most commonly used first-line ARVs

The entry of many manufacturers producing quality- assured generic ARVs, dramatic price reductions, and the development of innovative FDCs all indicate a largely decentralized and efficient market by conventional measures. Purchase arrangements likely contributed to fierce competition among producers of older ARVs, as GFATM funding was distributed to more than 100 countries that each made independent purchase decisions. Disaggregated purchasing promoted competition for products and geographic market niches among producers. The absence of blocking patents in India, where most of the generic ARVs are produced, and efforts by importing governments to overcome patent barriers also contributed to a competitive, efficient global market for older ARVs.

2. The roles of WHO and the FDA have had mixed effects on development and uptake of new ARV formulations

Quality Certification: WHO Prequal and the FDA maintained a level playing field by assuring that producers were competing on ARVs of similar quality, and corrected information asymmetries around quality for purchasers. However, delays in quality certification can also create delays in country uptake of products, as demonstrated by the

three-year wait to use PEPFAR funds for the most commonly-used FDC (3TC/NVP/d4T). These programs must perform at optimal efficiency to support the timely maturation of global ARV markets.

Treatment Guidelines: WHO also exerted substantial leverage in dictating demand for certain ARVs through its HIV/AIDS treatment guidelines. The 2003 guidelines consolidated demand around four first-line regimens, which covered 94% of people on ART as of 2006; 80% were on regimens available as generic FDCs [33]. Such consolidation of demand created incentives for manufacturers to enter the generic ARV market and develop innovative FDC products to support these regimens. In contrast, WHO's 2006 guidelines listed more than 20 first-line regimens. This increase in treatment options, among other factors, may have created disincentives for manufacturers to develop FDCs of the newer regimens. The 2009 WHO Guidelines have now come full circle, reducing the number of recommended first-line regimens to six, which may again facilitate the consolidation of demand around a few ARVs and encourage manufacturers to produce and develop FDCs of the newly recommended regimens.

3. Newly recommended WHO ARVs are much more expensive due to patent status and/or immature generic markets, creating concern for countries' abilities to adopt new guidelines

Generics markets for newer ARV regimens have not yet matured, as demonstrated by high prices, low demand, small numbers of manufacturers, and only a few three-in-one FDCs. Of particular concern are regimens that include newer ARVs such as tenofovir, which are priced at least 3 times more than older regimens. In the absence of measures to decrease drug prices and/or increase funding, countries may be forced to choose between treating fewer people with newer and "better" regimens or treating more people with older and "less desirable" regimens.

To date, generic competition has been the only proven method to promote sustained and substantial price reduction. However, implementation of the TRIPS Agreement in developing countries means that medicines patents are becoming more widespread and severely restricting or eliminating generic competition for newer ARVs.

Such patents could severely restrict or eliminate generic competition. Least developed countries, however, have a waiver from TRIPS obligations on pharmaceutical patents and data protection until 2016.

Gilead has offered voluntary licenses to multiple firms to produce tenofovir, which has enabled competition in production. Many of these licenses include restrictions - for ex-

ample, regarding API sources and eligible export markets [34]. It is too soon to evaluate any impacts of these restrictions.

For those ARVs which are widely patented, additional interventions beyond voluntary licensing will be needed to address intellectual property barriers in both importing and exporting countries. TRIPS flexibilities such as compulsory licensing, non-observation of pharmaceutical patents (allowed for least-developed country WTO members until at least 2016), application of high standards of patentability in national law, and patent pools will be needed to promote market efficiency, reduce prices, and facilitate the use of new FDCs. Such measures have been employed with success in a growing number of countries, but still remain under-utilized relative to need [9,34]. Particularly for essential medicines such as those included in the WHO guidelines, governments, international organizations and other relevant actors should ensure that patent barriers do not stand in the way of widespread, equitable access.

4. Fixed-dose combinations may have been determinants of market prices for their component ARVs

Generic three-in-one FDCs -- strongly recommended by WHO -- were introduced in 2003 at prices much lower than the sum of their generic ARV component prices the previous year. It is possible that manufacturers priced some FDCs aggressively to gain market share and, therefore, created new benchmarks for pricing the component medicines (in addition to other factors such as volume, economies of scale, and robust competition). If so, FDCs may exert a positive influence on ARV markets, above and beyond their public health or logistical advantages.

5. Large-scale purchasing initiatives, including pooled procurement, have transformed some disaggregated markets into consolidated markets comprised of a few key purchasers and the manufacturers they choose to supply their ARVs

PEPFAR and UNITAID have increasingly used pooled procurement, whereby Western third-party organizations purchase medicines on behalf of funding recipients, pooling ARV volumes of several countries into larger, fewer transactions. In 2008, UNITAID and PEPFAR together accounted for 84% of the global market for FTC and 77% for TDF (Figure 7). Meanwhile, both PEPFAR and UNITAID have usually contracted with two or three manufacturers and awarded the majority of their purchases to one or two. The chosen manufacturers then typically dominate the market. These procurement policies may discourage other producers from incurring the costs

to develop and produce quality-assured ARVs, thereby decreasing the number of competitors in the market.

The GFATM's Voluntary Pooled Procurement (VPP) program will introduce yet another large-scale purchaser that will further consolidate the number of buyers. Whereas the original design of the GFATM placed medicine procurement in the hands of national principal recipients, VPP will encourage them to pool ARV volumes through third-party procurement. To date, third- party operators involved in VPP include the Supply Chain Management System (SCMS), which conducts pooled procurement for PEPFAR, and CHAI, which handles pooled procurement for UNITAID. If these arrangements persist, SCMS and CHAI will be purchasing on behalf of all the major donors. In this case, the market will no longer be a disaggregated and heterogeneous "open" market of more than one hundred national-level buyers, but instead will be concentrated around a few large-scale purchasers.

Pooled procurement is attractive to donor organizations and governments for a number of reasons. Some organizations may have superior information about supplier costs, the benefits of which (e.g. lower prices), can be shared with others through pooling. Pooled procurement may also reduce overall transaction costs, since fewer transactions occur. If economies of scale are very important at the transaction level, these are more likely to be realized through a few very large transactions rather than many small ones. Pooled procurement might be especially attractive to governments of smaller countries with minimal procurement capacity and limited powers to negotiate with suppliers; it might also be viewed as a solution in countries with documented corruption in procurement.

In practice, however, these benefits may not be realized. Pooled procurement requires the harmonization of registration, intellectual property policies, ARV selection, and demand forecasting across countries and organizations, which can entail substantial coordination costs. Other transaction costs are associated with financial transfers and currency fluctuations. In addition, because pooled procurement is usually handled by staff in developed countries, with higher salaries and overhead, administrative costs may not be lower. Pooled procurement may also lead to dependence by low- and middle-income countries on outside parties, detracting from efforts to strengthen country health systems and build capacity.

The ultimate goal of all these programs is to improve public health. While impossible to determine from this analysis, it is likely that the market approach that best serves public health is a mixture of several different procurement strategies as observed with earlier WHO-recommended first-line ARVs. In this scenario, the large purchasers such as PEPFAR could drive global prices lower but there was still sufficient purchase power remaining in Global Fund countries to facilitate competition among manufacturers

who did not win the larger PEPFAR contracts. A completely disaggregated market may not yield the lowest possible prices while a completely pooled market will likely reduce the number of producers in the long term.

6. For efficient ARV markets, short-term gains must be balanced with long term goals

Global health initiatives are under considerable pressure to document their impact and success. However, for organizations charged with intervening in markets, the indicators for success are not necessarily clear. Examples of short-term goals for market-based initiatives might include ARV price reduction and the development of improved formulations; however, reaching these goals is not necessarily synonymous with building efficient global ARV markets.

In addition, a focus on short-term gains may prove detrimental to market evolution in the long run. The global market is evolving towards greater concentration on the demand side, with the emergence of a few large-scale purchasers, who in turn are encouraging greater concentration on the supply side, by granting tenders to only a few dominant manufacturers. While the immediate effect of lower ARV prices obtained through initiatives such as pooled procurement is attractive, the long-term impact on market efficiency remains a concern. Generally speaking, markets with only a few buyers and suppliers are characterized by both monopoly and monopsony power, and generally function less efficiently. For example, manufacturers may try to offset the discounts they offer large- scale purchasers by increasing prices charged to countries not included in these large-purchase schemes. Demand outside of the large-purchase schemes may be too low to sustain the existing manufacturers and may discourage new ones. Markets dominated by a few manufacturers are more vulnerable to price-fixing and collusion.

7. Conventional market analysis tools may be inadequate for assessing markets and the effects of interventions on ARV markets because these markets are complex and changing rapidly

Systematically identifying market failures and assessing market competition are themselves complex tasks. In theory, perfectly competitive markets exhibit a sufficient number of suppliers and purchasers with perfect information on products; comparable product quality across suppliers; and, freedom from barriers to market entry or exit. In this theoretical scenario, resources are allocated efficiently and competition between suppliers results in lower costs [35]. In practice, however, there is no consensus on definitions or characteristics of a well-functioning market, even by the international community now committed to improving global markets as a means of increasing ac-

cess to treatment. As noted by the National Academies' Committee on the Economics of Antimalarial Drugs in 2004, "[t]here are no firm rules for judging 'good' prices, or 'healthy' competition." [36].

In addition, standard tools to assess competitive markets are inappropriate in contexts where it is crucial to have dynamic efficiency - i.e., to maintain incentives for continued innovation, quality improvements and development of new treatments. In the short run, perfect competition between suppliers that results in prices close to marginal cost creates static, not dynamic, efficiency; in this case, no supplier expects to profit from additional investment in research and development for new medicines or formulations. Sustainable prices, on the other hand, are those that exceed the marginal cost of production, allowing suppliers to earn a return on research and development investments and creating incentives for additional innovation.

A truly efficient ARV market might, therefore, offer not the lowest prices per se, but the lowest prices possible while at the same time ensuring continued innovation of quality products in optimum formulations. Price is undeniably an important factor in access, and lower prices enable greater access for the same level of funding. However, a narrow focus on price alone may drive prices to lowest acceptable levels for manufacturers and leave no additional funds to invest in the development of pediatric formulations, FDCs, heat-stable ARVs, and other formulation improvements. Driving prices too low could also create disincentives for manufacturers to enter or remain in the market, especially smaller manufacturers who are unable to shift costs across multiple product lines. Lastly, a focus on price without consideration for supplier performance (e.g., ability to provide the desired amount of medicines in a timely manner, may result in lower prices but increased stock-outs due to sub-par distribution services. Similarly, effective quality assurance systems must be in place in order for ARV markets to deliver the desired health outcomes.

Limitations and areas for further research

This study provides a comprehensive overview of global policies and ARV market trends suggesting certain causal relationships, but our descriptive methods cannot ascertain causality or pinpoint the impact of a given intervention on the market. We limit this paper to relationships between a few global initiatives and market trends and do not incorporate the potential market impact of many other key players, including HIV/AIDS activists, civil society organizations, national governments, foundations, and other international organizations. In addition, our data does not capture 100% of the market but rather include only ARV procurements reported to GFATM and WHO, the majority of which are funded by GFATM, PEPFAR, and UNITAID. A few larger,

middle-income countries – notably Brazil, South Africa, and Thailand (accounting for 26% of people on ART in the developing world [1]) - purchase large amounts of ARVs with a mix of national and international funds, and do not report their national purchases to the GFATM or WHO. Based on publicly- available information, we estimate that our data capture 27% of purchases from Brazil, South Africa, and Thailand and therefore represent the vast majority of ARV purchases in developing countries. Ideally we would incorporate national ARV purchase data to better understand the important roles these countries play in shaping the global ARV market. For example, some have suggested that Brazil's purchase of active principle ingredients (APIs) and domestic production of ARVs facilitated competition and price reduction for both APIs and ARVs in donor-funded markets [9]. To understand these impacts more clearly, we would need additional purchase data for both APIs and ARVs in these key countries; we encourage national governments to provide their purchase data to the WHO Global Price Reporting Mechanism in order to enable improved understanding of and policy interventions in global ARV markets.

We furthermore recognize certain limitations with regards to the quality and reliability of source data. The ARV transactional data, in particular, required substantive cleaning. While we believe we have done due diligence by scrutinizing, systematically cleaning, and validating every transaction, some reporting errors may still exist.

In addition, we note the disappearance of historical transactional data that had previously been posted by WHO and GFATM. For this paper, we used 2002-2008 purchases downloaded from the WHO and GFATM on 1 June, 2009 and 1 September, 2009, respectively; but observed that some historical transactions we were able to download on earlier dates were not present in the downloaded data we used for this paper. Similarly, we noted differences in dates and ARVs listed on various updates of FDA approval and WHO Prequal lists and use information downloaded from these two organizations on 3 January, 2010.

Due to the absence of comprehensive, reliable, publicly- available data on patents and other intellectual property barriers in many low- and middle-income countries, we were unable to include this information in our analyses. We recognize the importance of national policies and registrations in market evolution, but had no access to this information. We lacked access to market intelligence for active principle ingredients, intermediates, and production costs; we also have no information on the use of wholesale procurement agencies. In the discussion section we hypothesize about aggressive pricing and incentives/disincentives for development of FDCs by manufacturers, but we did not conduct interviews with manufacturers to confirm our speculations.

Despite these limitations, our research provides valuable insight for those working to promote market efficiency in order to increase access to ARVs. This paper lays out the first logical steps toward better understanding the many ways that initiatives of international organizations affect ARV markets, and can be used to inform basic monitoring and evaluation systems of those organizations involved with market dynamics. Many organizations now routinely compile market intelligence data, but it needs to be made publicly available in reliable, synchronized and ready-to-use formats to support day-to-day procurement, decision making, and evaluation of interventions.

Lastly, we note the need to follow this work with research using predictive and econometric methods to build a more solid evidence base for policy making. That said, isolating the impact of a single intervention amidst the ever-changing and crowded landscape of a global market may not be possible and/or may require adaptation or development of new research methods.

Finally, any gains in market efficiency and access to ARVs must ultimately be linked to health outcomes to ensure that the overarching public health goals are achieved. This paper examines relationships between global policies and market dynamics but additional research is needed to better understand relationships between these types of policies and health outcomes (e.g., resistance, treatment failure, progression to second- and third-line regimens).

Conclusion

Rapid scale-up in access to ART from 2003-2008 was facilitated by global policies and initiatives that resulted in a fairly efficient global marketplace for older ARVs. However, due to a range of factors, markets for the newly recommended ARVs have been slower to deliver the price reductions and improved formulations seen in the past. WHO Guidelines heavily shape demand, and their relative complexity may help or hinder the achievement of economies of scale in pharmaceutical manufacturing. Certification programs assure ARV quality but can also delay uptake of new formulations. Donor procurement policies, including pooled procurement, may alter ARV market structure by reducing the number of buyers and sellers, rendering the market less competitive in the longer-term and requiring careful monitoring. Improved understanding of ARV markets is required in order to ensure that interventions have their intended impact, i.e. to provide quality-assured ARVs in acceptable formulations at sustainable prices. Global consensus is needed on the ultimate goals of market-based interventions to ensure that short-term gains do not result in detrimental long-term market effects. This will involve clarifying and agreeing on definitions of market efficiency, indicators to monitor market

evolution, and methodologies to identify market failures and assess market impacts of policy interventions.

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Chapter 4.2

The global pediatric antiretroviral market: analyses of product availability and utilization reveal challenges for development of pediatric formulations and HIV/AIDS treatment in children

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Abstract

Background

Important advances in the development and production of quality-certified pediatric antiretroviral (ARV) formulations have recently been made despite significant market disincentives for manufacturers. This progress resulted from lobbying and innovative interventions from HIV/AIDS activists, civil society organizations, and international organizations. Research on uptake and dispersion of these improved products across countries and international organizations has not been conducted but is needed to inform next steps towards improving child health.

Methods

We used information from the World Health Organization Prequalification Programme and the United States Food and Drug Administration to describe trends in quality-certification of pediatric formulations and used 7,989 donor-funded, pediatric ARV purchase transactions from 2002-2009 to measure uptake and dispersion of new pediatric ARV formulations across countries and programs. Prices for new pediatric ARV formulations were compared to alternative dosage forms.

Results

Fewer ARV options exist for HIV/AIDS treatment in children than adults. Before 2005, most pediatric ARVs were produced by innovator companies in single-component solid and liquid forms. Five 2-in1 and four 3-in-1 generic pediatric fixed-dose combinations (FDCs) in solid and dispersible forms have been quality-certified since 2005. Most (67%) of these were produced by one quality-certified manufacturer. Uptake of new pediatric FDCs outside of UNITAID is low. UNITAID accounted for 97-100% of 2008-2009 market volume. In total, 33 and 34 countries reported solid or dispersible FDC purchases in 2008 and 2009, respectively, but most purchases were made through UNITAID. Only three Global Fund country recipients reported purchase of these FDCs in 2008. Prices for pediatric FDCs were considerably lower than liquids but typically higher than half of an adult FDC.

Conclusion

Pediatric ARV markets are more fragile than adult markets. Ensuring a long-term supply of quality, well-adapted ARVs for children requires ongoing monitoring and improved understanding of global pediatric markets, including country-based research to explain and address low uptake of new, improved formulations. Continued innovation

in pediatric ARV development may be threatened by outdated procurement practices failing to connect clinicians making prescribing decisions, supply chain staff dealing with logistics, donors, international organizations, and pharmaceutical manufacturers. Perceptions of global demand must be better informed by accurate estimates of actual country-level demand.

Background

Accessing quality treatment and care remains an uphill battle for families of children living with HIV/AIDS in resource-poor settings. For many years, the lack of easy-to- use pediatric formulations for some antiretroviral (ARV) medicines and the high costs of others hindered efforts to deliver medical care to this vulnerable population [1].

From an industry perspective, the disincentives to develop and produce pediatric ARVs are numerous and powerful. Pediatric ARV markets are always smaller and less attractive than adult markets. In the United States and Europe, HIV infections in infants and young children have been nearly eliminated [2], leaving little demand for pediatric ARV formulations in these markets.

In order to develop new pediatric dosage forms for use in developing countries with larger pediatric ARV demand, additional research must first be conducted in children, including costly clinical trials, bioequivalence, bioavailability, dose-ranging, and pharmacokinetic studies [3,4]. The implementation of comprehensive services to prevent mother-to-child transmission (PMTCT) of HIV remains low in many countries [5]; however, if recent initiatives to reduce vertical HIV transmission are successful [6], pediatric antiretroviral demand will further diminish, reducing any returns on investment for developing pediatric ARVs. After development, the per-unit production costs of pediatric ARVs are likely high because small quantities impede the realization of economies of scale in production and distribution [3].

Further compounding these disincentives are the innate complexities of pediatric formulation markets. Numerous products are needed in varying strengths to accommodate changing doses as children grow, which fragments the pediatric market for a given ARV into even smaller niches. Moreover, as children move through infancy, toddler, and childhood stages, the optimal dosage form changes as well. Liquids (syrups, suspensions, and solutions) are needed to treat infants but pose logistical challenges: many need refrigeration and, because of large bottle sizes and heavy weight, are difficult for families to carry home. In low resource settings, measuring and delivering the correct liquid doses can also be challenging. Powders and dispersible tablets that can be mixed with

water are an option, but they require access to clean water and often have unpleasant tastes that are unacceptable to infants. As children get older and the necessary volumes of liquid ARVs become too large, they require other products, such as chewable tablets and sprinkles, until they reach an age when they can swallow solid tablets [7].

Despite these market disincentives for pharmaceutical manufacturers, fortunately, important advances have recently been made in the development and production of pediatric ARV formulations quality-certified by the World Health Organization (WHO) Prequalification Progamme [8], the United States (US) Food and Drug Administration (FDA) [9,10], or other stringent regulatory authorities. This progress can be credited to persistent lobbying and innovative interventions from HIV/AIDS activists, civil society organizations, and international organizations.

Médecins Sans Frontières, for example, has consistently drawn attention to the particularly glaring neglect of children in HIV/AIDS treatment programs and suggested that the lack of child-friendly versions of ARVs contributes to high rates of HIV/AIDS deaths in children under two years of age [11,12]. In November 2004, the United Nations Children's Fund (UNICEF) and WHO held a technical consultation on improving access to appropriate pediatric ARV formulations during which experts identified missing pediatric formulations considered to be high priority and discussed ways to galvanize pharmaceutical companies to produce them [7]. Shortly thereafter, two global initiatives were launched. Unite for Children, Unite Against AIDS, was begun by UNAIDS, UNICEF, and others in 2005 as a platform for all partners engaged in pediatric HIV/AIDS programs [13]. The first WHO Model List of Essential Medicines for Children was released in 2007 [14] and Make medicines child size, led by WHO, was launched in late 2007 to raise awareness and improve access to medicines that are safe for children under age 12 [15].

