Abstract

Purpose

A number of strategies have aimed to assist countries in procuring antiretroviral therapy (ARV) at lower prices. In 2009, as the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) commenced a voluntary pooled procurement scheme however, the impact of the scheme on ARV prices remains uncertain. This study aims to estimate the effect of VPP on drug prices using Efavirenz as a case study.

Methods

This analysis uses WHO Global price report mechanism (GPRM) data from 2004 to 2013. Due to the highly skewed distribution of drug Prices, a generalized linear model (GLM) was used to conduct a difference-in-difference estimation of drug price changes over time.

Results

These analyses found that voluntary pooled procurement reduced both the ex-works price of generic Efavirenz and the incoterms price by 16.2% and 19.1%, respectively (P<0.001) in both cases. The year dummies were also statistically significant from 2006 to 2013 (P<0.001), indicating a strong decreasing trend in the price of Efavirenz over that period.

Conclusion

Voluntary pooled procurement significantly reduced the price of 600mg generic Efavirenz between 2009 and 2013. Voluntary pooled procurement therefore offers a potentially effective strategy for the reduction in HIV drug prices and the improvement of technical efficiency in HIV programming. Further work is required to establish if these findings hold also for other drugs.

Introduction

Global health initiatives and international non-government organisations (NGOs) such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), the President’s Emergency Plan for AIDS Relief (PEPFAR) and the Clinton HIV/AIDS Initiative (CHAI) have used a number of strategies to procure antiretroviral therapy (ARV) at lower prices. Common strategies include negotiation (Seoane-Vazquez & Rodriguez-Monguio 2007; Wilson et al. 2012) and a range of procurement mechanisms (Waning et al. 2009).

Historically, the funding mechanism of GFATM was based on the country coordination mechanism (CCM), which was initiated after receiving a grant proposal from the government.
Within this system, medicine procurement was effectively left to each principal recipient (PR) (Waning et al. 2010; Waning et al. 2009; Tren et al. 2009), and Ripin et al. (2014) refer to this as a ‘distributed country-led’ model. Under this arrangement, each country was free to select its own supply chain and procurement companies, and to set policies to manage tendering, purchasing and ordering (Ripin et al. 2014). GFATM would then disburse the funds for the procurement once the country’s proposal was approved. Finally, each principal recipient (PR) would procure the ARV drugs. Under CCM, the Ministry of Health or another implementing body may negotiate ‘directly’ with manufacturers or contract with logistics companies using GFATM funding (Tren et al. 2009).

There are a number of price reduction strategies available for HIV drugs: pooled procurement, differential pricing and generic competition:

a) Pooled procurement involves purchasing drugs in bulk for multiple buyers, to reduce the cost of the drugs and is based on the principles of economies of scale (Waning et al. 2009). Multiple buyers are grouped into a single group to obtain the benefits of pooled procurement.

b) Price differentiation based on the income of consumers, can maximize profits for manufacturers. In this instance, price differentiation or differential pricing occurs when low and middle income countries are sold the drugs at lower prices than high income countries (Moon et al. 2011).

c) Generic competition is a strategy where price is reduced by supplying multiple generic versions of drugs after the patent for the branded equivalent drug has expired. Perez-Casas (2000) showed that the price of a branded drug can be reduced by generic competition. In Brazil, generic competition lowered the branded price of stavudine, lamivudine and nevirapine from $10,439 to $631, while the generic price dropped to $800 from $2,767.

In 2009, GFATM commenced voluntary pooled procurement (VPP), wherein purchases were pooled at the national level, increasing the negotiating power of purchasers (Reich & Bery 2005). Under the VPP system, each PR country may volunteer to join the procurement programme, but are not obligated to do so. Between 2009 and 2011, 47 countries joined the scheme, usually to purchase one or more of five key health products: ARVs for HIV, artemisinin-based combination therapy (ACTs) for malaria, long-lasting insecticidal bed nets (LLINs), rapid diagnostic tests (RDTs) for Tuberculosis (TB), and condoms. Overall, 307 million daily doses of antiretroviral drugs were procured and approximately 336,000 people received ARV therapy with drugs purchased through voluntary pooled procurement (GFATM 2012).