On the implementation side, both the United States' President's Emergency Plan for AIDS Relief (PEPFAR)[16] and UNITAID[17] made commitments to prioritize the needs of children. The Clinton Health Access Initiative (CHAI) [18] and the Supply Chain Management System (SCMS) [19] conduct large-scale purchasing on behalf of UNITAID and PEPFAR, respectively. Given the substantial overlap of funding in some countries by UNITAID, the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM) [20], and PEPFAR, agreements were made with countries and major donors that UNITAID would initially be the primary source of funding for pediatric ARVs (D Jamieson, SCMS, personal communication) in those countries. Such coordination allows for optimization of resources and avoidance of service duplication. In countries where UNITAID and PEPFAR are not active, GFATM-supported HIV/AIDS programs procure their ARVs independently.

The will of these international organizations to invest in pediatric antiretroviral therapy (ART) created incentives for producers to enter the market, as manufacturers could be relatively certain of a minimum volume of purchases from reliable clients [21,22]. The ensuing scale-up of ARV delivery to children in developing countries then progressed dramatically. Whereas only 10% of children in need were being treated in 2005, 38% were receiving ART by the end of 2008 [5]. However, despite these advances in product development and treatment coverage, the literature suggests that retaining children in HIV/AIDS programs remains problematic [23,24]. In 2009 the Clinton Foundation reported infant losses to follow-up of 32% (in Cameroon) and 53% (in an eight-country meta-analysis) [25].

Clearly, critical challenges remain. Three out of five children needing ART are not receiving it [5]. A preliminary examination of ARV purchase data suggests that many countries are not yet using new, improved pediatric formulations [26,27]. Finally, there are a number of ARVs for which appropriate pediatric formulations are still not available. According to Médecins Sans Frontières, appropriate pediatric formulations are still lacking for a range of important ARVs, including efavirenz, darunavir and other ritonavir-boosted protease inhibitors (in addition to lopinavir/ritonavir) [28].

Most pediatric fixed-dose combinations (FDCs) developed to date have included stavudine and zidovudine. Aside from low demand, few barriers existed for the development of these products. A substantial amount of research had already been conducted on these ARVs in children, patents were generally absent or unenforced [29], and manufacturers had lots of experience producing adult versions. In contrast, for newer ARVs, little research has been conducted in children, patent barriers are more widespread, and manufacturers have less experience producing adult FDCs containing these ARVs. To ensure that companies develop pediatric versions of these medicines, a better understanding is needed of both the supply and the demand side of the pediatric ARV market. However, to date, no research has been published on the characteristics or the evolution of this market.

In order to fill this knowledge gap, this paper examines trends in the availability of WHO-recommended ARVs in quality-certified pediatric formulations, and describes the rate and extent of product uptake across developing countries and among international donors to guide next steps towards improving child health.

Methods

We utilized an ARVmarket intelligence database comprised of data from multiple sources, including product approvals by the US FDA [9,10] and certifications by the WHO Prequalification Progamme [8]. This database is described in more detail elsewhere [30-32]. Into it we merged 2009 transactional data of donor-funded ARV purchases provided directly to researchers by the Clinton Health Access Initiative (CHAI) [18] on behalf of UNITAID [17] and the Supply Chain Management System (SCMS) [19] on behalf of PEPFAR [16] as well as publicly posted transactions in the WHO Global Price Reporting Mechanism [27] and the GFATM Price Quality Report [26] from 2002-2009. Information and algorithms in the market intelligence database were used to clean and validate ARV transactional data, which was then limited to purchases made for ARV formulations predominantly used in children (Figure 1).

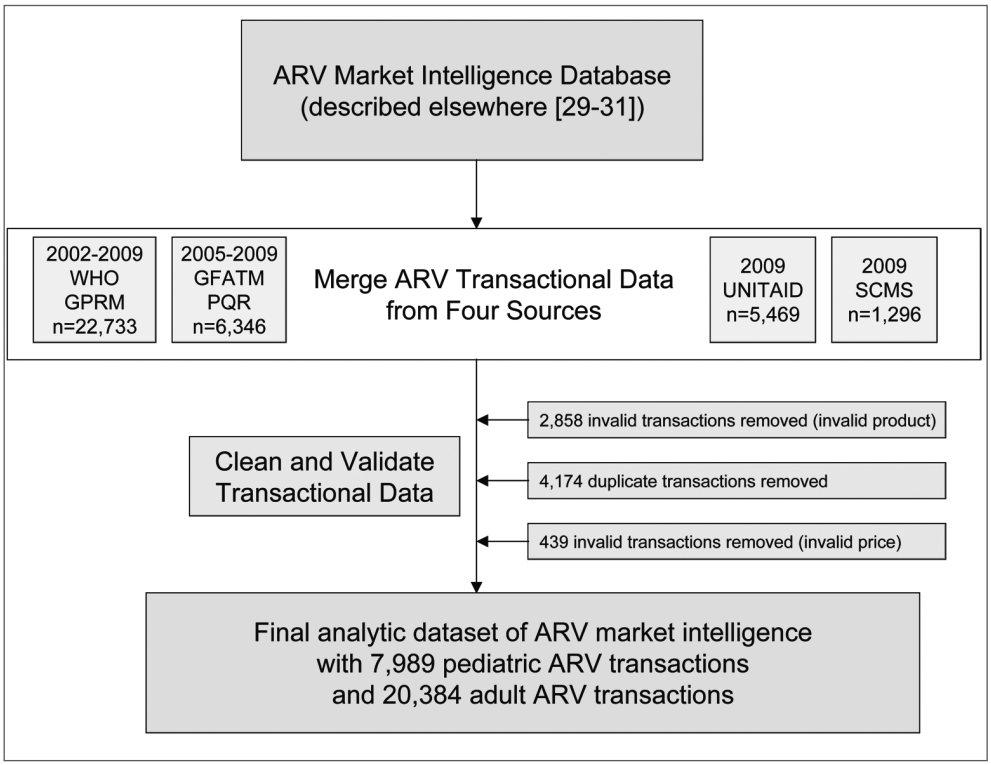

Figure 1. Data overview

We examined trends in quality-certification of pediatric ARVs by WHO [8] and the FDA [9,10] in relation to treatment regimens recommended by WHO for infants and children [33,34]. We also described purchase trends for pediatric ARV formulations (liquid, solid, dispersible), including numbers of purchasing countries, from 2004 to 2009. A solid product is defined as a medicine intended to be swallowed, while a dispersible ARV tablet dissolves when placed in a small amount of water. Liquids are syrups, solutions and suspensions. We differentiate single-component ARVs from FDC dosage forms with the labels "single" and "FDC". We describe FDC products using a "/" between ARVs included in a given FDC and use the terms brand and innovator interchangeably to denote the initial developer of a medicine.

We calculated trends in purchaser (GFATM, SCMS, UNITAID) market share by value for brand and generic pediatric dosage forms from 2002 to 2009. For FDC versions of pediatric ARVs, we provided percent purchaser market share by volume for 2008 and 2009.

Price comparisons of ARV dosage forms (pediatric FDC, liquid, and adult FDC) were calculated using prices paid by CHAI/UNITAID based upon WHO- recommended doses [33,34] and presented as price per person per year in United States dollars (USD). All ARV prices provided by GFATM, WHO, CHAI, and SCMS in USD were adjusted to the January-December 2009 time period using the annual US Consumer Price Index [35].

Results

Priority pediatric ARVs: WHO recommendations, production and purchase trends

In 2007, the WHO Paediatric Antiretroviral Working Group identified a total of 40 priority pediatric ARV products (19 urgent, 10 high, and 11 important) for pediatric HIV/AIDS treatment (Table 1) [33]. Only 17 of the 40 pediatric ARV products were categorized by WHO as "ideal" dosage forms. Sixteen of the 40 recommended ARV products were actually produced and purchased by countries for pediatric HIV/AIDS treatment. Some new pediatric products originally produced and purchased are no longer in demand because subsequent changes in dosing guidelines meant the new formulations no longer matched the revised dosing recommendations. In 2009, the WHO Expert Committee on the Selection and Use of Essential Medicines revised the list of priority pediatric ARVs to include 17 of the 18 ARVs originally categorized as ideal in 2007 (Table 1) plus one new formulation (ABC60/NVP50/ZDV60) and one new ARV (atazanavir) [36].

Pediatric ARV Dosage Form	2007 WHO Recommendation	Ideal Dosage Form	Produced and purchased	2009 WHO Recommendation
3TC30/NVP50/ZDV60	Urgent	yes	yes	yes
3TC30/NVP60/ZDV60	Urgent			
3TC75/NVP100/ZDV150	Urgent			
3TC30/ZDV60	Urgent	yes	yes	yes
3TC75/ZDV150	Urgent			
3TC30/d4T6	Urgent	yes	yes	yes
3TC75/d4T15	Urgent			
3TC30/NVP50/d4T6	Urgent	yes	yes	yes
3TC20/NVP35/d4T5	Urgent		yes	
3TC30/NVP50/d4T7	Urgent			
3TC60/NVP100/d4T12	Urgent		yes	
3TC40/NVP70/d4T10	Urgent		yes	
NVP 50	Urgent	yes		yes
NVP 100	Urgent			
LPV100/r25	Urgent	yes	yes	yes
LPV90/r22.5	Urgent			
ABC 60	Urgent	yes	yes	yes
ABC 120	Urgent			
ABC 150	Urgent			
EFV 100	High	yes	yes	yes
EFV 600	High		yes	
ABC60/3TC30	High	yes	yes	yes
ABC150/3TC75	High			
ZDV 60	High	yes		yes
ZDV 100	High		yes	
ABC60/3TC30/ZDV60	High	yes		yes
ABC150/3TC75/ZDV150	High			
d4T 6	High	yes		yes
d4T 15	High			
ddI 125	Important		yes	
ddI 200	Important		yes	
3TC 30	Important	yes		yes
3TC 75	Important			
3TC 150	Important		yes	
EFV100/FTC35	Important	yes		yes
FTC 35	Important	yes		yes
RTV 25	Important	yes		yes
RTV 100	Important			
FPV*	Important	yes		yes
DRV*	Important			
ABC60/NVP50/ZDV60				yes
ATV*				yes

Table 1. Priority pediatric ARV formulations

**dose to be determined*

Overview of FDA-approved and WHO-prequalified pediatric ARVs

Prior to 2002, 23 of 24 (96%) FDA-approved pediatric formulations were produced by innovator companies (Figure 2), reflecting demand from patent-protected markets in the US and Europe. The establishment of the GFATM in 2002 created instantaneous demand for affordable ARVs in developing countries, many of which overcame intellectual property barriers to purchase low- cost generic medicines [29]. Eighteen pediatric ARVs (14 innovator and four generic) were certified by WHO in 2002, the first year of the program, but only three formulations were pre-qualified in the following three years.

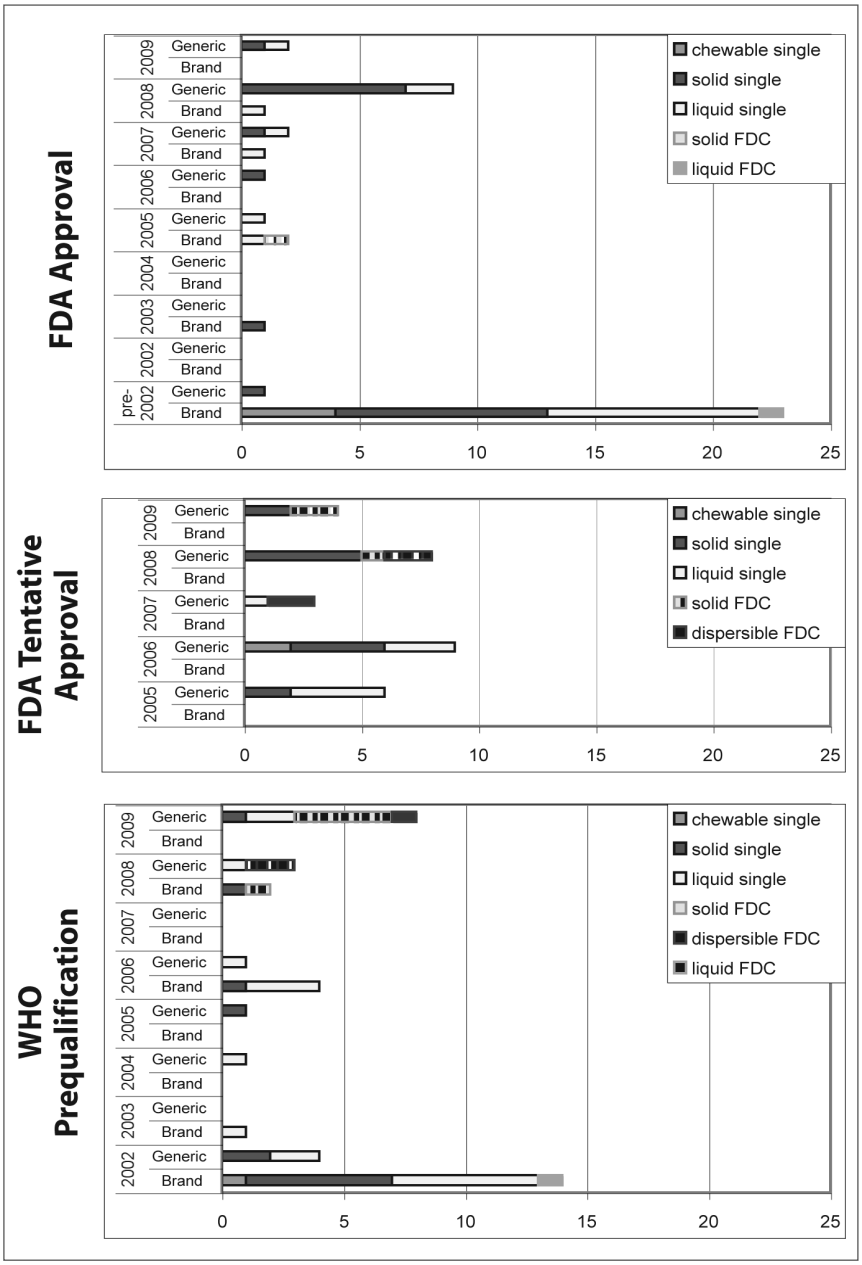

Figure 2. Trends in innovator and generic pediatric ARV formulations certified by WHO and FDA*

**Includes all pediatric ARV approvals for all manufacturers; overlap between FDA approval and WHO prequalification exists as some products are certified by both organizations*

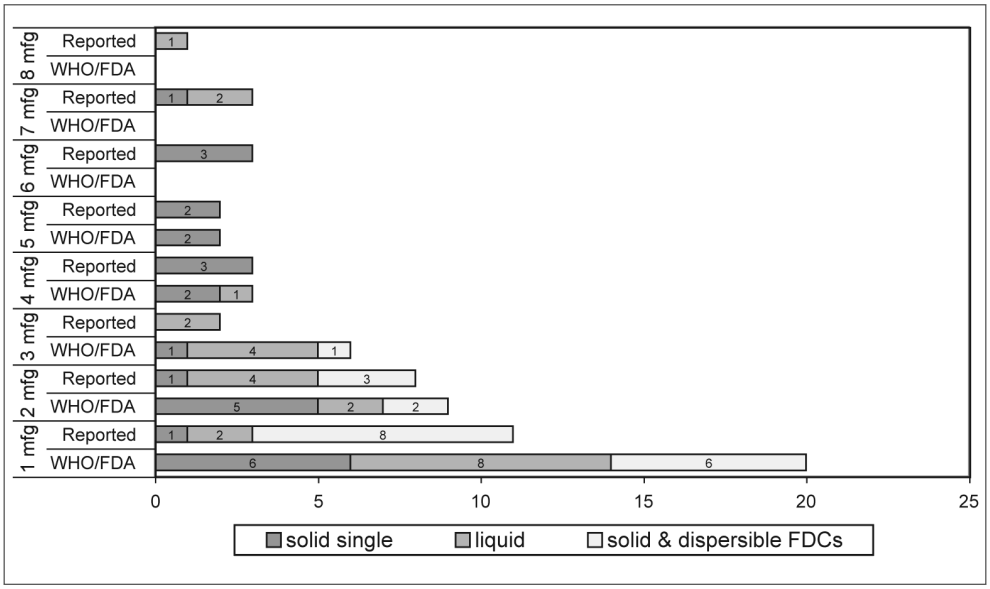

Figure 3. Number of manufacturers certified and reported to supply each pediatric ARV

Over the entire time period a total of 113 ARV formulations produced by eight innovator and eight generic manufacturers were certified. Most innovator ARVs were approved before 2005 and most generic ARVs were approved in 2005 or later. Examination of all certifications by dosage form reveals 44 liquid, 55 solid, seven chewable, and seven dispersible products. All dispersible products were generic and certified in 2007 or later.

For the majority of pediatric FDCs, only one manufacturer is quality-certified by either the WHO or the FDA. Six of nine (67%) solid and dispersible FDCs are produced by only one quality-certified manufacturer (Figure 3). Similar patterns exist for other pediatric ARV dosage forms with six solid single-component ARVs and eight liquid ARVs supplied by only one quality-certified producer.

Among pediatric ARVs purchased and reported (both quality-certified and non-quality certified), eight solid and dispersible FDCs were supplied by only one manufacturer (Figure 3). Many single component solid ARVs and liquid ARVs, however, were supplied by two or more manufacturers.

The 2002 WHO first-line treatment guidelines for infants and children included five ARVs and three regimens [37] (Table 2). In 2006, the WHO revised their guidelines to include six ARVs and six preferred first-line regimens [34]. Approximately 68% of all WHO and FDA product certifications were for ARVs recommended by WHO in

first-line regimens. Four and six preferred second-line regimens, all of which contain didanosine and a protease inhibitor, were listed on WHO 2002 and 2006 guidelines, respectively. A 2008 guidance by WHO listed three first-line regimens as well as three regimens for infants exposed to certain ARVs

Year of WHO Guideline	First-Line Regimen	Second-Line Regimen
2002	ZDV + 3TC + ABC	d4T + ddI + PI* or d4T + ddI + (EFV or NVP)
	ZDV + 3TC + (NVP or EFV)	d4T + ddI + PI*
2006 Preferred	(ZDV or d4T) + 3TC + (NVP or EFV)	ddI + ABC + PI**
	ABC + 3TC + (NVP or EFV)	ddI + ZDV + PI**
2006 Alternative	(ZDV or d4T) + 3TC + ABC	ddI + (EFV or NVP) +PI**
2008***	(ZDV or d4T or ABC) + 3TC + NVP	
	(ZDV or d4T or ABC) + 3TC + LPV/r	

Table 2. WHO-recommended regimens for infants and children

**PI options include LPV/r and NFV*
***PI options include LPV/r, SQV/r, and NFV*
****Infants <12 months of age*

Because limited research has been conducted in children with HIV/AIDS, fewer ARV treatment options exist for infant and children as compared to adults. This lack of pediatric research is particularly relevant for newer ARVs. Whereas tenofovir is now recommended by the WHO for first-line treatment of adolescents and adults [38,39] and is being widely adopted by countries, tenofovir is not recommended for use in infants and children due to insufficient research on safety and toxicity [34].

Because of interactions between nevirapine and rifampicin (anti-tuberculosis medicine), the WHO recommends use of efavirenz in place of nevirapine for HIV/AIDS in adults with tuberculosis co-infection [38]; however no data is available on safety and efficacy of efavirenz in children under three years of age [34].

Pediatric HIV/AIDS treatment options are further reduced if newborns were exposed to single dose nevirapine for PMTCT or maternal non-nucleoside reverse transcriptase inhibitor (NNRTI) therapy. When protease-inhibitors are used for first-line treatment in infants with NVP and/or NNRTI maternal exposure, infants and children are left with few ARV options for second-line treatment [40]. Whereas boosted darunavir, etravirine, and raltegravir are potential options in adults who fail protease inhibitor regimens [39], none of these options are available in pediatric formulations and little research on use of these ARVs in children has been conducted.

Only one pediatric ARV FDC (LPV/r) existed before the establishment of the GFATM and it was only available in a liquid form requiring refrigeration. The first pediatric 3-in-1 FDC to accommodate WHO-recommended first line regimens was quality-certified in 2007 (Table 3), lagging four years behind the first adult version.

Since 2005, a total of five 2-in-1 pediatric FDCs and four 3-in-1 pediatric FDCs had been FDA-approved and/or WHO-prequalified. Eight of these nine (89%) FDCs support first-line regimens. The first pediatric heat-stable, ritonavir-boosted protease inhibitor (LPV/r) was certified in 2005 and remains the only FDC available to support second-line treatment in children. The first dispersible tablets were approved in 2005 with five FDCs available by the end of 2009.

	2000	2005	2007	2008	2009
2-in-1 FDCs					
ABC60/3TC30				solid	
3TC30/d4T6				dispersible	
3TC60/D4T12				dispersible	
3TC30/ZDV60					solid
LPV100/RTV25		solid			
LPV80/RTV20 per ml	liquid				
3-in-1 FDCs					
ABC60/3TC30/ZDV60					solid
3TC30/NVP50/d4T6			dispersible		
3TC60/NVP100/d4T12			dispersible		
3TC30/NVP50/ZDV60					dispersible

Table 3. Initial quality certification of FDC pediatric ARVs*

**recommended on 2006 WHO pediatric HIV/AIDS treatment guidelines*

Purchase trends and market share for pediatric ARVs

Few countries purchased pediatric ARVs before 2004. The number of countries purchasing liquid and solid single-component pediatric ARVs increased steadily from 43 and 26, respectively in 2004 to 85 and 64, respectively in 2008 (Figure 4). These liquid and solid single-component products were reported by large numbers of countries across GFATM, UNITAID, and miscellaneous categories.

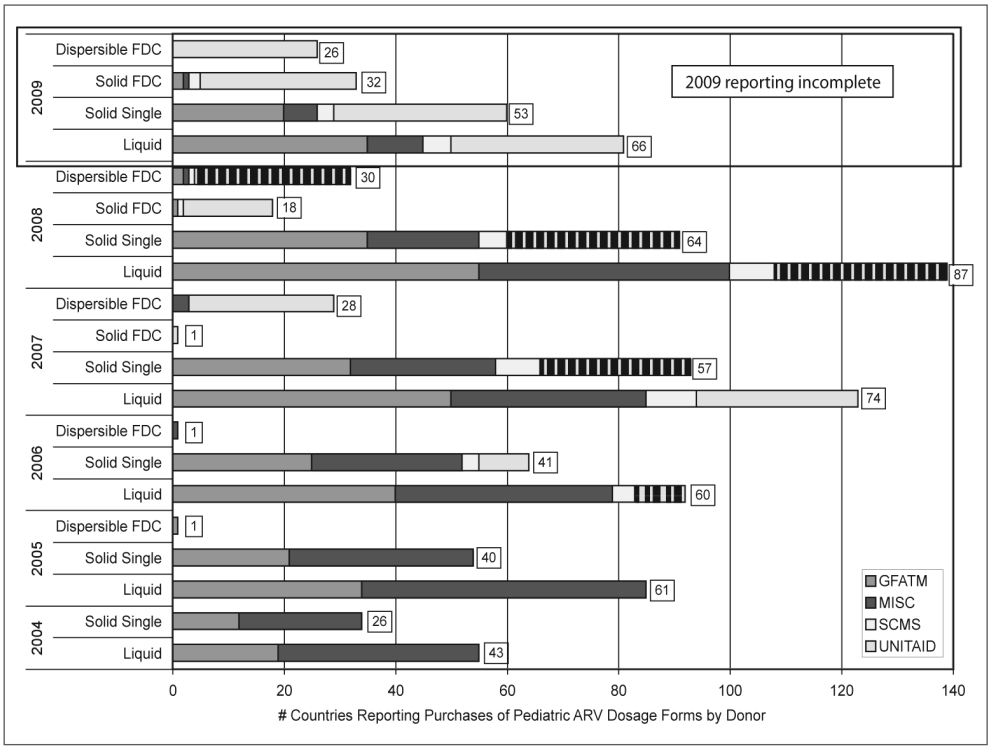

Figure 4. Country pediatric ARV purchase trends, by purchaser, 2004-2009*

**total number of unique countries purchasing ARV dosage form is indicated in text boxes (some overlap of countries across some donor programs)*

A total of 33 and 34 countries reported either solid or dispersible pediatric FDC purchases in 2008 and 2009, respectively. Pediatric FDC purchases, however, have been largely limited to countries supported by UNITAID, with 29 and 31 countries reporting FDC purchases (solid and dispersible) in 2008 and 2009, respectively. Only three GFATM countries reported pediatric FDC ARV purchases in 2008, while SCMS reported pediatric FDC purchases for only two countries in 2008 and 2009.

Looking more closely at purchase trends for different FDC dosage forms, purchases for dispersible FDCs were first reported in 2005 but increased sharply in 2007 with 28 countries reporting purchase transactions. UNITAID accounted for 26 of the 28 (93%) countries reporting dispersible FDC purchases. This trend continues through 2009 when UNITAD reported dispersible FDC purchases in 26 countries and no other purchases were reported outside of UNITAID.

Similar purchase trends are noted for solid pediatric FDCs whereby UNITAID reported purchase transactions for 16 and 28 countries in 2008 and 2009, respectively, while very few countries outside of UNITAID reported solid FDC transactions.

The total donor-funded pediatric ARV market increased from approximately US $5 million in 2004 to $34 million in 2008, with total 2009 purchases likely to be more than $40 million once reporting is complete (Figure 5). While the pediatric ARV market has grown rapidly, its current size is a small fraction of the US $500 million reported thus far in 2009 for adult ARV solid dosage forms.

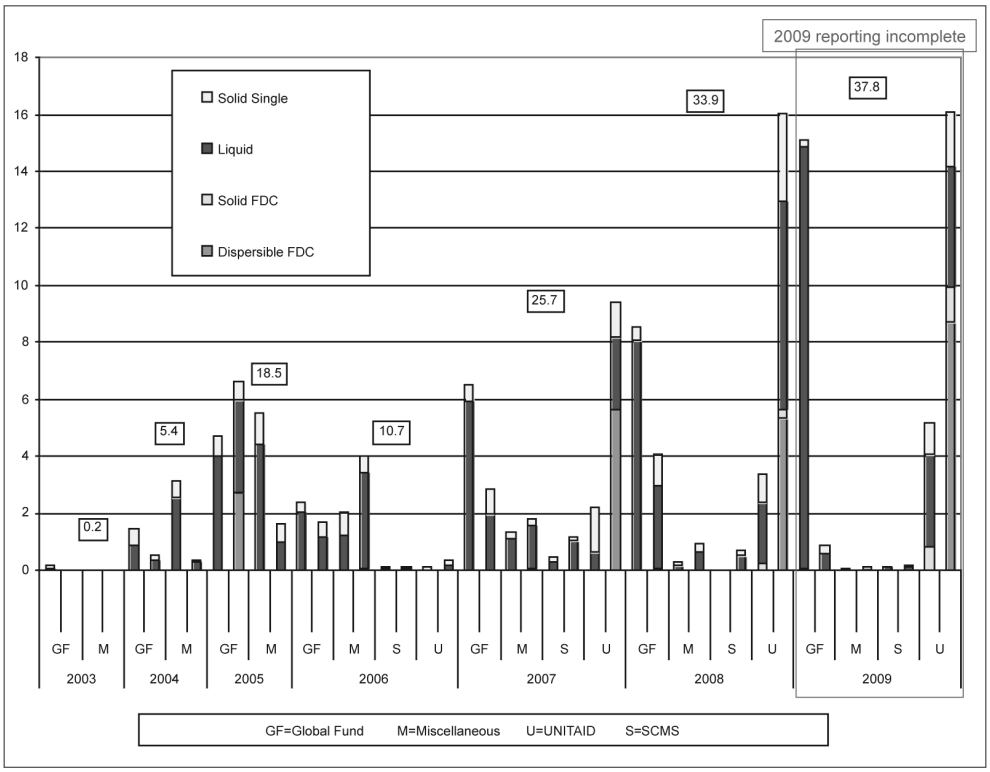

Figure 5. Pediatric ARV market trends (value), 2003-2009

From 2007 to 2009 UNITAID accounted for 62-93% of generic purchases, while the GFATM accounted for 62-74% of all innovator purchases. Careful examination of 2009 GFATM brand purchases reveals that the Russian Federation and South Africa account for 80% and 14% of all GFATM branded spending, respectively, and 59% and 10% of branded spending, respectively, of all donor purchases. The Russian Federation purchased five branded liquids (ZDV, NVP, 3TC, ddI, ABC) and South Africa purchased one branded liquid (LPV/r). The remaining GFATM countries account for only 6% of 2009 GFATM branded ARV purchases.

Further examination quantifies the low uptake of dispersible and solid pediatric FDCs outside of UNITAID. In 2008, UNITAID accounted for 100% of market volume for five of eight FDCs and 97-99% of market volume for the remaining three FDCs (Figure 6a). UNITAID held similar pediatric FDC market dominance in 2009 (Figure 6b).

Figure 6. Purchaser market share (volume) for solid & dispersible pediatric FDCs, 2008 and 2009

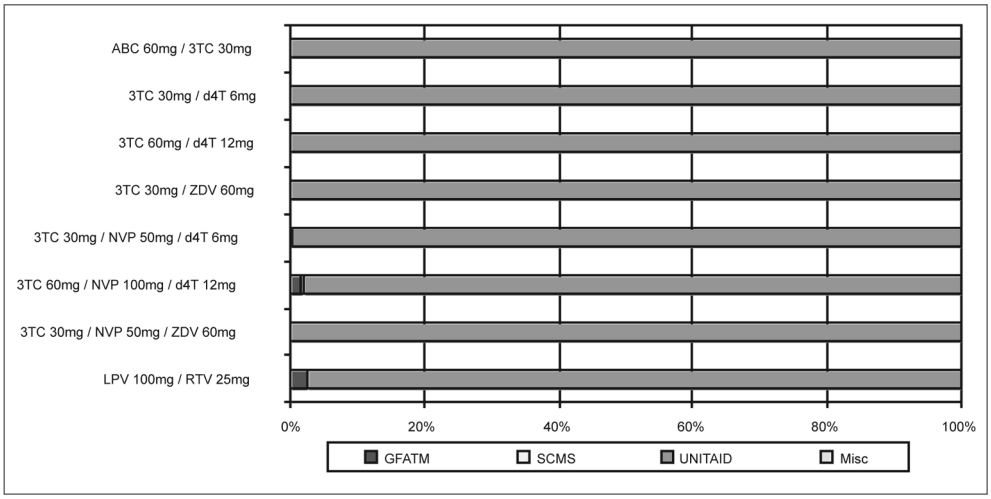

Figure 6a. Pediatric FDC ARV Market Share (volume) by purchaser, 2008

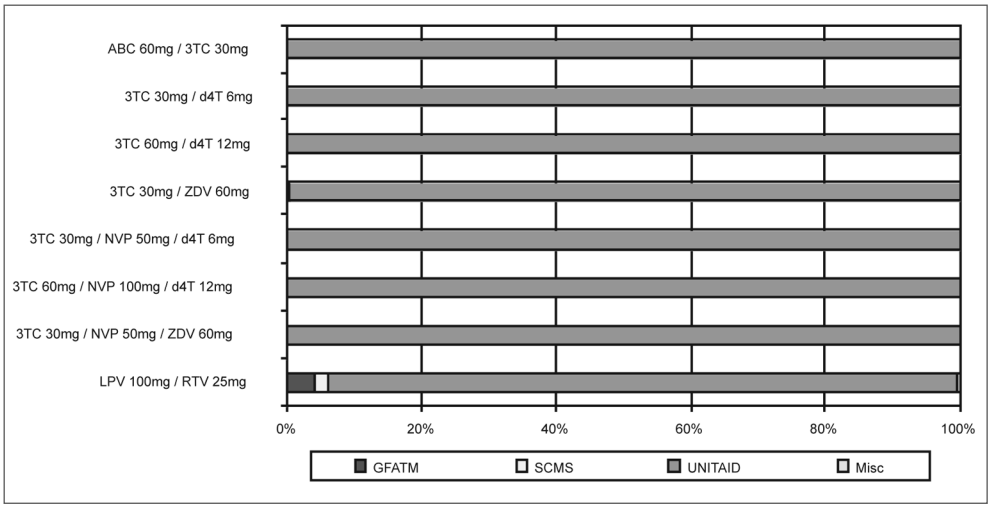

Figure 6b. Pediatric FDC ARV Market Share (volume) by purchaser, 2009

Price comparisons of pediatric ARV formulations

Prices for all pediatric ARV formulations continue to drop, with FDCs remaining consistently less expensive than liquid formulations (Table 4). Liquid alternativeswere 2.3-3.2 times more expensive than dispersible products for stavudine-based FDCs in 2009 and ranged from 1.4-1.6 times more expensive than solid versions of zidovudine- and abacavir-based FDCs.

		Pediatric Defined Daily Dose			2008 Price/Person/Year (USD)			2009 Price/Person/Year (USD)		
	Weight (kg)	Liquid (ml)	Pedi FDC (tab)	Adult FDC (tab)	Liquid	Pedi FDC	Adult FDC	Liquid	Pedi FDC	Adult FDC
2-in-1 FDCs										
ABC60/3TC30	5	6/6	2		175	-		142	89	
3TC30/d4T6**	5	6/12	2		69	27		52	23	
3TC60/D4T12**	10	12/24	2	1	139	50	29	105	40	24
3TC30/ZDV60	5	6/12	2		71	44		56	40	
LPV100/RTV25	15	5	4	2	323	306	287	286	268	228
3-in-1 FDCs										
ABC60/3TC30/ ZDV60	5	6/6/12	2		181	-		194	-	
3TC30/NVP50/ d4T6**	5	6/10/12	2		122	33		83	29	
3TC60/NVP100/ d4T12**	10	12/20/24	2	1	244	54	40	166	52	37
3TC30/NVP50/ ZDV60**	5	6/10/12	2		123	56		86	53	

Table 4. Price comparison of ARV dosage forms, 2008-2009*

**based upon UNITAID prices reported by Clinton HIV/AIDS Initiative*
***dispersible FDC*

Some treatment programs treat children with half of an adult FDC once they reach weights of at least 10 kg. Prices for half of a stavudine-based adult FDC are 29-42% less expensive than the two stavudine-based pediatric FDCs.

Discussion

In past years, great strides have been made in bringing to market quality-certified, pediatric ARV FDCs in dosage forms appropriate for use in low-resource settings. Activists, international organizations and national governments have successfully lobbied for the development and production of pediatric ARV products. Five new 2-in-1 and four new

3-in-1 pediatric FDCs have been quality-certified by the WHO or FDA since 2005 in dosage forms appropriate for use in low resource settings. These new products include the first heat-stable, ritonavir-boosted protease inhibitor and five ARVs available as dispersible tablets, a formulation typically more acceptable to children than liquids and substantially less expensive, easier to store, less costly to distribute to health care facilities, and easier for care takers to carry home than liquid alternatives. The new solid and dispersible pediatric FDCs offer ease of administration and more reliable dosing than crushing or multiple-splitting of adult FDCs.

Despite these advantages, however, country purchases for ARVs in less desirable dosage formulations (liquid and solid, single-component ARVs) continue to show annual increases while uptake of the new solid and dispersible FDCs has been remarkably low outside of UNITAID-funded programs. UNITAID accounted for 97-100% of total market volume for all solid and dispersible pediatric FDCs purchased with donor-funds in both 2008 and 2009.

The GFATM provided funds to 116 countries for HIV/AIDS in 2008 [41] while UNITAID reported financing pediatric HIV/AIDS treatment in 44 countries by the end of 2009 [42]. The GFATM, SCMS, and UNITAID agreed that UNITAID would lead pediatric ARV procurement in countries they support, with UNITAID reporting pediatric ARV FDC purchases for 29 and 31countries in 2008 and 2009, respectively. Only three and two countries from GFATM and SCMS, respectively, reported pediatric FDC ARV purchases in 2008. While donor coordination explains lack of FDC purchases in GFATM countries also receiving UNITAID funds, uptake of new pediatric FDCs in GFATM countries without UNITAID funding is remarkably low.

This study cannot explain the reasons for low uptake of improved pediatric formulations outside of UNITAID. Our results reveal the importance of additional operational research to identify barriers to product use. Still, we present some potential challenges at country level that may prevent or delay adoption of new products. To start, country-based staff may be unaware of recent developments and availability of new pediatric formulations. There may be reluctance to use new formulations, such as dispersible tablets, in regions where these types of medicines are not historically or currently used. Regulatory barriers, registration costs and difficulties, the need to revise treatment guidelines and the need to retrain all prescribers and care- givers may also contribute to underutilization. Countries may be locked into long-term contracts that preclude them from switching to improved products or their demand may be too low to meet some suppliers' minimum purchase requirements.

To change from currently used ARVs to the new pediatric formulations may also produce challenges in supply chain management. Demand forecasting (i.e. determining the

amount of medicine needed for country programs) is a challenging and complicated task [43] and insufficient focus has been placed on improving outdated procurement practices. It is possible that in the transition phase from one set of ARVs to another, the number of pediatric products in warehouses and on facility shelves increases substantially, making demand forecasting more complicated for some period of time. Thus, such transitions need to be carefully planned and monitored in order to avoid wastage and stock shortages.

It is also possible that the types of pediatric products created to date are not the products most desired at country level, or that practitioners and caregivers prefer to use half of an adult FDC instead of pediatric FDCs, when possible. Using adult FDCs for children in lieu of pediatric FDCs may simplify supply chain management of ARVs (procurement, storage, distribution, inventory management) as well as prescribing, dispensing, and administration by the caregiver. Lastly, countries may currently be in the process of transition and we are now observing a time lag between decisions to switch to newer products and actual implementation of those decisions.

While it is thus understandable for a number of reasons that the adoption of new, improved pediatric ARVs is a time-consuming process, such inertia may have undesirable side effects. For instance, it may falsely signal to pharmaceutical companies that the markets for improved pediatric ARVs are smaller than anticipated because of logistical and acceptability problems, deterring entry of new manufacturers and scale-up of production among existing ones [28].

International organizations and countries already face challenges obtaining existing pediatric ARV medicines. Reports that Bristol-Myers Squibb will encounter interruptions in the production of pediatric didanosine have created great concern for upwards of 7,000 children treated with this medicine [44,45]. Bristol-Myers Squibb is currently the only quality-certified producer of pediatric didanosine tablets and the amount of didanosine currently available may be insufficient to meet the needs of children on treatment during the period of supply interruption. Médecins Sans Frontières reports difficulty purchasing the quality-certified pediatric 3TC/ZDV due to low-volume purchase requests (G Arreghini, Médecins Sans Frontières, personal communication). Médecins Sans Frontières also notes difficulty obtaining the quality-certified pediatric ABC/3TC/ZDV, a new FDC not purchased by CHAI/UNITAID and therefore in low demand.

Even when pediatric ARVs are procured by large-scale purchasers like UNITAID, an unfortunate paradox comes into play in pediatric HIV/AIDS treatment: the more that pediatric ARV formulations are tailored to the needs of specific sub-groups, the less demand there is for a given product. This becomes particularly problematic in convincing companies to produce age-appropriate strengths of fixed-dose combination ARVs

in multiple formulations. The WHO list of priority ARVs needs to be complete but also succinct, to aggregate demand around the most important products and avoid the development and production of ARVs that go unused by countries.

Because of the inherent disincentives for manufacturers in the pediatric ARV market, extreme care must be taken to ensure that price negotiations between producers and large-scale purchasers are conducted in a manner that ensures sufficient profit to sustain prices and stabilize the market over the long term. Activists, civil society organizations, researchers, international organizations and others must not only lobby for pediatric investments, but also monitor the movement of manufacturers in and out of the pediatric market, the extent and rate of new product uptake and their impact on child health. If countries are in a transition to new products, it is important for donors and suppliers to know and predict the amount of time needed for such transitions.

Operational research to identify and address reasons for low product utilization is a critical next step towards meeting two major global targets for 2015: Millennium Development Goal (MDG)-4, calling for a two-thirds reduction in mortality rates for children under five, and MDG-6, which aims to halt and begin to reverse the spread of HIV [46].

Success in the case of pediatric HIV/AIDS treatment cannot be determined only by market availability of new and improved ARV products. Until the barriers to uptake can be identified and addressed, and country demand stabilizes, organizations like UNITAID which offer the equivalent of advance market commitments will be needed to encourage the entry of new manufacturers and "hold the market" until countries can adopt the newer formulations.

Limitations

While we systematically cleaned and validated purchases [30-32], it is possible that misreported purchases are still present in our analytic data set. The historical GFATM ARV transactional data posted in WHO GPRM, in particular, required considerable cleaning. We note a substantial number of ARV transactions in the "miscellaneous" category. Most of these miscellaneous transactions were reported by procurement agencies and we suspect many of these miscellaneous reports are actually purchases made by GFATM recipients. ARV transactions for GFATM recipients have been inconsistent in both the older GFATM Purchase Price Report and the WHO GPRM. We observed many instances over the past few years when transactions appeared and disappeared from both of these databases.

For this paper, we used 2002-2009 purchases down-loaded from the WHO and GFATM on 1 May, 2010. We noted the absence of SCMS, UNITAID, and GFATM purchases in the WHO GPRM after April 2009 and therefore obtained this information directly from those organizations. The GFATM data was publicly available on its website. CHAI provided ARV purchase data to researchers on behalf of UNITAID without restrictions and SCMS staff provided transactional data to researchers under conditions that they review and comment on manuscripts utilizing their data prior to submission.