The VPP mechanism is mainly implemented by a procurement services agent (PSA), working on behalf of a principal recipient country.¹ Although the GFATM may facilitate communications between the principal recipient and the procurement services agents (PSA), the GFATM does not act as an agent (GFATM 2011). The principle recipient sends a request with product specifications, quantities and delivery dates to the Procurement Services

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¹ The Global Fund hires local fund agents (LFA) such as Price Waterhouse Coopers (PWC) and KPMG who monitor and oversee grant performance. Their role is different from PSA (Tren et al. 2009; Donoghue et al. 2005).
Support (PSS) team. The PSA invites bids from manufacturers and submits price quotations to the principle recipient (GFATM 2011). The principle recipient then decides whether they accept the price quoted. The PSA can act for multiple principles in a single transaction, thus effectively ‘bulk buying’ for a number of purchasers. In theory, bulk purchasing of this sort is expected to lead to price reductions in commodities (Wafula et al. 2014; Waning et al. 2010).

Pooling procurement would be expected to increase procurement efficiency and reduce transaction costs (Reich & Bery 2005), further reducing the cost of drugs purchased. Pooled procurement is a form of cooperation between buyers and suppliers using the purchasing power that buyers have (Huff-Rousselle 2012). The purpose of pooled procurement is to provide sustainable supply of commodities, reduce transaction costs and the total price paid for ARV (World Health Organisation 2015). Therefore, appropriately conducted pooled procurement is likely to help low income countries access to ARV.

However, there is a paucity of evidence regarding the effect of bulk purchasing and VPP on procurement prices in practise. Waning et al. (2009) tried to estimate the impact of global strategies such as large volume purchasing and the Clinton Health Access Initiative’s (CHAI) price negotiation on antiretroviral drug prices, using the global price purchasing mechanism (GPRM) database. They carried out an analysis using bulk purchase as a proxy for pooled procurement. They concluded that large purchase volumes did not necessarily reduce drug prices. While their study found no beneficial price effect in the case of a single buyer, a study of VPP would enable the exploration of a potential price effect when bulk purchasing is conducted on behalf of multiple buyers. Wafula et al. (2014) studied procurement prices after the introduction of VPP, using 115 completed questionnaires from 69 countries. In that study, two-thirds of those who had used the VPP system replied that VPP made procurement cheaper, although that reduction was not quantified as this study was based on the interviews. Wafula et al. (2013), in a separate study, also analysed regional and temporal trends in the costs of malaria-related commodities using procurement data from 79 countries. They concluded that VPP resulted in significant declines in the cost of malaria rapid diagnostic tests (RDTs) and long-lasting insecticide-treated nets (LLINs). The impact of VPP on antiretroviral drugs was, however, not explored.

In addition to the studies already cited above, other studies have explored drug prices using procurement data. Danzon et al. (2013) examined the effect of income and competition on drug prices using GPRM data and IMS health data for the period 2004–2008. GPRM data was used to compare procurement prices, while IMS data was used to compare retail prices. The authors found that the income of a country was not associated with the drug prices and the availability of generic competition did not reduce the price of drugs. However, they also found that procurement based on tendering that stimulates price competition can reduce the prices of ARVs. Lucchini et al. (2003) studied ARV price variation in Africa and Brazil. They used an econometric analysis with multiple linear regressions for 13 sub Saharan African countries in their study of price variation, using data from Medecines Sans Frontiers (MSF). As with Danzon et al. (2013), they found no clear relationship between basic indicators like GDP per capita and the ex-manufacturer prices for generic and original drugs across countries. Wirtz et al. (2009) carried out a study of price comparison of ARV drugs in order to identify factors

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2 IMS health is a private company offering information regarding health care.
related to lower drug prices. In contrast with Danzon et al. (2013) and Lucchini et al. (2003), they concluded that countries defined as ‘lower-middle income’ and ‘upper-middle income’ tended to pay significantly more for ARVs than ‘low-income countries’. They did not focus on compulsory licensing but demonstrated that differential pricing is not applied in proportion to the income per capita of country. No study has yet, to our knowledge, formally explored the impact of VPP on antiretroviral drug prices.