Recent interventions to improve the quality of transactions in the GFATM PQR have resulted in longer delays from the time countries report purchases to public posting. Our data therefore underestimate 2009 GFATM purchases. It is possible that GFATM-supported countries purchased new pediatric formulations in 2009 that do not yet appear in publicly posted data. In addition, some organizations (i.e., World Bank, PEPFAR purchases outside of SCMS, Médecins Sans Frontières) do not report ARV purchases to the WHO GPRM. Similarly, governments that purchase ARVs with their own funds do not report transactions to WHO. Delays in reporting, data restrictions imposed by some donors, and unwillingness to report ARV purchases will limit the ability to monitor and evaluate global ARV markets in a timely and unbiased manner.

We limited our analytic data set to ARV formulations used predominantly in children and infants. Our analyses did not include three ARVs (3TC150, EFV600, and DRV) listed as pediatric ARVs by WHO (Table 1) as these are more commonly used for adults.

We calculated ARV regimen prices for new and liquid formulations using UNITAID/CHAI-reported prices because UNITAID was the only consistent purchaser of FDCs. These prices may not accurately reflect prices paid by countries outside of UNITAID programs. We acknowledge that some programs may still be splitting adult FDCs into quarters or crushing adult FDCs for use in children. We did not compare pediatric FDC prices to quarters of adult FDCs because WHO recommends against splitting adult tablets more than one time [33].

Liquid ARV prices are the most difficult to clean and validate given the multitude of different ways countries have misreported purchases. The Russian Federation accounted for more than 80% of GFATM brand purchases in 2008. It is possible that the Russian purchases were reported in error, but prior benchmarking price analysis of ARV purchases in the Former Soviet Union revealed that Russian prices (confirmed with procurement staff) were consistently and remarkably higher than other countries [47].

In addition, these Russian purchases passed through new quality improvement processes implemented when the new PQR system at the GFATM was recently established.

Conclusion

Treatment of children with HIV/AIDS is a high priority for the international community. However, ensuring that needed pediatric medicines are developed and delivered to those who need them remains a complex, challenging task. In order to improve performance in this area, a better understanding of the pediatric ARV market is needed – where it is performing well, and where substantial market failures persist.

This study has demonstrated that the pediatric ARV market is not simply a smaller version of the adult market (described elsewhere [30-32]). Compared to HIV/ AIDS treatment options for adults, far fewer ARVs have been proven safe and effective in children. Whereas multiple donors and countries buy substantial quantities of adult first-line ARVs, one international institution, UNI- TAID, plays a dominant role in the pediatric market, buying an overwhelming proportion of some pediatric ARVs. Pediatric markets become fragmented into niches with little demand as manufacturers develop more acceptable, age-appropriate pediatric products, and adopting improved formulations may present logistical challenges in some countries. While most adult FDCs are produced by several quality-certified manufacturers, many pediatric FDCs have only one quality-certified manufacturer, leaving HIV/AIDS treatment programs highly dependent on a single supplier to meet global demand.

Ensuring a long-term supply of high-quality, effective, affordable and well-adapted ARVs for children in different age groups will require ongoing monitoring and improved understanding of the global pediatric ARV market. Furthermore, much research is required at country level to understand better why uptake of new, improved formulations has been so slow, and what can be done to accelerate children's access to quality AIDS care in resource-poor settings. Continued innovation in pediatric ARV development may be threatened by out-dated procurement practices failing to connect clinicians making prescribing decisions, supply chain staff dealing with logistics, donors, international organizations, and pharmaceutical manufacturers. Perceptions of global demand must be better informed by accurate estimates of actual country-level demand.

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Chapter 4.3

A lifeline to treatment: the role of Indian generic manufacturers in supplying antiretroviral medicines to developing countries

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Abstract

Background

Indian manufacturers of generic antiretroviral (ARV) medicines facilitated the rapid scale up of HIV/ AIDS treatment in developing countries though provision of low-priced, quality-assured medicines. The legal framework in India that facilitated such production, however, is changing with implementation of the World Trade Organization Agreement on Trade-Related Aspects of Intellectual Property Rights, and intellectual property measures being discussed in regional and bilateral free trade agreement negotiations. Reliable quantitative estimates of the Indian role in generic global ARV supply are needed to understand potential impacts of such measures on HIV/AIDS treatment in developing countries.

Methods

We utilized transactional data containing 17,646 donor-funded purchases of ARV tablets made by 115 low- and middle-income countries from 2003 to 2008 to measure market share, purchase trends and prices of Indian-produced generic ARVs compared with those of non-Indian generic and brand ARVs.

Results

Indian generic manufacturers dominate the ARV market, accounting for more than 80% of annual purchase volumes. Among paediatric ARV and adult nucleoside and non-nucleoside reverse transcriptase inhibitor markets, Indian-produced generics accounted for 91% and 89% of 2008 global purchase volumes, respectively. From 2003 to 2008, the number of Indian generic manufactures supplying ARVs increased from four to 10 while the number of Indian-manufactured generic products increased from 14 to 53. Ninety-six of 100 countries purchased Indian generic ARVs in 2008, including high HIV-burden sub-Saharan African countries. Indian-produced generic ARVs used in first-line regimens were consistently and considerably less expensive than non-Indian generic and innovator ARVs. Key ARVs newly recommended by the World Health Organization are three to four times more expensive than older regimens.

Conclusions

Indian generic producers supply the majority of ARVs in developing countries. Future scale up using newly recommended ARVs will likely be hampered until Indian generic producers can provide the dramatic price reductions and improved formulations observed in the past. Rather than agreeing to inappropriate intellectual property obliga-

tions through free trade agreements, India and its trade partners - plus international organizations, donors, civil society and pharmaceutical manufacturers - should ensure that there is sufficient policy space for Indian pharmaceutical manufacturers to continue their central role in supplying developing countries with low-priced, quality-assured generic medicines.

Background

India has emerged as a world leader in generic pharmaceuticals production, supplying 20% of the global market for generic medicines [1]. The emergence of generic sources supplying quality antiretroviral (ARV) medicines at prices much lower than originator prices undoubtedly accelerated the global scale up of HIV/AIDS treatment. From 2002 to 2008, more than 4 million people were started on antiretroviral therapy (ART) in developing countries [2].

To date, the vast majority of people in low- and middle-income countries have been with generic ARVs produced by Indian manufacturers unhampered by patent and other intellectual property restrictions [3]. This absence of intellectual property barriers also resulted in the development of improved ARV formulations, such as paediatric dosage forms and fixed-dose combination (FDC) ARVs whereby two or more ARVs are combined into one tablet. As of the end of 2009, the United States Food and Drug Administration and the World Health Organization (WHO) Prequalification Programme approved or pre-qualified 57 adult FDCs and 31paediatric ARV tablets produced by Indian generic manufacturers but only eight adult FDCs and 14 paediatric ARV tablets produced by non-Indian and originator manufacturers [4-6].

The intellectual property framework that positioned India as the "pharmacy of the developing world", how- ever, is rapidly changing. In 2005, India was obliged to amend its patent law to allow product patents on medicines to comply with the World Trade Organization (WTO) Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS). The introduction of product patents in India is severely constraining generic competition and supply, particularly for newer medicines. Now, there is a threat that the limited policy space that remains will be further constricted by bilateral or regional free trade agreements. Unfortunately, many free trade agreements that have been concluded or are being negotiated between industrialized and developing countries contain measures that restrict access to medicines [7].

Agreements involving India are of particular concern because of the country's role as a worldwide supplier of low-priced generic medicines. For example, current free trade

agreement negotiations between the European Union and India [8,9] include measures that delay or restrict competition from generic medicines, including: patent term extensions beyond the 20 years required by TRIPS; data exclusivity (that could delay the registration of generic medicines); and border enforcement measures that could block international trade in generic medicines when they are suspected of infringing patents in the countries through which they transit. These types of border measures blocked medicines from reaching patients in Africa and Latin America in 2008 and 2009 when European customs authorities seized Indian-produced generics transiting via Amsterdam airport on suspicion that they infringed Dutch patents [10]. All of these measures can delay or restrict competition from generic medicines and are in direct conflict with the 2001 WTO Doha Declaration on TRIPS and Public Health, and medical ethics [8,9].

A better understanding of the role that Indian generic medicines producers play in HIV/AIDS treatment in developing countries will shed light on the potential consequences of recently proposed intellectual property measures for global public health. While their relative importance is widely recognized, reliable quantitative estimates of generic ARVs supplied by Indian producers are not available. The purpose of this paper is to quantify the extent to which Indian pharmaceutical manufacturers have contributed to HIV/AIDS treatment in developing countries to better understand the potential implications of current and future policies that may hamper or restrict market entry of generic ARV manufacturers and generic competition.

Methods

We obtained donor-funded ARV purchase transactions over the 2003-2008 period from the WHO Global Price Reporting Mechanism, the Global Fund to Fight AIDS, Tuberculosis and Malaria's Price & Quality Reporting Tool, and UNITAID as provided by the Clinton Health Access Initiative [11-14]. Antiretroviral transactional data was systematically cleaned and validated using a market intelligence database described elsewhere [15-17]. We excluded transactions for liquid ARV formulations, which resulted in an analytic data set containing 17,646 donor-funded purchases of ARV tablets and capsules made by 115 countries (Figure 1).

Market share by volume is calculated in person-years for Indian generic, non-Indian generic and brand ARVs using WHO-recommended adult doses for persons weighing more than 60 kilogrammes (kg) [18,19]. We provided estimates of producer market share for all ARVs, but also calculated market share among three ARV market niches: paediatric ARVs (all classes), adult nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), and adult protease inhibitors (PIs).

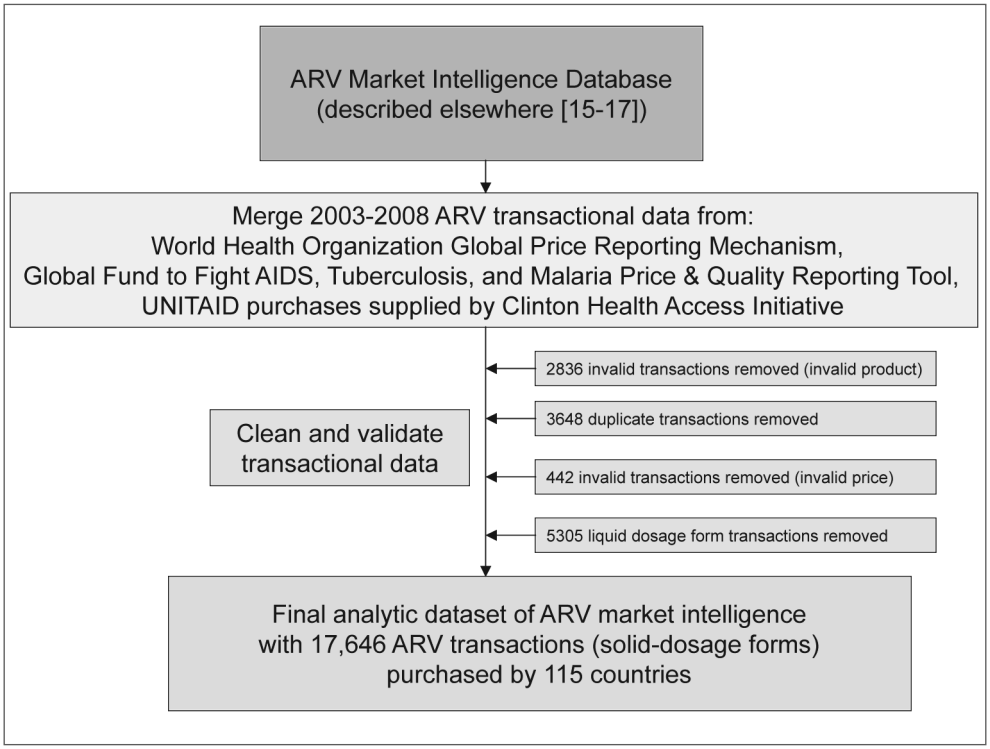

Figure 1. Description of analytic data set

We compared purchase trends for Indian generic, non-Indian generic and brand ARVs, summarizing the number of manufacturers, products/dosage forms, purchases, purchasing countries and value (in US dollars).

We calculated 2008 antiretroviral regimen prices for the most commonly used first-line regimens recommended by the WHO in its 2003 and 2006 treatment guidelines for adults weighing more than 60 kg [18,19]. We expressed regimen prices as price per person per year. Because most ARV price distributions were skewed dramatically by a few high price outliers, we presented regimen prices using median and quartile prices to accurately convey central tendencies. We differentiate regimen composition by using a "+" when multiple tablets are used to create a regimen (e.g., 3TC+NVP+TDF) and a "/" for FDC formulations (e.g., 3TC/NVP/d4T). We plotted 2003-2008 trends in generic ARV regimen prices along with those of innovator ARV regimens offered through differential or tiered prices, as reported to Médecins Sans Frontières (MSF) in its "Untangling the web of ARV price reductions" [20]. We obtained all ARV prices in United States dollars and adjusted them to the January-December 2008 period using the annual US Consumer Price Index [21].

Results

Our results confirm the prominence of Indian generic manufacturers in the supply of antiretroviral medicines to developing countries. Since 2006, Indian-produced generic ARVs have accounted for more than 80% of the donor-funded developing country market, and comprised 87% of ARV purchase volumes in 2008 (Figure 2).

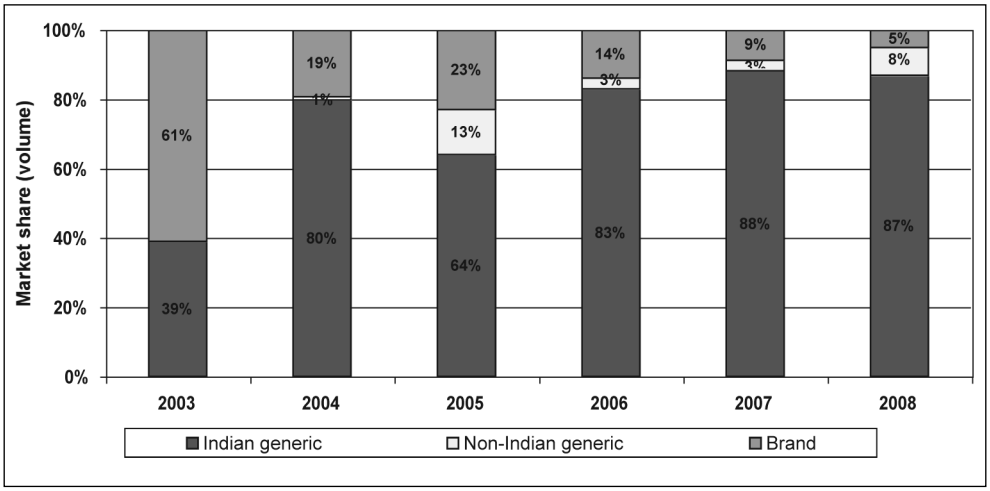

Figure 2. Overall ARV market share (volume) for Indian generic, non-Indian generic and originator (brand) manufacturers, 2003-2008

The proportion of ARVs produced by Indian manufacturers is even higher within certain market niches. In 2008, Indian-produced generics accounted for 91% of paediatric ARV volume and 89% of adult NRTI and NNRTI purchases (Figure 3). In contrast, originator companies accounted for the majority (81%) of purchase volumes for adult protease inhibitors (PIs), with Indian generics accounting for only 19%.

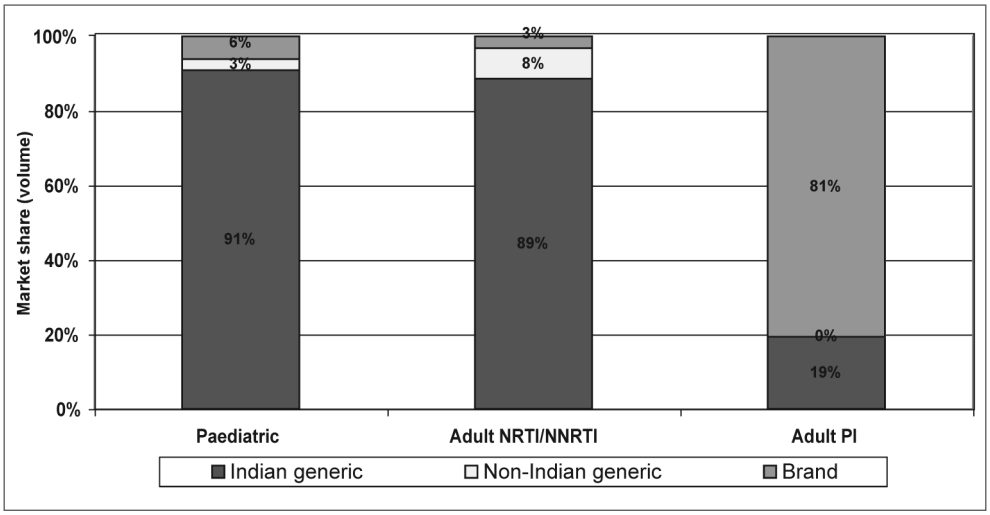

Figure 3. Adult and paediatric ARV market share (volume) for Indian generic, non-Indian generic and originator (brand) manufacturers, 2008

The value of the donor-funded, developing country ARV market has exhibited dramatic annual growth over the past several years. By 2008, Indian generic ARVs accounted for 65% of the total value (US$463 million) of ARV purchases reported, while non-Indian generic and innovator ARVs accounted for 13% and 22% of market value, respectively (Table 1). The number of Indian generic manufacturers supplying ARVs to low- and middle- income countries increased from four to 10 from 2003 to 2008, while the number of Indian-produced generic ARV products increased from 14 to 53 over th same period (Table 1).

	2003	2004	2005	2006	2007	2008
# Countries reporting any ARV purchase	15	69	86	86	90	100
Indian generic ARVs						
# manufacturers	4	8	6	7	9	10
# products/dosage forms	14	31	30	37	47	53
# purchases	62	740	1142	1273	2433	5906
# purchasing countries	11	55	70	78	81	96
NRTIs	11	53	66	74	80	92
NNRTIs	6	51	65	63	75	93
PIs	4	17	20	26	31	37
value (USD millions)	0.67	43.84	86.54	93.40	188.08	301.38
Non-Indian generic ARVs						
# manufacturers	0	2	3	2	3	6
# products/dosage forms	0	5	19	15	18	15
# purchases	0	10	228	124	201	316
# purchasing countries	0	4	10	13	20	29
NRTIs	0	2	9	11	20	25
NNRTIs	0	2	4	3	6	5
PIs	0	0	1	0	0	0
value (USD millions)	0	0.12	27.38	3.72	14.34	58.76
Originator ARVs						
# manufacturers	6	8	8	7	7	8
# products/dosage forms	18	32	33	39	40	39
# purchases	35	654	1146	976	1284	1116
# purchasing countries	8	50	75	77	79	88
NRTIs	4	40	57	66	63	57
NNRTIs	4	31	52	36	22	14
PIs	4	32	58	67	73	82
value (USD millions)	1.64	29.80	74.39	56.51	83.02	102.62

Table 1. Purchase trends for Indian generic, non-Indian generic and originator ARVs, 2003-2008

In 2008, 96 of 100 countries reported ARV purchases from Indian generic producers, while only 29 countries reported purchases from non-Indian generic manufacturers (Table 1, Figure 4). Most countries reported purchases of innovator PIs whereas far fewer countries reported generic PI purchases, most likely due to lower prices offered through tiered pricing schemes for brand lopinavir/ritonavir in 2003-2008. The number of countries purchasing Indian-produced generic PIs, however, has steadily increased over the years as global PI volumes have increased and generic pricing has become more competitive with originator tiered prices.

Figure 4. Countries reporting purchases of Indian generic ARVs in 2008

Analysis of Indian-produced generic ARV purchase trends by country reveal India's own reliance on the availability of generic ARVs as demonstrated by nearly 2200 purchases of Indian-produced generic ARVs (Table 2) totaling nearly US$26 million in 2008. Volumes associated with these purchases were sufficient to treat more than 200,000 people with first-line regimens and more than 1000 people with second-line regimens. India reported no purchases for non-Indian generic or innovator ARVs in 2008. Sub-Saharan African countries with high HIV/AIDS disease burdens comprise the remaining top 10 purchasers of Indian-produced generic ARVs (Table 2).

Purchase volume rank	Country	% of ARV volume supplied by Indian generic producers	Value of Indian-produced generic ARV purchases (USD million)	# Indian-produced generic ARV dosage forms purchased
1	India	100	25.9	14
2	United Republic of Tanzania	96	27.3	13
3	Nigeria	84	27.1	28
4	Ethiopia	96	27.6	24
5	Mozambique	99	15.3	16
6	Zambia	94	20.7	19
7	Namibia	99	15.3	23
8	Democratic Republic of the Congo	99	11.4	25
9	Kenya	82	10.2	14
10	Cameroon	93	15.0	30

Table 2. Summary of Indian-produced generic ARVs for countries with highest 2008 purchase volumes

Robust competition among manufacturers has contributed to substantial price reductions for generic ARVs over the past several years. The most commonly used first-line adult regimen (lamivudine/nevirapine/ stavudine30) dropped from $414 per person per year in 2003 to $74 per person per year in 2008 for Indian-produced generics (Figure 5). While regimen prices for non-Indian generic were similar to Indian generic ARVs from 2004 to 2006, by 2008 the non-Indian generic price was two times higher than the Indian generic price. Innovator prices for this first-line regimen, both actual prices contained in our database and survey prices reported to MSF [20], were consistently much higher than generic ARVs across all years. In 2008, innovator regimen prices reported to MSF were 4.5 and 7.7 times higher than Indian generic prices, depending upon the tiered-price category of the purchasing country (Figure 5) [20].

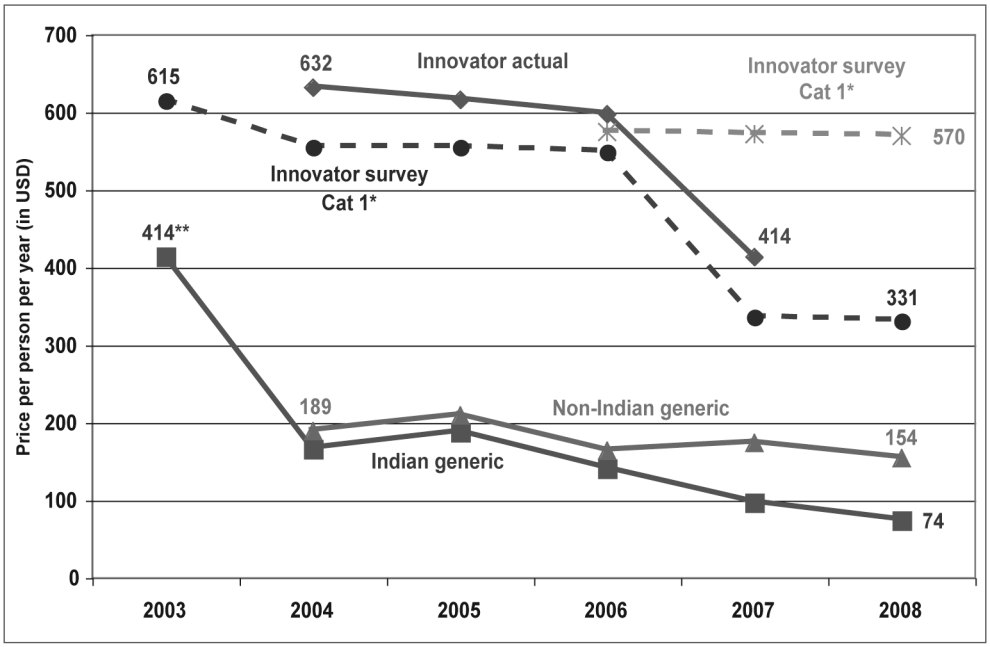

Figure 5. Price trends for generic 3TC/NVP/d4T30 (fixed-dose combination) and innovator 3TC+NVP+d4T30 (3 individual tablets), 2003-2008

**Survey prices provided by innovator companies under tiered-pricing [20]*
***2003 price is for three individual ARVs (1st FDC purchase reported in 2004)*

Among many concerns around the future of global ART scale-up are higher prices for new WHO-recommended, first-line regimens that utilize zidovudine or tenofovir in place of stavudine [19,22]. As of 2008, the Indian generic global median price for newly recommended tenofovir-based regimens ranged from $246 to $309 per person per year, notably 3.3 to four times higher than the price of the most commonly used older regimen (3TC/NVP/d4T30) (Table 3). Identical regimens, comprised of non-Indian generic and innovator ARVs, are considerably more expensive than the Indian generic versions.

	Indian generic median price (25th, 75th)	Non-Indian generic median price (25th, 75th)	Innovator actual median price (25th, 75th)	Innovator survey price** Cat 1, Cat 2
First-line regimens from 2003 WHO guidelines:				
3TC/NVP/d4T30	74 (63, 88)	154* (137, 712)	N/A	331, 570
EFV+3TC/d4T30	131 (126, 193)	229* (196, 656)	N/A	349, 789
3TC/NVP/ZDV	120 (118, 123)	142 (142, 142)	519* (496, 991)	444, 663
EFV+3TC/ZDV	183 (177, 260)	326 (254, 348)	491 (475, 801)	434, 854
New first-line regimens from 2009 WHO guidelines:				
3TC+NVP+TDF	246 (230, 273)	340 (321, 767)	575 (519, 1254)	490, 867
EFV+3TC+TDF	298 (283, 369)	415 (381, 711)	546 (498, 1064)	508, 1086
FTC/TDF+NVP	257 (247, 301)	387 (386, 537)	641 (569, 1116)	538, 986
EFV+FTC/TDF	309 (300, 397)	461 (446, 480)	612 (548, 926)	556, 1205

Table 3. First-line ARV regimen prices comparisons, 2008

N/A insufficient sample size to estimate price
**regimen prices calculated by summing up prices of 3 component ARVs*
***Médecins Sans Frontières, "Untangling the web of ARV price reductions" [22]*

Discussion

These analyses quantify and confirm the exceptional role that India has played in providing quality ARVs at low prices to people with HIV/AIDS in developing countries. More than 80% of all donor-funded ARVs purchased since 2006 were supplied by Indian generic manufacturers. Price reductions noted for commonly used historical first-line regimens were a result of robust generic competition among Indian manufacturers in an environment largely void of intellectual property barriers [23,24]. Countries across sub-Saharan Africa with high HIV/AIDS burdens, as well as India, are heavily reliant on the availability of Indian-produced generic ARVs to support their national treatment programmes.

Trade-related and intellectual property-related threats to the supply of generic medicines from India are coming at a time when the prospects of ART scale-up are already cloudy. New WHO guidelines recommending early initiation of ART [22] will result in increased numbers of people in need of treatment. At the same time, countries are

trying to adopt the new ARV regimens recently recommended by WHO [19,25]. These newer ARVs offer better side-effect and tolerability profiles, but some of the key ARVs are more widely patented and are much more expensive than regimens used in the past. These WHO changes are welcome and help eliminate historical inequities whereby people in resource-poor countries receive a different standard of care than those in rich countries. However, country budgets within the Global Fund to Fight AIDS, Tuberculosis, and Malaria have been cut [26], while pledges and contributions appear flat, raising concerns that funds will not be available in-country to adopt the new WHO recommendations [19,22,25].

Limitations

Our study captures only donor-funded purchases and not those made by government-funded HIV/AIDS treatment programmes through such countries as Brazil, South Africa and Thailand. Similarly, we had no access to comprehensive and reliable data on patents and other intellectual property barriers and were, therefore, unable to quantitatively examine these issues in our study. While we systematically cleaned and validated all transactional data, we cannot be confident that we have identified all reporting errors in publicly available data. Prices are inconsistently reported to the Global Fund and the WHO Global Price Reporting Mechanism. Whereas some organizations, such as UNITAID and the Supply Chain Management System arm of the United States President's Emergency Plan for AIDS Relief, provide prices for drug costs only, Global Fund-supported countries often report prices that include not only drug costs, but also add-on costs, such as transport, insurance and taxes.

We attribute ARV price reduction primarily to generic competition, but we note that these price decreases were also spurred through the efforts of HIV/AIDS activists, civil society organizations, national governments, foundations and other international organizations.

Despite these limitations, our research provides valuable quantitative information demonstrating the critical role that Indian generic pharmaceutical manufacturers play in the global treatment of HIV/AIDS in developing countries. These results can and should be used in ongoing and future discussions around intellectual property and access to medicines.

Conclusions

Free trade agreements that may create new intellectual property obligations for India can increase ARV prices, impede the development of acceptable dosage forms, and delay access to newer and better ARVs. Such measures can undermine the international goal to achieve universal access to HIV/AIDS interventions and the 2001 WTO Doha Declaration on TRIPS and Public Health [25]. Rather than agreeing to inappropriate intellectual property obligations, India and its trade partners - along with international organizations, donors, national governments, civil society and pharmaceutical manufacturers - should ensure that there is sufficient policy space for the Indian generic industry to continue its central role in supplying developing countries with low-cost, quality-assured generic medicines.

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Chapter 5

Discussion: Back to the Future – Lessons Learned and Implications For the Next Wave of Pharmaceutical Policy Research in Developing Countries

Brenda Waning

Discussion

This chapter offers a discussion centered around five key findings from this body of work, implications of research results, and suggested next steps to improve both pharmaceutical policy research and access to medicines initiatives.

1. The research findings refute conventional wisdom about which policy strategies improve access to medicines

Using publicly available data that was routinely collected but seriously underused, and by applying the atypical analytic methods, these studies provide timely results with direct implications for national governments, donors, and international organizations working to improve access to medicines in developing countries. While not originally designed to do so, most of the study results refute conventional wisdom about which interventions and practices actually promote access to medicines.

Assessments of national policies in chapter two challenge assumptions about medicine prices and market competition in rural regions. Contrary to popular belief, chapter 2.1 shows that **viable pharmaceutical markets can be fostered in even remote rural villages with the right combination of policies and incentives** [1]. The study also shows that **interventions to promote competition can have profound impact on medicine prices in private pharmacy outlets** that have historically operated under monopolistic conditions. These findings are of great importance to Kyrgyzstan where more than 60% of people live in rural areas [2] and the entire outpatient pharmacy sector was privatized following independence from the former Soviet Union [3].

The second Kyrgyz study counters prevailing views on "reasonable" medicine mark-ups applied by owners of rural, private pharmacies. Whereas many researchers and policy makers deem medicine mark-ups of 100% and more to be "excessive", study 2.2 reveals that **high medicine mark-ups up to 244% were needed to ensure that not-for-profit pharmacies broke even** across expense and revenue streams [4]. In sparsely populated areas, low inventory turnover and high transportation expenses contribute to formidable carrying costs, necessitating higher mark-ups than might be needed in urban areas. In these already isolated areas, further pressure to reduce prices may worsen access to medicines by removing the ability of pharmacy outlets to make even minimal profits. This could lead to pharmacy closures and create disincentives for others to open new pharmacy businesses. Policy makers commonly react to complaints of high medicine prices with knee-jerk regulatory price controls that limit maximum mark-ups, a practice generally believed to be effective for promoting access to medicines. This study suggests, however, that **most regulatory price limits imposed on medicines are arbitrary and can be harmful when policy-makers lack a clear understanding of pharmacy busi-**

ness structures. The study highlights the need to examine and interpret medicine mark-ups at the local level with due consideration for the costs of doing pharmacy business.

In chapter three, I challenge common assumptions about prices paid for antiretroviral (ARV) medicines purchased under large-scale, donor-funded global health initiatives. These "mega funds" require that recipients comply with numerous conditions and policies related to medicines procurement. The GFATM conditions, for example, include requirements to purchase quality-approved products, submission of supply chain management plans, mandatory reporting of all purchases, plus supervision and audits by external local fund agents. There was a general belief that these conditions would assure that countries purchased quality medicines at low prices. I show in chapter 3.1, however, that **even with strict donor-imposed procurement requirements, prices varied up to 20-fold across similar countries for equivalent or identical medicines** [5]. While the GFATM set out the right conditions, they themselves were not using the information they collected to appropriately monitor their recipients, and the publicly available information was not presented in a reliable and user-friendly format that facilitated procurement by country-based staff. This study also **debunked the common notion that generic medicines are consistently less expensive than branded versions.** The study reveals one important exception, where from 2004-2008 the generic versions of ARVs belonging to the class of protease inhibitors were substantially more expensive than their branded counterparts [5].

The most surprising and counterintuitive finding, perhaps, was the lack of relationship between medicine purchase volume and price. The mantra "buy more, pay less" has been repeatedly chanted and systematically accepted as a guiding principle in pharmaceutical procurement. Study 3.2 provides the first evidence that **purchase volume is not a consistent determinant of medicine price.** Only four of 19 medicines showed lower prices for medium or high volume purchases compared to those paid for low volume purchases, with price differences ranging from four to 21% [6]. I recommend policy makers and donors focus on other possible explanations of high medicine prices, such as timeliness of payment, purchasing lead time, registration barriers, and intellectual property restrictions. This study also revealed that **in most scenarios, differential or tiered pricing schemes for innovator medicines could not compete with prices charged by generic competitors**. Tiered pricing, which has recently been resurrected as an approach to increase access to patented medicines [7], will have limited impact on access to medicines as compared to interventions that promote generic entry and robust competition.

Finally, in chapter 4, I dispel beliefs about the ways in which various actors independently and collectively influence the evolution of pharmaceutical markets and access to

medicines. In chapter 4.1, I describe an "old" first-line ARV market (2002-2006) characterized by remarkable growth, healthy competition, rapid uptake of new products, and unprecedented price reduction [8]. Newer policies and strategies of donors and international organizations, however, are resulting in dramatic restructuring of the first-line ARV market. These market distortions may have long-term negative consequences for access to medicines. This study shows that **the more medicines and regimens WHO recommends on their treatment guidelines, the less likely that manufacturers can achieve economies of scale in production**. This could deter manufacturers from developing newly recommended ARVs, including fixed-dose combination medicines, and limit price competition. This study also reveals that while policies to ensure procurement of quality medicines are needed, **quality certification requirements of some donors can actually delay uptake of new and improved formulations**. Lastly, results suggest that **the proliferation and expansion of large-scale pooled procurement systems will likely lead to monopsony and monopoly markets**. In this scenario, the healthy ARV markets of the past -- where six to eight manufacturers vied for the business of more than 120 buyers -- will be replaced by a few buyers doing business with a few sellers, which could potentially limit price competition and jeopardize security of supply.

In chapter 4.2, I report that **successful incentives resulting in innovation and development of new formulations will not ensure that the new and improved products are actually purchased and used**. This study shows that the equivalent of advance market purchase commitments by UNITAID resulted in the development and production of new fixed-dose combination ARVs for children. These products were better adapted than liquid and single-component alternatives and widely purchased throughout UNITAID's 34 country programs [9]. But only three countries outside of the UNITAID program purchased the new, improved pediatric products [9]. I suggest many reasons for this lack of purchase, including the need to revise national treatment guidelines, retrain staff and caregivers, and address supply chain management issues. I conclude by noting the importance of additional qualitative research to identify barriers and inform interventions to improve uptake and promote innovation of products appropriate for use in developing countries.

The last study, presented in chapter 4.3, confronts claims that stricter intellectual property restrictions imposed on India will have limited impact on the global scale-up of HIV/AIDS treatment in developing countries. Here the results suggest that current **bilateral and multilateral trade negotiations with India will hinder future access to medicines, given that Indian-produced generic ARVs account for more than 80% of all donor-funded ARVs sold to developing countries** [10]. The study quantifies the actual stakes on the table for the first time, despite numerous past and current trade negotiations. This study also **dispels the myth that India produces ARVs only for**

export and does not use domestically-produced medicines. India, in fact, purchased *only* Indian-produced ARVs in 2008 and ranked fourth highest of all countries in terms of the value of Indian-produced ARVs purchased (US $25.9 million) [10].

2. Building a multidisciplinary evidence base for pharmaceutical policy is not only possible but essential

The collection of studies in this thesis demonstrates the importance of building an evidence base to support strategic and informed pharmaceutical policies that improve access to medicines in poor countries. Until there is a solid evidence-base to describe which policies are most effective, conventional wisdom will continue to dictate the development of pharmaceutical policy. It is equally important that researchers demonstrate how their findings can be used by donors and international organizations as they deliberate policies and strategies to promote access to medicines.

Pharmaceutical markets are ultimately determined by and comprised of a myriad of stakeholders, policies and behaviors; pharmaceutical policy research therefore requires interdisciplinary collaboration and mixed methods -- both qualitative and quantitative --that reflect the multi-dimensional aspects of policy making and pharmaceutical markets in the real world. Political dynamics, knowledge, and perceptions, for example, cannot be quantified in numbers. While not explicitly noted or contained within the focus of this thesis, I conducted numerous qualitative studies to support this body of research. In the Kyrgyzstan research, for example, I conducted focus groups, key informant interviews and a household study to better understand care-seeking practices that guided the design and interpretation of the subsequent quantitative studies described in this thesis [11-12]. This global policy research also included countless key informant interviews to derive research hypotheses and interpret research findings. Through qualitative research I unearthed a number of common assumptions underlying "conventional wisdom." Through more quantitative methods, I disproved many of them.

The richness of the approaches used and inferences made in these studies is a reflection of the collaborative and multidisciplinary approach I employed throughout this research. Collaborators spanned the disciplines of global public health, medicine, pharmacy, economics, epidemiology, patent law, intellectual property, and governance. No single discipline will provide the information, skills, and methods needed to examine complicated and intertwined relationships.

3. This research provides a model for knowledge transfer and incorporation of evidence into policy, bridging the gap between academic research and real-world decision-making

New knowledge generated from pharmaceutical policy research is only useful if results and recommendations are adopted and applied in access to medicines initiatives. The approaches used in this body of work were ground-breaking. I demonstrated the utility of routinely collected data that was otherwise underused and then provided practical examples as to how this information could be adapted across a wide array of users. The results of these studies have profoundly affected decisions and strategies of governments, donors, and international organizations, demonstrating the important contributions academic researchers can make in global health.

Pre-publication dissemination of results to a broad audience of policy makers, advocates, and other key stakeholders allowed key results to be used in a timely fashion. Swift dissemination is critical given that policy decisions are made quickly and often, but publications occur less often and move at glacial speeds. Academics are typically reluctant to disseminate their research findings pre-publication, for fear of getting "scooped" or having their manuscripts rejected by publishers because the information is no longer technically new.

Pharmaceutical policy research results are, therefore, typically disseminated through peer-reviewed journals and professional conferences. Ideally, researchers would choose open access journals to ensure access to readers in developing countries. Six of my seven studies were published in open access journals. But even when open access publication channels are used, they may not be the best means to reach the actual policy-makers.

Researchers must find ways to bridge the gap between academic research and pharmaceutical policy decision-making through strategic communication and dissemination of findings. Rather than relying largely on dissemination through peer-reviewed literature, researchers need to take advantage of avenues such as press releases, newspaper editorials, and news features to broadcast study findings with direct policy implications. A press release and subsequent dissemination through the wire has far more likelihood of reaching the desk of a policy-maker than a published manuscript. Policy briefs and briefing documents should be noted as prominently on a policy researcher's curriculum vitae as peer-reviewed publications.

Academic researchers need a better understanding of how policy decisions are actually made, by whom, and when. Effective uptake of research requires knowledge of who the influential decision makers are, how to access these pivotal players, and when policies are to be deliberated. Most policy decisions will not wait until prospective studies are conducted. If research results are to be used in policy making, results must be readily

available. This means academics must be visionary and anticipate policy issues of the future. Today's research must be designed to meet the policy agenda of the coming months and years.

4. The research questions I chose to ask and the studies' results had rapid and substantial real-world effects when incorporated into policy

On the basis of this work, the Kyrgyz government decided to scale up the rural pharmacy initiative pilot to additional rural regions. Researchers coordinated with the Asian Development Bank, the funders of the expansion, incorporating lessons learned from these studies into the justification and design of the scale-up. The financial documentation and accounting systems created for this research were given to the non-governmental organization managing the rural pharmacy initiative, replacing the old system of collecting and hand-counting numbers from hundreds of pieces of paper. The Kyrgyz Ministry of Health has discarded regulatory price controls as a feasible option to lower medicine prices.

Research comparing ARV prices paid across similar countries was used to strengthen accountability arrangements within and outside the GFATM. The analyses in chapter 3.1 led to requests from civil society organizations for further drill-down research in specific geographic regions. At the request of the Open Society Institute (OSI), I conducted offshoots of the analyses from chapter 3.1, not presented in this body of work, comparing ARV prices paid across countries of the former Soviet Union [13]. The OSI facilitated dissemination and utilization of these results by civil society organizations through a regional seminar held in Kiev [14], transforming academic findings into advocacy materials, and providing technical assistance to countries I identified as paying excessively high prices for ARVs. Their multi-pronged approach, based upon this research, built capacity within civil society organizations from several countries to lobby their governments for greater accountability of HIV/AIDS spending. Civil society organizations are now comparing their governments' purchases against those of other countries and advocating for more efficient spending. I also disseminated methods and analyses from this thesis through briefs published by organizations working to minimize corruption in the pharmaceutical sector [15].