To fill this gap in the evidence, this study aims to estimate the effect of VPP on the price of antiretroviral drugs, using difference-in-difference (DID) analysis of WHO GPRM data. The drug Efavirenz is chosen as a case study given the emphasis on fixed dose combination (FDC) therapy in the WHO HIV treatment guidelines (World Health Organisation 2004).

A significant proportion of patients are currently on Efavirenz. In 2012, approximately 16% of children were using Efavirenz based first-line regimens in low and middle income countries (World Health Organisation 2014). One study conducted in Sweden reported that among 276 HIV patients, 61% (168 patients) were given EFV as part of the initial regimen (Leutscher et al. 2013). In 2008, the number of people using Efavirenz was less than 2 million but expected to rise to more than 9 million by 2016 (World Health Organisation 2014). Given the expectation that approximately 16.8 million people will be using anti-retroviral therapy by 2016 (World Health Organisation 2014), and Efavirenz is increasingly being used as part of ARV administration, demand for the drug is likely to remain high.

Antiretroviral therapy generally requires a large number of tablets every day. In contrast, fixed-dose combinations (FDCs) need only once or twice daily doses, significantly simplifying the process of antiretroviral therapy (World Health Organisation 2010). Fixed-dose combination therapy tends also to be cheaper than more complex treatment schedules (Calmy et al. 2006) and is more easily preserved, as it does not need refrigeration. As a result, FDC therapy is especially useful in resource-limited countries in which cold storage may be absent or unreliable. Perhaps unsurprisingly, global organisations are increasing their commitment to FDC (Bowen et al. 2008) and non-nucleoside reverse-transcriptase inhibitors (NNRTI) such as Efavirenz or Nevirapine, which have a pivotal role in FDC therapy. Of these drugs, Efavirenz is widely held to have a smaller risk of virologic failure (The HIV-CAUSAL Collaboration 2012). Considering that the wider uptake of FDC therapy may, in itself, have lowered ARV prices in the procurement market (Waning et al. 2010), it becomes important to adopt a methodology that can isolate any additional price effects of voluntary pooled procurement.

Data

This analysis uses WHO Global Price Report Mechanism (GPRM) data from 2004 to 2013. This is a panel data set of information on transaction prices for antiretroviral drugs purchased by international donors and programmes in low- and middle-income countries. GPRM is an umbrella term for procurement data. It was developed from an earlier version of the Price and Quality Report (PQR), and the price data included in the Price and Quality Report is automatically fed into the GPRM (Hirsch et al. 2014). Procurement services agents (PSAs) are responsible for entering data into the price and quality report (PQR) system, and therefore also into the GPRM. Grant funded purchases conducted using voluntary pooled procurement,
are similarly reported to the PQR system by the procurement services agents (PSA) and so need not be entered by principal recipient (PR) countries (GFATM 2014). As the aim of this study is to estimate the overall impact of VPP on the mean change in a particular drug’s price in all locations, rather than any country-specific impact on prices, GPRM data appears to be appropriate for the purpose of this analysis.