The GFATM itself instituted many of our recommendations, including the creation of alerts when countries report exorbitant prices to the on-line reporting system; the use of regular benchmarking analyses as described in chapter 3.1; and the use of the OSI offshoot analyses to identify and investigate high and low-performing countries [13]. The GFATM also adopted recommendations around data scrutiny, management, validation, and presentation. I first presented issues with GFATM data quality in Geneva

in 2006, and GFATM initially responded defensively. But by 2009 it had retired its old reporting system and replaced it with an impressive new system [16] complete with the robust quality assurance processes that I conducted and recommended in our research. Whereas I estimated compliance with ARV procurement reporting to be approximately 30% in 2006, by 2010 reporting rates were above 90%. Finally, the GFATM's Office of the Inspector General has conducted an internal audit of the procurement and supply chain management, including the voluntary pooled procurement system, to assess, among many things, if the current design and operations are consistent with the GFATM's market dynamics principles [17].

The United Kingdom Department of International Development (DfID) has been the strongest supporter and user of these global policy research findings. Results and recommendations from studies included in this thesis and other offshoot analyses were incorporated into the development of the 2008 DfID Global HIV/AIDS Strategy [18-19] and discussed with many other organizations adopting market-based approaches to health. The methods used in the models I created for the UK are now being replicated in consultancies to identify market-shaping opportunities in the GFATM [20].

UNITAID has adopted many of my methodologies into its project assessments and market monitoring activities. My suggestions and requests to transform our analytic market intelligence system into a publicly available resource were met with funding from UNITAID and the Bill & Melinda Gates Foundation. Within one year the analytic database used in this thesis will be expanded and made public, modeling how academics can engage in data-sharing and the creation of public goods.

Perhaps the most striking and compelling use of this research, however, is by governments, civil society organizations, and other advocates fighting the intellectual property restrictions proposed under European Union-India free trade negotiations [21-22]. My research quantifying the role Indian generic manufacturers played in the global supply of ARVs starkly documented the stakes on the table; it presented results in a simplified manner that could be accessed, digested, and communicated to a broad audience as trade negotiations were underway [10]. This presentation, combined with a UNITAID press release [23] and proactive engagement of the media, sent our research results viral, appearing in newspapers, websites, and conference agendas across all regions of the world. Within four months of publication, the article was rated the second most accessed article of all time in the *Journal of the International AIDS Society[24].* These particular results are being used by advocates for access to medicines worldwide and are likely some of the most commonly cited results from pharmaceutical policy research in developing countries to date.

5. Future directions and challenges for access to medicines were discernible in the market and research environments in which I contextualized our work

In conducting this research over a period of several years, I have observed broader trends both in the market for medicines and in academic research that take us beyond our original objectives, and I make recommendations in three broad categories.

(a) Access interventions must consider the convergence of countries' health policies, industrial organization, economic development and political landscape

Pharmaceutical markets have changed substantially over the past few decades. Growth in these markets is rapidly shifting from high- to middle-income countries. While pharmaceutical markets in the United States and Europe will remain stagnant or experience minimal growth from 2008 to 2013, emerging markets such as India, Russia, Brazil, Mexico, Turkey, and South Korea are projected to increase upwards of 7-17% [25]. China's pharmaceutical market will experience the most growth, with expected increases up to 23% over the same time period [25]. Industrialization and economic development are driving the expansion of these markets, resulting in shifts of pharmaceutical production from developed to developing countries.

The BRICS (Brazil, Russia, India, China, and South Africa) countries, for example, have substantial capacity to produce medicines and are likely to assume increasing responsibility for the provision of health services to their populations.

As middle-income countries become less reliant on donor funds, the global market-share for medicines will shift from a donor-dominated market to a market split across a few dominant national purchasers. The government of South Africa is now self-funding for programs that reach 72% of people receiving HIV/AIDS treatment [26] in a country that is thought to represent approximately 25% of the global (low- and middle-income) market for ARVs [26]. Decisions made by "market anchor" countries like South Africa have ripple effects beyond their borders. Countries in the surrounding regions are increasingly looking to harmonize their policies, guidelines, and standards to those of dominant countries rather than global players.

The power base, therefore, may begin to shift towards a few middle-income countries with substantial buying power and influence on neighboring countries. Policies and minimum standards for medicines set by some of these national governments, however, are typically inconsistent and sometimes directly at odds with those set at global level by donors and international organizations. Global health organizations tend to set policies based upon minimum standards defined by the developed world, whereas national policies are designed to meet domestic goals, balancing business, trade, political, and economic development interests with those of the health sector. In South Africa, for

example, the donors have their own sets of conditions and policies while the government has a somewhat different set. This two-tiered system in many middle-income countries has resulted in a segmented market where some manufacturers are choosing to serve their own less-regulated markets instead of low-income markets that are highly regulated by donors.

Leading manufacturers in India are gravitating towards upstream research and development in lieu of final product formulation. Indian manufacturers are also seeking to serve high-income markets with medicines for cardiovascular disease, diabetes, and other chronic conditions. Re-orientation among leading Indian manufacturers may create opportunities for lower-level Indian manufacturers and local producers in low-income countries to establish down-stream production of medicines for low-income markets. This potential window of opportunity fuels highly politicized campaigns as to the feasibility and utility of local production in low-income countries.

In the north, pharmaceutical manufacturers from industrialized countries are turning their attention to emerging middle-income markets with acquisition of Indian and other generic firms as a means of increasing market share. At the same time, developing countries are negotiating bilateral, regional, and multilateral trade agreements and intellectual property requirements which will further define the future shape and size of pharmaceutical markets in both developing and developed countries.

The changing global health landscape requires new approaches to improve access to medicines in low- and middle-income countries. Donors currently limit the funds they provide to middle-income countries, but because of the growing interconnectedness of pharmaceutical markets, it may be necessary to spend more on interventions in middle-income countries to take advantage of the spillover effect they have elsewhere. If donors are only purchasing on behalf of the poorest countries, they will lose their leverage to shape global markets as the ultimate power will be held by countries such as India, China, and South Africa. **Donors will, therefore, need to redirect their strategies towards collaboration with governments of "market anchor" countries to ensure that national and global policies are harmonized and directed towards shared public health goals.**

In light of these changes in, among and between low- and middle income countries, global health organizations must bring together key stakeholders to discuss challenges, opportunities, and new approaches to advance public health goals. **Initiatives aiming to improve access to medicines through market interventions must take into account the interconnectedness of health policy, industrial organization, economic development and political factors at both global and national levels.**

(b) The access to medicines framework must be updated to keep pace with a changing world

The changing global health landscape and the shift towards market-based access interventions require a new vision of the access to medicines framework. The WHO access framework described in Chapter 1 (rational selection, affordable prices, sustainable financing, and reliable health and supply systems) is now more than two decades old and no longer fully reflects current issues or approaches to increase access to medicines. It was created to support national policy makers at a time when mega-funds were non-existent and most access to medicines initiatives were nationally-funded, public-sector programs. But globalization, development, and massive investments have resulted in a shift toward market-based approaches mounted through global initiatives.

Two newer access frameworks have recently been proposed, providing alternatives more suitable to the current environment. First, the Global Alliance for Tuberculosis Drug Development adopted a three-pronged access strategy comprised of affordability, adoption, and availability, the *AAA Strategy* [27]. Under this framework, anti-tuberculosis medicines must be affordable to the poorest patients, accepted and introduced by global, national, and local authorities, and efficiently distributed throughout the supply chain. While there are many similarities between the *AAA strategy* and the original WHO access framework, the *AAA* approach highlights the need to promote research and development of new products. And this need is dramatic, especially since few incentives exist for innovation and development of new medicines and formulations for low-volume, low-value developing country markets. For example, despite decades of investments in tuberculosis treatment, there are still no pediatric fixed-dose combination anti-tuberculosis medicines available for children. The lack of well-adapted and age-specific formulations creates a major barrier to access to medicines that can only be overcome through additional research and development.

The *AAA strategy* also includes another new critical component, namely product adoption. Experience over the past few decades shows that the mere availability of affordable and improved technologies does not translate into their use in developing countries, a situation demonstrated in a few recent studies. Nandakumar *et al.*, for example, describe dramatic differences in the rate and extent to which new medicines in the United States have been adopted, compared to technologies (e.g., artemisinin-combination therapies and hepatitis B vaccine) in developing country markets [28]. Other studies reveal market barriers for uptake of magnesium sulfate injection for the treatment of eclampsia and pre-eclampsia [29-30]. But the research is sparse. Whereas industrial economists have been tracking the diffusion of technologies in the developed world for several decades, little work has been done to measure adoption and diffusion of health technologies in developing country markets. Current access initiatives often aim to increase the rate and

extent to which new, improved products get adopted in developing country markets; but this approach is not reflected in the original access to medicines framework. The *AAA* framework corrects that gap.

The second alternative framework, developed by Reich and Frost, expands upon the *AAA strategy* with a "four A" framework, adding architecture to the availability, affordability, and adoption domains [31]. Architecture encompasses the global landscape of organizations and market players, the structures within and across organizations, and the need to coordinate activities in order to improve availability, affordability, and adoption of health products [31].

Both the *AAA strategy* and the Reich/Frost framework provide updated access models that better reflect today's issues and current access to medicines initiatives in developing countries. It is time for the WHO to revise the conceptual framework of its guidance to member states. An access framework more reflective of today's reality would facilitate the design and implementation of appropriate pharmaceutical policies and strategies to promote access to medicines in developing countries. A revised model could also support identification of priority pharmaceutical policy research questions as well as the design and execution of more rigorous methods to examine access to medicines issues**.**

(c) Data sharing and public goods: it's time for a paradigm shift in global health research and the role of academia

The field of public health lags behind other disciplines in data sharing. Whereas sciences such as genomics, bioinformatics, and neurology have made great strides in sharing research data, public health researchers for the most part continue to hoard the information they collect. Some donor organizations have established conditions and policies requiring researchers to share their data, but these requirements are either few and far between or poorly enforced.

Data-hoarding has become a norm deeply entrenched in academic culture; its roots are obvious. Academic promotions are typically based upon the number and type of a faculty member's publications, the number of times publications are accessed or cited (i.e. the impact factor), and fund-raising. Warnings to "publish or perish" are still pronounced by many university administrators. Publications are, in essence, the currency of academia, where the status of an academic researcher – and the foundation of personal satisfaction and ego gratification -- are largely determined by one's publication history. The sole possession of unique data sources leads to innovative research and the generation of new knowledge, all prerequisites to publication. Reinforcing this culture is the increased funding of academic positions with research grants. When a researcher's salary

comes from donor payments funneled through an academic institution, a track record in creating data sources, analyzing data, and publishing results is key to successful grant-writing. Withholding data and the methods to develop innovative data sources from others, therefore, is often necessary to ensure not just survival but also a climb up the academic ladder.

But data-hoarding by global health researchers works against the very public health and development goals we purport to pursue. Researchers typically create large analytic data sets to answer one or two primary research questions. While they may intend to further mine their data to answer additional questions, practicalities often dictate that they must move on to their next grant and in reality abandon the "old" data. But such data sources are potential goldmines for public health. They should be used and interpreted by other researchers to address different and equally important questions. International and civil society organizations, donors, and country researchers, for example, can use these data sources to advance global health goals. Perhaps the most compelling reason to share research data is to put information back in the hands of the people we are trying to serve. Data collected on people living in resource-limited settings should be available to them. Access to this information in developing countries would facilitate not only policy and strategy decisions, but also capacity-building for many local professionals: academic researchers, advocates, government officials, and programme managers.

The need for data sharing among those using market-based approaches to improve access to medicines is particularly compelling. Markets are highly complex -- comprised of and determined by many different players --and dynamic, with continuously shifting components. Layering on the policy decisions of multiple organizations adds another level of complexity to building and maintaining these databases. It is unlikely that any one academic will have access to the multitude of data sources needed to conduct this type of research. It is even more unlikely that multiple researchers would spend time and money to recreate these data sources to ask new research questions. And even if a few academics could create and update market intelligence databases, the data will have untapped potential utility if it is inaccessible to international organizations, policy makers, and other academics.

Organizations adopting market approaches must continuously monitor market dynamics to identify and address market bottlenecks, measure the impacts of their initiatives, and direct future global health strategies. **The time has come for academics, donors, governments, international organizations, non-governmental and civil society organizations to collaborate on the development, maintenance and use of market intelligence databases to support market-based initiatives.** Each global health player should submit routinely collected information into an exchange where data can be

cleaned, coded, combined, and repackaged into one large, publicly accessible resource or public health good. Data sharing by a few key organizations can benefit a multitude of users and result in a product whereby the "whole is greater than the sum of its parts".

Academics should play a pivotal role in creating such public goods for public health. The critical skills and resources needed to generate these data warehouses are abundant in academia. But engaging academics in sharing data and developing public health goods requires a shift in priorities and incentives**. University administrators need to replace their "publish or perish" mantra with "share and flourish", which requires changes in the current system of academic rewards.** There must be explicit expectation and recognition of data sharing in hiring and promotion schemes. Gardner recommends new citation and credit paradigms [32], while Klump *et al.* suggest rewards for data publication [33]. Many others, such as Boyer, recommend that academe acknowledge the importance of the "scholarship of application" [34]. A new impact factor could be measured in terms of research resulting in knowledge transfer, policy development, or changes in practice. The impact of public health research might even be measured by the number of lives saved, equity goals attained, and other assessments of global health initiatives. Academics working to improve public health in poor countries should not continue to accept impact measurements solely in terms of their premier journal publications or the grant monies they've secured for their institutions. **Because data sharing is risky business for academics, donors must find and support those who possess the passion and social capital necessary to shift the data-hoarding paradigm**.

The research presented in this thesis has shown that information on pharmaceutical markets and policies is widely available from numerous organizations. I've shown how it can be harnessed and transformed into large analytic data sets to support policy research, practices and policies of international organizations, and strategic planning. Donors are clearly willing to invest in creating public health goods in academia, as evidenced by the grants awarded for this research. A recent editorial in Open Medicine noted, "We believe the debate isn't about *whether* we will share data in the future but, rather, about *how* we will share it" [35]. I add my voice to this conversation, and urge that the sharing come about sooner rather than later.

Conclusion

This thesis advances pharmaceutical policy and research agendas by identifying new data sources and applying novel methods not typically used in pharmaceutical policy

research. In so doing I dispel numerous conventional wisdoms about which policies and practices improve access to medicines and offer evidence-based recommendations obtained through sound research.

I present research conducted at national and global levels. Findings from these studies have had dramatic impacts on policy and program decisions made by donors, international organizations, governments and others. Strategic dissemination, including pre-publication release of findings, direct communication with donors and key stakeholders, and publication in open access journals enabled research results to be used in real-time policy making.

Whereas a lack of readily-available information previously contributed to a dearth of pharmaceutical policy research in developing countries, transparency and accountability initiatives launched in an electronic era now provide robust data sources for pharmaceutical policy research. As donors, international organizations and governments look towards market interventions to improve access to medicines, there is a need to develop rich data sources that reflect the complex and dynamic policy and market environments. Academic and donor incentives are needed to promote data sharing and the creation of public goods whereby many organizations contribute information into publicly available global data exchanges that can be used to measure progress and impacts of access to medicines initiatives. I encourage academic public health researchers to adopt new paradigms of data sharing in lieu of data hoarding to advance global health goals.

Multidisciplinary approaches need to be developed and adapted as the global health and policy landscapes evolve. I describe extraordinary restructuring of the global pharmaceutical industry. Manufacturers in developed countries are acquiring those in developing countries while manufacturers in middle-income countries are redirecting their investments to upstream production and supply of high-income markets. At the same time, the governments of these emerging economies are assuming more responsibility for treating their population, leaving donors with less leverage to use policy to influence markets and access to medicines. National polices are coming head-to-head with donor polices and some manufacturers are choosing to supply local markets over highly regulated donor markets. Access to medicines initiatives of the future must consider the convergence of health policy, industrial organization, development and politics.

I also note the need for WHO to revise its 20-year old access to medicines framework to keep pace with a changing world. New access frameworks have been proposed that better reflect today's market-based approach, including domains such as medicine affordability, adoption, availability and architecture [27, 31]. These newer frameworks build upon historical models by targeting the rate and extent to which new, improved technologies are developed, adopted and diffused in developing countries. They also

highlight the intricate web of global, regional and local stakeholders who all play pivotal roles in access to medicines.

Finally, I note the need for pharmaceutical policy researchers to be actively engaged in policy dialogue. I suggest that by looking back through retrospective research we gain great insight on how polices will play out in the future. Whereas policy decisions don't wait for research results, findings that are readily available at the time a policy is deliberated can be used to inform decisions. This means that research conducted today must be done with a vision to address compelling issues we anticipate in the future. I also recommend dissemination of research results through mechanisms more likely to reach policy-makers in real time, namely press releases, news features, newspaper editorials, and policy briefs.

This body of research shows the time has come for pharmaceutical policy to move beyond decisions made according to conventional wisdom to those informed by evidence obtained from strategic, robust research. Data unavailability is no longer a valid excuse for the dearth of research in this arena. Academic researchers must adopt new approaches of data sharing to ensure the greatest public health benefit is derived from their research. Information obtained through global health research must be made available to those we purport to serve. The global health landscape is rapidly changing. So must the practices ensconced in academia that work against public health goals.

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Summary

The thesis begins with a general introduction of access to medicines and pharmaceutical policy research in **Chapter 1,** *Beyond conventional wisdom: innovative research methods to promote evidence-based pharmaceutical policies and improve access to medicines*. In this section, we describe more than three decades of global efforts to promote access to medicines in developing countries through pharmaceutical policy interventions. We note there is little evidence to guide pharmaceutical policy decisions at national or global level despite the global focus on access and an unprecedented influx of funds for HIV/AIDS, tuberculosis, and malaria over the past ten years. We suggest that the dearth of pharmaceutical policy research is likely due to a number of factors including unavailable or unreliable data, inadequate methods to address the effects of multiple determinants on multiple outcomes in complex health policy environments, lack of trained pharmaceutical policy researchers, and an overall complacency that academic research could never provide results in the timely fashion necessary to support real-time policy decision-making.

We show, however, a changing world in terms of publicly available information and global expectations. Efforts to promote transparency of information and accountability in spending have resulted in a wealth of new information posted in the public domain. This new information, however, is not well used by researchers, donors, international organizations, or governments. In addition, numerous donors, international organizations, and global health initiatives have recently adopted market-based approaches aimed at increasing access to medicines and diagnostics in developing countries. To date, however, there has been no clear definition of what it means to approach access from a market perspective, how to monitor markets for health commodities in developing countries, or how to assess the impacts of policy changes on market evolution in relation to access to medicines.

We provide a framework that portrays the supply and demand sides of pharmaceutical markets, the interactions between the supply and demand sides, and some determinants of market characteristics. We clarify our main goal: to further develop methodological approaches for examining pharmaceutical policy and access to medicines issues in developing countries, applying the aforementioned market framework. Specifically, we aim to identify and utilize new data sources made available through information collected and posted for non-research purposes and apply new analytic methods not typically applied in pharmaceutical policy research in developing countries. We address policies and access to medicines at both national and global levels.

Across chapters 2 through 4, we present seven published studies examining the implications of pharmaceutical policies in developing countries. In **Chapter 2**, *Local data for local policy: new data sources and methods to inform national policy on access to medicines*, we identify and transform existing, routinely-collected information into data that helps better understand regional and national pricing strategies for medicines in Kyrgyzstan. In Chapter 2.1, we harness medicines insurance claims to assess the impact of a newly established not-for-profit pharmacy network on medicine price competition in nearby privately owned pharmacies. The Kyrgyz government, in collaboration with a non-governmental organization and a local village health committee, established a network of pharmacies in 12 remote villages where no pharmacies previously existed. The pharmacy network was designed as a not-for-profit initiative aimed to increase access to medicines by making quality, affordable medicines physically available within the remote villages. We received anecdotal reports that private pharmacies found it necessary to lower their medicine prices and compete with the new pharmacy network, despite great distances between the private pharmacies and those in the not-for-profit network. To examine the impact of the new pharmacy network we used insurance claims data to conduct descriptive and multivariate time-series analyses on prices for 30 high-volume medicines before, during and after the establishment of the network.

Private competitor pharmacies changed their prices in reaction to not-for-profit pharmacies for 70% (21/30) of medicines studied. Competitors decreased their prices for 57% (17/30) of medicines and increased their prices for 13% (4/30) to match prices charged by the not-for-profit network. Even among the 30% (9/30) of medicines with no price difference at the end of the study, five of these nine medicines exhibited initial price reductions upon introduction of the not-for-profit network but were later increased to baseline high prices. Multivariate analyses confirmed descriptive findings and revealed significant price changes at private competitor pharmacies for 74% (14/19) of medicines examined, with 47% (9/19) exhibiting price decreases and 26% (5/19) exhibiting price increases to match not-for-profit prices.

The study reveals the power of competition to affect medicine prices, even in low-volume, remote regions. The not-for-profit pharmacy network not only met its desired goals of increasing physical and financial access to quality medicines in target villages, it also created a spill-over effect of price reduction for several medicines in private pharmacies located more than 20 kilometers away from the intervention villages. We highlight the importance of assessing the external impact of even localized interventions and encourage donors to support additional public-private initiatives that promote competition as a means of improving access to medicines.

The second Kyrgyzstan-based study in Chapter 2.2 examines medicine price mark-ups in relation to the amount of revenue needed to establish and sustain pharmacy businesses in rural Kyrgyzstan. While numerous surveys have been conducted to examine medicine mark-ups, these have typically been conducted without considering the minimal revenues needed to ensure the financial viability of pharmacy enterprises. Many attempts to establish not-for-profit pharmacies in developing countries have failed due to poor financial planning and management. Since the majority of people in developing countries seek care from private pharmacies, it is important to strike a balance between medicine pricing schemes and pharmacy sustainability. We again utilize existing, routinely collected information by way of financial and inventory documents from 12 outlets comprising the rural not-for-profit pharmacy network established in 2004 and employ cost accounting methods to examine minimum medicine mark-ups needed to sustain pharmacy businesses in rural Kyrgyzstan.

We show that pharmacy networks can be successfully established and managed with very low levels of financing when cost-sharing and social capital are available. Results show the not-for-profit network operated at a break-even profit level, overall, leaving little room for substantial price reduction in medicines. Mark-ups varied substantially across medicines, ranging from 32% to 244%. While the management of the not-for-profit network anticipated maximum medicine-mark-ups of 25% when establishing the pharmacies, low volume and high carrying costs resulted in mark-ups of 50-99% for 46% of products and more than 100% for 35% of products. Only 19% of medicines revealed mark-ups less than 50%. Because this pharmacy network enjoyed social and financial support unavailable to the private sector, we anticipate that minimum medicine mark-ups to sustain private pharmacy business would be even higher.

The study demonstrates that pharmacy level financial data is available and can be used to assess medicine mark-ups within the context of the cost to do business. Medicine price assessments done outside of this context may result in well-intentioned interventions to drive down medicine prices to levels that deter businessmen from opening and operating pharmacies and could, therefore, further worsen access to medicines, especially in remote regions. We also suggest that the use of price controls as a means of promoting access to medicines, in the absence of a clear understanding of local cost and revenue structures, imposes arbitrary and potentially damaging limits on pharmacy businesses.

In **Chapter 3**, *Innovative approaches to examine medicine prices and their relationships to policies at global level,* we apply robust cleaning and validation algorithms to existing procurement data collected by large-scale donors and international organizations and combine this data with information readily available from more than 20 other sources not typically used for research purposes. We demonstrate how otherwise unused and un-

reliable data can be transformed and used in pharmaceutical policy research to empower national purchasers, donors and policy makers. In the first study, presented in Chapter 3.1, we utilize 15,111 purchase transactions for donor-funded antiretroviral (ARV) medicines from July 2002 to June 2008 and provide the first comprehensive description of the emergence and evolution of the ARV market in developing countries following unprecedented HIV/AIDS funding by the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) in 2002 and the United States President's Emergency Plan for AIDS Relief (PEPFAR) in 2004.

Our study reveals dramatic price reductions across nearly all ARVs. Generic ARVs belonging to the classes of nucleoside reverse-transcriptase inhibitors (NRTIs) and non-nucleoside reverse-transcriptase inhibitors (NNRTIs) revealed cumulative price decreases of 62% and 72%, respectively, while generic ARVs in the class of protease inhibitors (PIs) showed a 37% price reduction. Branded NRTIs and NNRTIs showed less price reduction, with cumulative price decreases of 12% and 29%, respectively, while branded PIs exhibited an 80% price reduction. Generic NRTI and NNRTIs were consistently less expensive than branded versions, but generic PIs were generally more expensive than branded versions. We found extreme variation in prices paid for ARVs across similar countries. Price variations ranged up to 10-fold and 20-fold for generic and brand ARVs, respectively, in low-income countries and up to nine-fold and 16-fold for generic and brand ARVs, respectively, in middle-income countries.

Our study documents dramatic price reductions presumably achieved through generic competition. We also highlight unexplained and substantial variability in prices paid for the same ARVs across similar countries. We suggest that donors and international organizations ensure reliability of ARV purchase data and make it available in an easy-to-use format to national procurement agents engaged in price negotiation. We also suggest that donors more actively monitor prices paid by their recipients to identify and assist countries paying excessively high prices for ARVs.

In Chapter 3.2 we build upon the donor-funded ARV transactional data set, merging additional existing information from numerous other sources to examine impacts of pharmaceutical policies and strategies on ARV prices. We utilized generalized estimating equation linear regression on 7,253 ARV procurement transactions to estimate the impact of three global price reduction strategies: pooled procurement arrangements, third-party price negotiation of generic ARVs, and differential pricing of branded ARVs.

We found no association between price and volumes purchased for 19 of 24 ARV dosage forms examined. For five of 19 ARVs, high-volume ARV purchases ranged 4-21% less expensive than medium- or low-volume purchases. Nine of 13 generic ARVs were priced 6-36% lower when purchased under third-party price negotiation arrangements

made by the Clinton HIV/AIDS Initiative. In general, branded ARVs offered under differential pricing schemes could not compete with generic prices, with 15 of 18 branded ARVs priced 23-498% higher than generic counterparts.

Our study provides important and timely input into the design of a voluntary pooled-procurement mechanism under discussion at the GFATM. While conventional wisdom suggests "buy more, pay less", this study demonstrates purchase volume is not a reliable driver of ARV prices and suggests pooling arrangements may not be the most desirable mechanism to improve national procurement efficiency and may result in the creation of monopsonies and other market distortions. We suggest consideration of alternative approaches to reduce ARV prices, including improvements in financial management, removal of barriers to generic competition, improved ARV forecasting, and technology transfer.

Research presented in **Chapter 4** moves beyond price analyses towards a better understanding of how pharmaceutical markets emerge and evolve in relation to pharmaceutical policies made at global level. The first study in Chapter 4.1 describes the interconnectedness of decisions made by international organizations and donors and specific implications for market evolution of first-line ARV medicines in developing countries. We build upon our prior ARV data sets to create a market intelligence database comprised of information from more than thirty different sources. Using 12,958 donor-funded ARV purchase transactions from 2002-2008 and other data contained in the ARV market intelligence database, we examine relationships between first-line ARV market trends and World Health Organization HIV/AIDS treatment guidelines, WHO Prequalification Programme and US Food and Drug Administration ARV approvals, and procurement policies of GFATM, PEPFAR, and UNITAID.

We show that early WHO HIV/AIDS treatment guidelines that listed only four regimens and five ARVs consolidated demand around a few products, thereby creating incentives for generic producers to enter the market and offer competitive prices. When WHO later expanded first-line treatment guidelines to include 24 different first-line regimens, demand became scattered across numerous products, creating uncertainty among manufacturers, and few fixed-dose combination ARVs were developed to support the numerous new first line regimens. ARV purchase volumes increased greater than 15-fold immediately following their recommendation by WHO, showing the dramatic role WHO HIV/AIDS treatment guidelines play in shaping the global ARV market.

We also show how quality approvals by the WHO Prequalification and US FDA influence market dynamics. Uptake of fixed-dose-combination ARVs was delayed in PEPFAR-funded programs until the US FDA approved the first FDC product in 2006, three years later than the WHO Prequalification approval needed for purchases with GFATM

programs. Still, we describe a highly competitive market for first-line ARVs that quickly emerged after GFATM and PEPFAR were established. Within a few years the market is characterized by increasing demand for a few key ARVs, the presence of several quality-assured manufacturers, more than 100 individual buyers, and falling prices.

We show, however, that recent procurement policies by PEFPAR, GFATM and UNITAID are likely to affect market structure. Under traditional GFATM schemes, ARV procurement was managed by each individual recipient country and created market conditions whereby 6-8 manufacturers could compete for business and split the global market. New ARVs recommended by WHO, UNITAID and PEPFAR together accounted for 50-85% of 2008 market volume. Both UNITAID and PEPFAR procure under pooled procurement arrangements and award contracts to only 1-2 suppliers. As donors increase the use of pooled procurement mechanisms, the market will likely consolidate to fewer suppliers than historically observed under disaggregated purchasing and may present challenges for long-term supply and competition.

In this landmark paper we demonstrate how ARV markets can and should be monitored in a comprehensive and integrated manner and conclude by advising donors and international organizations to consider how their policy decisions may impact the long-term evolution of global ARV markets to ensure these markets remain viable and competitive.

In Chapter 4.2 we utilize our ARV market intelligence database to describe challenges encountered in the availability and utilization of pediatric ARV medicines in developing countries. Using 7,989 pediatric ARV purchases and other data in the database, we measure uptake, dispersion, and prices paid for pediatric ARV formulations across countries and programs from 2002 to 2009. We reveal describe a fragile pediatric ARV market with few incentives for manufacturer entry. Global volumes are low and ironically become lower and less attractive when manufacturers develop more age-appropriate formulations.

While pressure from activists and incentives from donors have resulted in the development of new pediatric FDC products, most of these FDCs are produced by only one manufacturer. Uptake of pediatric FDCs has been much lower than the forecasted and expected demand. UNITAID accounted for 97-100% of pediatric FDC market volume in 2008 and 2009. Only three countries reported purchase of pediatric FDCs outside of UNITAID programs, despite price savings and clinical advantages over liquid and other alternatives. We again highlight the pros and cons of large-scale, pooled procurement initiatives. In the case of pediatric ARVs, some organizations note difficulty obtaining pediatric ARVs not procured through the dominant pooled purchaser, suggesting that dominant large-scale buyers are dictating the global supply of ARVs.

We also show that creating pressure and incentives to produce low-demand products is insufficient and must be accompanied by interventions to facilitate uptake of new products into health systems. We suggest that introducing new pediatric products likely requires revision of all treatment guidelines as well as retraining of all practitioners and caregivers, and may further complicate procurement and distribution systems. We note that pediatric ARV markets are not lucrative and will become less appealing if current efforts to prevent mother-to-child HIV transmission are successful in reducing the number of HIV-positive children. Still, there is considerable need for continued innovation in pediatric ARV formulations.

We caution that the development of new pediatric ARVs may be in jeopardy if we cannot assure manufacturers of a minimum quantity of sales. We recommend that donors monitor new product utilization as described in our paper and that further research be conducted at country level to identify barriers to uptake and dispersion. We stress the need for improvements in global forecasting that more accurately estimate the likelihood that a new product will be adopted at country level rather than estimating demand based upon disease burden.

The last study, presented in Chapter 4.3, highlights the critical role Indian generic ARV producers have played to date in the global scale-up of HIV/AIDS treatment. Using 17,646 donor-funded ARV transactions from 2003-2008 and other data from our market intelligence database, we reveal that Indian-produced generic ARVs accounted for more than 80% of annual ARV purchase volume since 2004. Ninety-six of 100 countries reported purchase of Indian-produced generic ARVs in 2008. Indian generics accounted for 91% of pediatric and 88% of adult NRTI and NNRTI purchases in 2008. Prices for Indian-produced first-line ARV regimens were markedly less than prices for non-Indian generic and branded versions. While branded products have typically dominated the PI market, Indian generics have begin to acquire PI market share, representing 19% of 2008 PI purchase volume. Newly recommended ARVs are substantially more expensive than ARVs used to date and without generic competition among Indian producers, it is unlikely that we will experience the price reductions observed in the past.

We express concern that ongoing and future bilateral and multilateral trade agreements being negotiated with India may result in higher prices and fewer innovations in formulation development and may therefore jeopardize future access to safer and more effective ARVs in developing countries. We recommend that India and its trade partners ensure that sufficient policy space remain for India to continue playing its central role in supplying developing countries with low-priced, quality-assured generic medicines.

The thesis concludes with Chapter 5, *Back to the future: lessons learned and implications for the next wave of pharmaceutical policy research in developing countries.* In this chapter

we provide a general summary of key lessons learned and suggest next steps for access to medicines initiatives. We discuss how our research findings delivered evidence to refute common conventional wisdoms prevalent in global health communities. We stress the importance of setting a high bar for data management standards among those who post and use publicly available data to ensure research validity and reproducibility. We make strong recommendations for a paradigm shift towards data sharing and public goods among global health researchers. We describe the application and uptake of our research findings by key decision makers, providing a model for how researchers can support knowledge transfer and incorporate evidence into policy. We discuss future directions and challenges for access to medicines initiatives and suggest multidisciplinary research approaches to predict and address these forthcoming issues.

Samenvatting

Dit proefschrift begint met een algemene inleiding over de toegankelijkheid van geneesmiddelen en onderzoek naar farmaceutisch beleid in **Hoofdstuk 1,** *Voorbij conventionele wijsheid: vernieuwende onderzoeksmethodes om farmaceutisch beleid gebaseerd op bewijs te bevorderen en de toegankelijkheid van geneesmiddelen te verbeteren.* In dit onderdeel beschrijven wij meer dan drie decennia van globale inspanningen om de toegankelijkheid van geneesmiddelen in ontwikkelingslanden te bevorderen door interventies in het farmaceutisch beleid. Wij zien dat er weinig bewijs is om als leidraad te dienen voor farmaceutische beleidsbeslissingen op nationaal of internationaal niveau, ondanks de internationale focus op toegankelijkheid en een ongekende stroom van gelden voor HIV/AIDS, tuberculose en malaria in de laatste tien jaar. Wij suggereren dat het gebrek aan onderzoek naar farmaceutisch beleid waarschijnlijk te wijten is aan een aantal factoren waaronder onbeschikbare of onbetrouwbare gegevens, ontoereikende methodes om de gevolgen van verschillende determinanten op verschillende uitkomsten in complexe omgevingen van gezondheidsbeleid te bestuderen, een gebrek aan opgeleide onderzoekers inzake farmaceutisch beleid en een algehele genoegzaamheid dat academisch onderzoek nooit vroeg genoeg resultaten zou kunnen opleveren om het nemen van politieke beslissingen te ondersteunen.

Wij tonen echter een veranderende wereld aan in termen van publiek beschikbare informatie en internationale verwachtingen. Inspanningen om transparantie van informatie en verantwoordelijkheid in uitgaven te bevorderen, hebben geleid tot een rijkdom van nieuwe informatie die beschikbaar is in het publieke domein. Deze nieuwe informatie wordt echter niet goed aangewend door onderzoekers, donoren, internationale organisaties of overheden. Bovendien hebben talrijke donoren, internationale organisaties en internationale gezondheidsinitiatieven zich marktgeoriënteerde benaderingen toegeëigend die het verhogen van de toegankelijkheid van geneesmiddelen en diagnostiek in ontwikkelingslanden tot doel hebben. Tot op heden is het echter onduidelijk wat het betekent om de toegankelijkheid vanuit een marktperspectief te benaderen, hoe de markten voor gezondheidsproducten in ontwikkelingslanden te controleren, of hoe de gevolgen te beoordelen van politieke veranderingen in de marktontwikkeling met betrekking tot de toegankelijkheid van geneesmiddelen.

Wij leveren een kader waarin vraag en aanbod van de farmaceutische markten, de interacties tussen vraag en aanbod en enkele determinanten van marktkarakteristieken beschreven worden. Wij verduidelijken onze belangrijkste doelstelling: het verder ontwikkelen van methodologische benaderingen om het farmaceutische beleid en de problemen rond de toegankelijkheid van geneesmiddelen in ontwikkelingslanden te onderzoeken met toepassing van het bovengenoemde marktkader. In het bijzonder wil-

len wij nieuwe gegevensbronnen met informatie die voor niet-onderzoeksdoeleinden verzameld en openbaar gemaakt is, identificeren en gebruiken; en nieuwe analytische methoden die normaliter niet toegepast worden in farmaceutisch beleidsonderzoek in ontwikkelingslanden toepassen. Wij bespreken beleidsmaatregelen en toegankelijkheid van geneesmiddelen zowel op nationaal als op internationaal niveau.

In hoofdstuk 2 tot en met 4 presenteren wij zeven gepubliceerde studies die de implicaties onderzoeken van farmaceutische beleidsmaatregelen in ontwikkelingslanden. In **Hoofdstuk 2**, *Lokale gegevens voor een lokaal beleid: nieuwe gegevensbronnen en methodes om het nationaal beleid op de hoogte te brengen van de toegankelijkheid van geneesmiddelen*, identificeren en transformeren we bestaande, routinematig verzamelde informatie in gegevens die de regionale en nationale prijsstrategieën voor geneesmiddelen in Kirgizië duidelijker maken. In Hoofdstuk 2.1 maken wij gebruik van verzekeringsgegevens om de gevolgen te beoordelen van een nieuw opgericht apothekersnetwerk zonder winstoogmerk op de prijsconcurrentie inzake geneesmiddelen in nabijgelegen apotheken in particulier eigendom. De Kirgizische regering, in samenwerking met een niet-gouvernementele organisatie en een gezondheidscommissie van een lokaal dorp, richtte een apothekersnetwerk op in 12 afgelegen dorpen die daarvoor nog nooit over een apotheek hadden beschikt. Het apothekersnetwerk was ontworpen als een initiatief zonder winstoogmerk met als doel de toegankelijkheid van geneesmiddelen te verhogen door het fysiek beschikbaar maken van betaalbare medicijnen van goede kwaliteit in de afgelegen dorpen. Wij ontvingen anekdotische rapporten dat particuliere apotheken het nodig vonden hun medicijnprijzen te verlagen en te concurreren met het nieuwe apothekersnetwerk, ondanks de grote afstanden tussen de particuliere apotheken en de apotheken in het netwerk zonder winstoogmerk. Om de gevolgen van het nieuwe apothekersnetwerk te onderzoeken, hebben wij gegevens van verzekeringsclaims gebruikt om beschrijvende en multivariate analyses van tijdreeksen uit te voeren op de prijzen voor 30 veelgebruikte geneesmiddelen voor, tijdens en na de oprichting van het netwerk.

Particuliere concurrerende apotheken veranderden hun prijzen als reactie op de apotheken zonder winstoogmerk voor 70% (21/30) van de bestudeerde geneesmiddelen. Concurrenten verlaagden hun prijzen voor 57% (17/30) van de geneesmiddelen en verhoogden hun prijzen voor 13% (4/30) om overeen te komen met de prijzen van het netwerk zonder winstoogmerk. Zelfs bij de 30% (9/30) van geneesmiddelen zonder prijsverschil op het einde van de studie, vertoonden vijf van deze negen geneesmiddelen initiële prijsverlagingen bij de introductie van het netwerk zonder winstoogmerk. Later werden deze prijzen echter verhoogd tot de aanvankelijke hoge prijzen. Multivariate analyses bevestigden beschrijvende bevindingen en toonden belangrijke prijsveranderingen aan bij particuliere concurrerende apotheken voor 74% (14/19) van de onderzochte geneesmiddelen, waarbij 47% (9/19) prijsverlagingen vertoonde

en 26% (5/19) prijsverhogingen om overeen te komen met de prijzen van het netwerk zonder winstoogmerk.

De studie toont de macht van concurrentie om geneesmiddelenprijzen te beïnvloeden aan, zelfs in het geval van afgelegen kleinschalige gebieden. Het apothekersnetwerk zonder winstoogmerk heeft niet alleen de gewenste doeleinden bereikt, namelijk het verhogen van de fysieke en financiële toegankelijkheid van geneesmiddelen van goede kwaliteit in de dorpen uit de doelgroep, het creëerde ook een nuttig neven-resultaat van prijsverlaging voor verschillende geneesmiddelen in particuliere apotheken op meer dan 20 kilometer afstand van de interventiedorpen. Wij benadrukken het belang van het beoordelen van de externe gevolgen van vergelijkbare plaatselijke interventies en moedigen donoren aan verdere openbare/particuliere initiatieven die concurrentie promoten als middel om de toegankelijkheid van medicijnen te verbeteren, te ondersteunen.

De tweede studie gebaseerd in Kirgizië in Hoofdstuk 2.2 onderzoekt (winst)marges van geneesmiddelen in relatie tot de inkomsten die nodig zijn om apotheekpraktijken op te richten en te onderhouden in het rurale Kirgizië. Terwijl veel onderzoeken zijn uitgevoerd om (winst)marges van medicijnen te onderzoeken, werden deze over het algemeen uitgevoerd zonder rekening te houden met de minimale inkomsten die noodzakelijk zijn om de financiële levensvatbaarheid van apotheekondernemingen te verzekeren. Veel pogingen om apotheken zonder winstoogmerk op te richten in ontwikkelingslanden mislukten door een slechte financiële planning en beheer. Aangezien de meerderheid van de bevolking in ontwikkelingslanden geneesmiddelen van particuliere apotheken betrekt, is het belangrijk een evenwicht te vinden tussen prijszettingsregelingen voor geneesmiddelen en duurzaamheid van apotheken. Wij maken opnieuw gebruik van bestaande, routinematig verzamelde informatie door middel van financiële documenten van 12 verkooppunten die samen het rurale apothekersnetwerk zonder winstoogmerk, opgericht in 2004 vormen en we gebruiken boekhoudmethoden om de minimale marges van geneesmiddelen, die noodzakelijk zijn om apotheekondernemingen te onderhouden in het rurale Kirgizië, te onderzoeken.