GPRM data contain two types of prices: *ex-works* prices and International Commercial Terms (*incoterm*) prices. *Ex-works* prices refer to the wholesale price at the manufacturer’s site, while *incoterm* prices reflect which side, either seller or buyer, covers payment and risks (Médecins Sans Frontières 2015). *Incoterms* prices are expected to reflect real procurement prices because the procurement process involves shipping charges such as freight and transport fees, which are not appropriately reflected in *ex-works* prices. *Incoterms* includes *ex-works* price and other 10 rules: FCA (Free Carrier); CPT (Carriage Paid To); CIP (Carriage And Insurance Paid To); DAT (Delivered At Terminal); DAP (Delivered At Place); DDP (Delivered Duty Paid); FAS (Free Alongside Ship); FOB (Free On Board); CFR (Cost and Freight); CIF (Cost, Insurance and Freight); EXW (Ex works) (International Chamber of Commerce 2010).

The main *Incoterms* rules applied for VPP countries from 2009 to 2013 were: EXW (Ex works: 68%), CIP (Carriage And Insurance Paid To: 14%), and FCA (Free Carrier: 13%). Those non-VPP countries for the same period were; CIP (Carriage And Insurance Paid To: 27%), FCA (Free Carrier: 25%), and EXW (Ex works: 15%). This text has also been inserted in the appendices (Appendix 6).

Information as to whether a country procured ARVs through VPP was obtained from the Price and Quality Reporting System (PQR) data (Appendix 1). A total of 25 out of 107 countries volunteered for VPP to procure generic Efavirenz between 2009 and 2011 (Appendix 1). GPRM data specify country, dosage, *incoterm* and *ex-works* unit prices, number of units, and manufacturer. Under VPP, Efavirenz was procured by only one logistics company, the Partnership for Supply Chain Management (PFSCM) (Appendix 2). This study focuses on 600mg Efavirenz, given that the 600mg dosage makes up more than 60% of all procured Efavirenz (appendix 3). A total of 25 out of 107 countries volunteered for VPP to procure generic Efavirenz between 2009 and 2011 (Appendix 1), however, countries may procure Efavirenz through VPP or other programmes. To include only Efavirenz procured by VPP, observed data was dropped if the manufacturers in the GPRM data and price quality reporting (PQR) data did not match. 121 observations over 10 years were retained for a treatment group of 25 countries, while 482 were from a control group of 82 countries.

**Methods**

Difference in difference estimation of the impact of voluntary pooled procurement on drug prices in this study can be expressed using Equation (1) (Greene 2012; Cameron & Trivedi 2005).
\[ y_{it} = \beta_1 \text{VPP} + \beta_2 \text{Year} + \beta_3 \text{VPP} \times \text{Year} + \beta_4 \text{transaction volume} \]
\[ + \beta_5 \text{HIV prevalence} + \beta_6 \text{GNI} + \beta_7 \text{CPI} + \beta_8 \text{Expenditure} \]
\[ + \beta_9 \text{Tax} + \beta_{10} \text{Generic competition} + \beta_{11} \text{Country} + \epsilon_{it} \] (1)

where, VPP is a dummy variable equalling 1 for those countries that utilised VPP and 0 for those not using VPP. Year is a set of year dummy variables representing years with the label/name corresponding to the relevant year, spanning 2004 to 2013 and generated from a reference year of 2004. Since VPP was implemented in different countries for different periods from 2009, the interaction term of VPP (Treatment) \( \times \) Year (Post) is the main variable of interest, and the coefficient of this term is the effect of VPP on procurement prices (Greene 2012). Subscripts \( t \) and \( i \) refer to year and country, respectively, while \( \epsilon_{it} \) is the error term.

Due to the highly skewed distribution of drug prices, a generalised linear model (GLM) was employed in the estimations. GLM is an estimation strategy well suited to modelling skewed data (Glick et al. 2014). Several other models have been suggested for skewed data including ordinary least square (OLS) on log transformed data, and a GLM with a log link and Gamma or Poisson distributions. The first approach using log transformation has the challenge of necessitating a smearing factor. Exponentiation of the mean of the logs generates the geometric mean of the skewed dependent variable (in this case costs), which is a downward-biased estimate of the arithmetic mean (Glick et al. 2014). To avoid this problem, a smearing factor, \( \hat{z} = 1/N \sum_{i=1}^{N} e^{(x_i - \hat{z})} \) should be used where \( z_i \) corresponds to the log of cost and \( \hat{z}_i \) corresponds to the treatment-group-specific mean of the log. However, results using this smearing factor can be inconsistent. In contrast, GLM predicts the mean of the log without using a smearing factor and thus tends to yield more consistent results.

GLM does however, entail assumptions about the underlying distribution (Cameron & Trivedi 2005; McCullagh & Nelder 1989). The modified park test for the data suggests the choice of the Gamma distribution for the GLM, presenting the coefficient of 2.037 (P-value=0.7374). When the coefficient is approximately 2, Gamma distribution is recommended whereas Poisson is chosen when the coefficient is 1. In addition, high p-value presents that Gamma distribution cannot be rejected. As a result, a GLM with a log link and Gamma distribution was chosen for this study. All analyses were carried out with Stata, Version 12 (StataCorp, College Station, Texas, USA).

To capture country-level heterogeneity, a fixed-effects model was used in the analysis. In practice, it is hard to assume that it was only VPP that affected the procurement prices. The fixed-effects model is a good method to control the endogeneity owing to a time-invariant omitted variable (Cameron & Trivedi 2005). In other words, the fixed-effects model is robust to unobserved time-invariant omitted variables. As commands in STATA (version 12) for GLM do not fully support fixed effects, country dummies were included as subject-specific intercepts for fixed effects. We implemented the Hausman test with the null hypothesis that the preferred model is random effects (RE) vs. the fixed effects (FE): Chi2(16)=61.75 (P value<0.001). Therefore, the more appropriate model for the data in the study is confirmed as a FE model.
Considering the literatures for factors associated with prices for HIV drugs (Wirtz 2009; Chirac 2002; Moon et al. 2011; Waning et al. 2009; Lucchini et al. 2003; Danzon et al. 2013; Schustereder & Juetting 2008; Pérez-Casas 2000; Danzon & Chao 2000; Barton 2001; Giaccotto et al. 2005; Gray & Matsebula 2004; Baltagi & Moscone 2010; Olcay & Laing 2005; Bac & Yannick 2002) and the panel data of a drug price that will be used in this study, seven independent variables at country level were included in the model (Table 1): transaction volume of 600mg Efavirenz, HIV prevalence, tax revenue as percentage of GDP, gross national income (GNI), consumer price index (CPI), public health expenditure as % of total health expenditure, and number of generic manufacturers. Transaction volume is the sum of the product of quantity per package and the number of packages, and it is obtained from WHO GPRM. The number of generic manufacturers presents a generic competition in the market, which is in line with the study by Danzon et al.(2013). Among the studies identifying the importance of these independent variables in analyses of drug prices, only four carried out their analyses using procurement data (Lucchini et al. 2003; Danzon et al. 2013; Wirtz 2009; Waning et al. 2009). Consequently, the association between procurement and these likely independent variables will be investigated further in this study.

**Sample size**

This study uses a sample size of 25 treatment countries and 82 control countries. There is no general guideline on the minimum treatment group size for country level difference in difference analysis. Jones and Schneider (2010) explored the association between global inequality in income and national average IQ using 23 countries of treatment group and 63 comparisons. Slaughter (2001) performed difference in difference analysis at country level with four countries belonging to the European Economic Community (EEC) as a treatment group and 54 countries in the control group, in order to see how trade liberalisation contributes to per capita income convergence across countries. These examples demonstrate that country level difference in difference analysis is generally based on unbalanced data. Considering also the sample size norms established by these studies, the sample size proposed for this study is likely to be acceptable.