Wij tonen aan dat apothekersnetwerken met succes kunnen worden opgericht en beheerd met een zeer lage financiering wanneer kosten worden gedeeld en sociaal kapitaal beschikbaar is. De resultaten tonen aan dat het netwerk zonder winstoogmerk op basis vankostendekkend winstniveau werkte, maarover het algemeen weinig ruimte overliet voor substantiële prijsverlagingen van geneesmiddelen. Marges van geneesmiddelen varieerden substantieel, van 32% tot 244%. Terwijl het management van het netwerk zonder winstoogmerk maximale marges verwachtte van 25% bij het oprichten van de apotheken, resulteerden een lage omzet en hoge financieringskosten in marges van 50-99% voor 46% van de producten en van meer dan 100% voor 35% van de producten.

Slechts 19% van de geneesmiddelen vertoonden marges van minder dan 50%. Omdat dit apothekersnetwerk sociale en financiële steun genoot die niet beschikbaar was voor de particuliere sector, verwachten wij dat minimale marges om de particuliere apotheekonderneming te onderhouden zelfs hoger zouden zijn.

De studie toont aan dat financiële gegevens op apotheekniveau beschikbaar zijn en gebruikt kunnen worden om de marges van geneesmiddelen te beoordelen in de context van de kosten die nodig zijn om een bedrijf te beheren. Prijsbeoordelingen van geneesmiddelen buiten deze context zouden kunnen resulteren in goedbedoelde interventies om medicijnprijzen te laten zakken tot een niveau waarop ondernemers afgeschrikt zouden worden om apotheken te openen en te leiden, waardoor de toegankelijkheid van geneesmiddelen verder zou kunnen verslechteren, in het bijzonder in afgelegen regio's. Wij suggereren ook dat het gebruik van prijscontroles als middel om de toegankelijkheid van geneesmiddelen te promoten, in de afwezigheid van een duidelijk inzicht in lokale kost- en opbrengststructuren, willekeurige en mogelijk schadelijke beperkingen kan toebrengen aan apotheekpraktijken.

In **Hoofdstuk 3**, *Vernieuwende benaderingen om geneesmiddelenprijzen en hun relaties met beleidsmaatregelen op internationaal niveau te onderzoeken,* passen we krachtige opschonings- en validatie-algoritmen toe op bestaande inkoopgegevens, verzameld door grootschalige donors en internationale organisaties. We combineren deze gegevens met gemakkelijk beschikbare informatie uit meer dan 20 andere bronnen die normaal gesproken niet gebruikt worden voor onderzoeksdoeleinden. Wij tonen aan hoe anders ongebruikte en onbetrouwbare gegevens kunnen worden omgevormd en gebruikt in het onderzoek naar farmaceutisch beleid om nationale afnemers, donoren en beleidsmakers te ondersteunen. In de eerste studie, in Hoofdstuk 3.1, gebruiken we 15,111 kooptransacties voor door donoren gefinancierde anti-retrovirale (ARV) geneesmiddelen van juli 2002 tot juni 2008. Daarmee leveren we de eerste uitvoerige beschrijving van het ontstaan en de ontwikkeling van de ARV-markt in ontwikkelingslanden, die volgt op nooit eerder geziene HIV/AIDS subsidies van het 'Global Fund to Fight AIDS, Tuberculosis and Malaria' (GFATM) in 2002 en het Amerikaanse 'President's Emergency Plan for AIDS Relief' (PEPFAR) in 2004.

Onze studie toont dramatische prijsverminderingen in bijna alle ARV's. Generieke ARV's behorend tot de klassen van nucleoside reverse-transcriptase inhibitoren (NRTI's) en non-nucleoside reverse-transcriptase inhibitoren (NNRTI's) vertoonden cumulatieve prijsverlagingen van respectievelijk 62% en 72%, terwijl generieke ARV's in de klasse van protease inhibitoren (PI's) een prijsverlaging van 37% toonden. Originele NRTI's en NNRTI's toonden een kleinere prijsvermindering met cumulatieve prijsverlagingen van respectievelijk 12% en 29%, terwijl originele PI's een prijsverlaging van 80% ver-

toonden. Generieke NRTI's en NNRTI's waren consequent minder duur dan originele middelen, maar generieke PI's waren over het algemeen duurder dan originele PI's. We stelden extreme prijsvariaties vast voor ARV's in vergelijkbare landen. Prijsvariaties liepen op tot het tienvoudige en het twintigvoudige voor respectievelijk generieke ARV's en originele ARV's in landen met een laag inkomen tot het negenvoudige en zestienvoudige voor respectievelijk generieke ARV's en original ARV's in landen met een gemiddeld inkomen.

Onze studie documenteert dramatische prijsreducties die waarschijnlijk teweeg gebracht zijn door generieke concurrentie. We belichten ook onverklaarde en aanzienlijke prijsverschillen voor dezelfde ARV's in vergelijkbare landen. Wij suggereren dat donoren en internationale organisaties de betrouwbaarheid van de ARV aankoopgegevens garanderen en deze beschikbaar maken in een gebruiksvriendelijk formaat voor nationale gremia die betrokken zijn bij de inkoop en prijsonderhandelingen. We suggereren ook dat donoren de prijzen die betaald zijn door hun afnemers actiever monitoren teneinde landen die extreem hoge prijzen voor ARV's betalen te identificeren en te helpen.

In Hoofdstuk 3.2 baseren we ons op de door donoren gefinancierde transactionele ARV-gegevens, terwijl we bijkomende bestaande informatie van talrijke andere bronnen samenvoegen om de gevolgen van farmaceutische beleidsmaatregelen en strategieën betreffende ARV-prijzen te onderzoeken. We maakten gebruik van 'generalized estimating equation' (GEE) lineaire regressie op 7.253 ARV inkooptransacties om de gevolgen van drie wereldwijde prijsreductiestrategieën in te schatten: regelingen voor gezamenlijke inkoop van geneesmiddelen, prijsonderhandeling door een derde partij over generieke ARV's en uiteenlopende prijsstelling van originele ARV's.

We hebben geen verband gevonden tussen prijs en ingekochte volumes voor 19 van de 24 onderzochte ARV doseringsvormen. Voor vijf van de 19 ARV's, waren grootschalige ARV-aankopen tussen de 4 en de 21% goedkoper dan de gemiddelde of kleinschalige aankopen. Negen van de 13 generieke ARV's waren 6-36% goedkoper wanneer ze ingekocht werden op grond van afspraken over prijsonderhandelingen door een derde partij gemaakt door het 'Clinton HIV/AIDS Initiative'. In het algemeen konden originele ARV's, aangeboden onder uiteenlopende prijsstellingen, niet concurreren met generieke prijzen; 15 van de 18 originele ARV's waren 23-498% hoger geprijsd dan de generieke tegenhangers.

Onze studie levert een belangrijke en tijdige inbreng in het ontwerp van een vrijwillig mechanisme voor gezamenlijke inkoop dat in behandeling is bij het GFATM. Terwijl de conventionele wijsheid "koop meer, betaal minder" suggereert, toont deze studie aan dat aankoopvolume geen betrouwbare drijver is van ARV prijzen en suggereert zij dat groepsafspraken misschien niet het meest gewenste mechanisme zijn om de nationale

aanbestedingsefficiëntie te verbeteren. Bovendien kan dat resulteren in het creëren van monopsonies en andere marktverstoringen. Wij raden het overwegen van alternatieve benaderingen om de ARV-prijzen te verlagen aan, waaronder verbeteringen in het financieel beheer, het wegnemen van belemmeringen voor generieke concurrentie, een verbeterde prognose van ARV gebruik en overdracht van technologie.

Onderzoek voorgesteld in **Hoofdstuk 4** gaat verder dan prijsanalyses en door naar een beter inzicht in hoe farmaceutische markten ontstaan en zich ontwikkelen in relatie tot farmaceutische beleidsmaatregelen gemaakt op wereldwijd niveau. De eerste studie in Hoofdstuk 4.1 beschrijft de onderlinge verbondenheid van beslissingen gemaakt door internationale organisaties en donoren en specifieke implicaties voor marktontwikkeling van eerstelijns ARV geneesmiddelen in ontwikkelingslanden. We bouwen voort op onze voorafgaande ARV gegevens om een gegevensbestand voor marktinformatie te creëren bestaande uit informatie uit meer dan dertig verschillende bronnen. Door 12,958 door donoren gefinancierde ARV aankooptransacties uit de periode 2002-2008 te gebruiken, alsmede andere gegevens uit het gegevensbestand voor marktinformatie, onderzoeken we relaties tussen eerstelijns ARV marktontwikkelingen en richtlijnen voor de behandeling van HIV/AIDS van de Wereldgezondheidsorganisatie (WHO), goedkeuring van het 'WHO Prequalification Programme en US Food and Drug Administration ARV' en beleidsmaatregelen van GFATM, PEPFAR, en UNITAID.

Wij tonen aan dat vroege WHO richtlijnen inzake de behandeling van HIV/AIDS, die slechts vier therapieën en vijf ARV's vermeldde, de vraag consolideerde rond enkele producten, waarbij ze drijfveren creëerden voor generieke producenten om op de markt te komen en competitieve prijzen aan te bieden. Toen de WHO later de richtlijnen voor eerstelijns behandeling uitbreidde om 24 verschillende eestelijns therapieën toe te voegen, werd de vraag verspreid over talrijke producten, wat onzekerheid creëerde onder de fabrikanten. Enkele vaste dosis combinatie (fixed-dose combinations; FDC) ARV's werden ontwikkeld om de vele nieuwe eerstelijns therapieën te ondersteunen. Onmiddellijk na de aanbeveling van de WHO namen de ARV aankoopvolumes meer dan 15-voudig toe, wat de dramatische rol aantoont van de WHO richtlijnen voor de behandeling van HIV/AIDS in het vormgeven van de internationale ARV markt.

We tonen ook aan hoe kwaliteitsgoedkeuringen van het WHO Prequalification en US FDA de marktdynamiek beïnvloeden. Opname van vaste dosis combinatie ARV's werd vertraagd in door PEPFAR gesubsidieerde programma's totdat de US FDA het eerste FDC product in 2006 goedkeurde, drie jaar later dan de goedkeuring van de WHO Prequalification, die noodzakelijk was voor de aankopen binnen GFATM programma's. Toch beschrijven wij een hoogst competitieve markt voor eerstelijns ARV's die snel nadat GFATM en PEPFAR opgericht werden ontstond. Binnen een paar jaar werd de

markt gekarakteriseerd door een toenemende vraag naar enkele sleutel ARV's, de aanwezigheid van verscheidene fabrikanten waarvan de kwaliteit verzekerd is, meer dan 100 individuele inkopers en dalende prijzen.

We tonen echter aan dat het recente inkoopbeleid van PEFPAR, GFATM en UNITAID naar alle waarschijnlijkheid de marktstructuur zal beïnvloeden. Onder traditionele GFATM schema's, werden ARV inkopen beheerd door elk afzonderlijk ontvangend land en creëerden ze marktvoorwaarden waarbij 6-8 fabrikanten concurreerden en de wereldwijde markt konden verdelen. Nieuwe ARV's die aanbevolen werden door de WHO, UNITAID en PEPFAR namen samen 50-85% van het marktvolume in 2008 voor hun rekening. Zowel UNITAID als PEPFAR kopen gezamenlijk in en wijzen contracten toe aan slechts 1-2 leveranciers. Aangezien donoren meer gebruik maken van gezamenlijke inkoopregelingen, zal de markt waarschijnlijk consolideren tot minder leveranciers dan historisch waargenomen onder uitgesplitste inkoop en zou dit voor uitdagingen kunnen zorgen voor de lange termijn levering en concurrentie.

In deze referentiestudie tonen wij aan hoe ARV-markten gecontroleerd kunnen en dienen te worden op een algehele en geïntegreerde manier. We besluiten met het advies aan donoren en internationale organisaties om na te gaan wat voor gevolgen hun beleidsbeslissingen kunnen hebben op de lange termijn ontwikkeling van globale ARV-markten en om er voor te zorgen dat deze markten levensvatbaar en concurrerend blijven.

In Hoofdstuk 4.2 maken we gebruik van ons ARV gegevensbestand voor marktinformatie om uitdagingen waarmee we geconfronteerd werden op het gebied van de beschikbaarheid en gebruik van ARV geneesmiddelen voor kinderen in ontwikkelingslanden te beschrijven. Door 7,989 inkopen van ARV/s voor kinderen en andere gegevens in de database te gebruiken, meten we opname, verspreiding en prijzen die betaald zijn voor ARV formuleringen voor kinderen in landen en programma's van 2002 tot 2009. We beschrijven een kwetsbare markt voor ARV's voor kinderen met weinig drijfveren voor de instap van fabrikanten. Wereldwijde volumes zijn laag en worden ironisch gezien lager en minder aantrekkelijk als fabrikanten formuleringen ontwikkelen die beter aan leeftijd zijn aangepast.

Terwijl druk van activisten en drijfveren van donoren resulteerden in de ontwikkeling van nieuwe FDC producten voor kinderen, worden de meeste van deze FDC's geproduceerd door slechts één fabrikant. Opname van FDC's voor kinderen is veel lager geweest dan de voorspelde en verwachte vraag. UNITAID nam 97-100% van het marktvolume van FDC's voor kinderen voor zijn rekening in 2008 en 2009. Slechts drie landen maakten melding van de inkoop van FDC's voor kinderen buiten de UNITAID programma's, ondanks prijsbesparingen en klinische voordelen ten opzichte van vloeibare formuleringen en andere alternatieven. Opnieuw belichten we de voor- en

nadelen van grootschalige, gezamenlijke inkoopinitiatieven. In het geval van ARV's voor kinderen merken sommige organisaties moeilijkheden op bij het verkrijgen van ARV's voor kinderen die niet waren aangeschaft door de dominante gezamenlijke inkoper, wat suggereert dat dominante grootschalige inkopers de wereldwijde bevoorrading van ARV's dicteren.

We tonen ook aan dat het creëren van druk en drijfveren om producten waar een kleine vraag naar is te fabriceren, onvoldoende is en vergezeld dient te gaan van interventies die de opname van nieuwe producten in het gezondheidssysteem vergemakkelijken. We geven aan dat de introductie van nieuwe producten voor kinderen waarschijnlijk een herziening van alle behandelingsrichtlijnen alsook de heropleiding van alle beoefenaars in de gezondheidszorg en zorggevers vereist en dat het de aankoop- en distributiesystemen verder zou kunnen compliceren. We merken op dat markten van ARV's voor kinderen niet winstgevend zijn en minder aantrekkelijk zullen worden indien de huidige inspanningen om de HIV- transmissie van moeder op kind te voorkomen erin zullen slagen om het aantal HIV-positieve kinderen te verminderen. Toch is er een aanzienlijke behoefte aan voortdurende vernieuwing wat ARV-formuleringen voor kinderen betreft.

We waarschuwen ervoor dat de ontwikkeling van nieuwe ARV's voor kinderen risico zoukunnen lopen als we de fabrikanten geen minimale omzet kunnen garanderen. We raden aan dat donoren het gebruik van nieuwe producten controleren zoals beschreven in ons onderzoek en dat verder onderzoek uitgevoerd wordt op nationaal niveau om belemmeringen van opname en verspreiding te identificeren. We benadrukken de behoefte aan verbeteringen in wereldwijde voorspellingen zodat de waarschijnlijkheid dat een nieuw product op nationaal niveau zal aangenomen worden, zorgvuldiger kan worden ingeschat in plaats van het inschatten van de vraag op basis van ziektelast.

De laatste studie, gepresenteerd in Hoofdstuk 4.3, benadrukt de cruciale rol die Indiase producenten van generieke ARV's tot op heden gespeeld hebben in de wereldwijde groei van de HIV/AIDS behandeling. Met behulp van 17.646 door donoren gefinancierde ARV transacties tussen 2003-2008 en andere gegevens uit onze gegevensbank voor marktinformatie, tonen we aan dat sinds 2004 generieke ARV's geproduceerd in India meer dan 80% van het jaarlijkse ARV inkoopvolume in beslag nemen. Zesennegentig van de 100 landen vermeldden de inkoop van generieke ARV's geproduceerd in India in 2008. Indiase generieken vertegenwoordigden 91% van de NRTI en NNRTI inkopen voor kinderen en 88% van de NRTI en NNRTI inkopen voor volwassenen in 2008. Prijzen van eerstelijns ARV therapieën geproduceerd in India waren duidelijk lager dan prijzen voor generieke en originele versies van niet-Indiase origine. Terwijl merkproducten de PI-markt normaal gesproken domineerden, zijn Indiase generieke geneesmiddelen begonnen het PI-marktaandeel te veroveren, met een vertegenwoordiging van 19% van

het PI-inkoopvolume in 2008. Nieuw aanbevolen ARV's zijn aanzienlijk duurder dan ARV's die tot heden gebruikt werden en zonder de generieke concurrentie onder de Indiase producenten, is het onwaarschijnlijk dat we de prijsverlagingen uit het verleden opnieuw zullen meemaken.

We zijn bezorgd dat de lopende en toekomstige bilaterale en multilaterale handelsovereenkomsten waar over onderhandeld wordt met India, zouden kunnen resulteren in hogere prijzen en minder vernieuwing in de ontwikkeling van formuleringen en dat zij daarom de toekomstige toegankelijkheid van veiligere en effectievere ARV's in ontwikkelingslanden in gevaar zouden kunnen brengen. We raden aan dat India en haar handelspartners garanderen dat er voldoende beleidsruimte blijft bestaan voor India om haar centrale rol te blijven spelen in de bevoorrading van ontwikkelingslanden met goedkope, generieke geneesmiddelen van voldoende kwaliteit.

Het proefschrift besluit met Hoofdstuk 5, *Terug naar de toekomst: lessen en implicaties voor het vervolgonderzoek naar farmaceutisch beleid in ontwikkelingslanden.* In dit hoofdstuk geven we een algemene samenvatting van de belangrijkste lessen en geven we de volgende stappen voor initiatieven voor de toegankelijkheid van geneesmiddelen aan. We bespreken hoe onze onderzoeksbevindingen bewijs hebben geleverd om gemeenschappelijke conventionele wijsheden die heersen in wereldwijde gezondheidscommissies te weerleggen. We benadrukken het belang van het stellen van hoge eisen aan gegevensbeheer onder degenen die openbaar beschikbare gegevens plaatsen en gebruiken om de validiteit en reproduceerbaarheid van onderzoek te verzekeren. We doen krachtige aanbevelingen voor een paradigmaverplaatsing naar de uitwisseling van gegevens en openbare goederen onder internationale gezondheidsonderzoekers. We beschrijven de toepassing en opname van onze onderzoeksbevindingen door de belangrijkste beslissingsnemers, door een model te leveren waarmee onderzoekers kennisoverdracht kunnen ondersteunen en bewijs kunnen incorporeren in het beleid. We bespreken toekomstige richtingen en uitdagingen voor de initiatieven inzake toegankelijkheid van geneesmiddelen en stellen multidisciplinaire onderzoeksbenaderingen voor om de hierop volgende problemen te voorspellen en aan te spreken.

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List of Publications

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Brenda Waning obtained a Bachelor of Pharmacy degree from the Massachusetts College of Pharmacy and Health Sciences in Boston, USA in 1988. Upon graduation she worked nearly ten years in a Boston-based teaching hospital in several clinical and managerial roles. She obtained a Master of Public Health Degree, concentrating in epidemiology and biostatistics, at Boston University School of Public Health in 1996. In 1997 she joined the faculty at Massachusetts College of Pharmacy where she taught courses in Pharmacoepidemiology, Pharmaceutical Law & Regulation, and Drug Literature Resource & Evaluation. She served on the faculty at Boston University School of Public Health from 2003 to 2008 where she conducted teaching, training, research, and consulting on pharmaceutical policy at global level and in numerous developing countries. In 2008, Brenda moved to the Boston University School of Medicine where she served as Director of Pharmaceutical Policy, leading her department's initiatives in pharmaceutical policy research and consulting. In the same year she joined the Utrecht WHO Collaborating Centre for Pharmacoepidemiology and Pharmaceutical Policy Analysis in the Netherlands under which umbrella the work presented in this thesis was conducted. In 2010 Brenda assumed the role of Coordinator of Market Dynamics at UNITAID, a WHO-partnership based in Geneva where she leads a team responsible for monitoring trends in HIV/AIDS, tuberculosis, and malaria markets, identifying potential solutions to access problems, and assessing the public health and market impact of UNITAID's interventions.