Nevertheless, to compensate for the relatively small number of observations for VPP attending countries and further bolster the results of this analysis, a simulation using wild cluster bootstrap was conducted. This simulation technique, based on re-sampling, is widely used in DID analysis to check the robustness of the result (Conley & Taber 2011; Bertrand et al. 2012). It has been shown that wild cluster bootstrap can work well in providing conservative p-values even for 3 treated groups and 27 control groups (Imbens & Kolesar 2012). A further advantage of using the wild cluster bootstrap, is to reduce the risk of over-rejection by adjusting the size of standard error (Cameron & Miller 2015). The key idea of using the wild cluster bootstrap is to rely on the fact that model errors of a given cluster are correlated over time, preserving the observed correlation in errors by drawing errors on the basis of original errors (Cameron & Miller 2015).
Results

Table 1 presents the descriptive statistics for this study. Means of *incoterms* prices and *ex-works* prices are substantially and significantly different between the treatment group and the control group (*p*-value <0.001). Among the covariates, GNI (*p*-value=0.0033) and CPI (*p*-value<0.001) were statistically different between the treatment group and the control group. These results show the possibility that VPP has an impact on the reduction of drug prices and that GNI and CPI will be significantly different between VPP attending countries and others.

In Table 1, the mean incoterms price for pre-intervention and post intervention for VPP and non VPP countries are 0.56 and 0.65, respectively. These fall to 0.15 and 0.2 after intervention. Therefore, there is a 73% reduction in the price for VPP countries and a 69% reduction for non-VPP countries. Likewise, for ex-works prices, VPP have a mean of 0.52 and 0.14 pre- and post- intervention respectively, amounting to a 73% price reduction. In non-VPP countries, ex-works prices are 0.6 and 0.18 pre- and post- intervention respectively, amounting to a 70% price reduction. In both cases the price reduction is higher for VPP countries.

[Table 1 here]
Distribution of drug prices

The histogram of *ex-works* price and *incoterms* price presents the skewed distribution of drug prices (Figure 1). This histogram shows that using GLM would be appropriate for this study.

[Figure 1 here]
The assumption of a common trend

A critical assumption of using a DID estimator is to check whether common time trends hold (Cameron & Trivedi 2005; Blundell & Dias 2009; Angrist & Pischke 2009). The availability of the DID estimator relies on the assumption that the underlying ‘trends’ in the outcome variable are similar for both treated and untreated groups in a pre-treatment period. In other words, the dependent variable should present a common trend before treatment in both the treatment and control groups. Although visually checking the trend with a graph is still recommended (Angrist & Pischke 2009), Autor (2003) developed an econometric method to check a common trend assumption using lagged and lead variables.

From figure 2, it appears that the common trend assumption holds for both incoterms prices and ex-works prices. In addition, this graph shows that there was no external shock, or so-called ‘Ashenfelter’s dip’, before treatment (Ashenfelter 1978). This assumption was again checked with the Autor (2003)’s method. This method establishes whether the treatment effect exists before and after the treatment using lag and lead variables. If lead and lag variables are significant, it implies that the effect of treatment existed before and after the treatment. If that is the case, the common trend assumption will not hold.
Table 2 shows the result of testing for the assumption of a common trend based on Autor’s method. Other things being constant, GLM regression including lag and lead variables was carried out. Country effects estimated from this regression using leads and lags for the common trend can be seen in Appendix 4. Lag 1 and lag 2 are the coefficients of the lagged variable of interaction term ‘Treatment X Post’, while lead1 and lead2 are the coefficients of the lead variable of interaction term ‘Treatment X Post’. The p-value of the lead variables in the table 2 is statistically insignificant, showing that the effect of VPP before treatment is close to zero. If the trends between treatment and control group are sufficiently similar, then lead2 and lead1 will be insignificant. In other words, DID is not significantly different between treatment and control group in the pre-treatment period. Synthetic control method, which synthesises hypothetical counterfactuals with the weighted average of other control groups, was not used because the common trend holds (Abadie & Gardeazabal 2003). In sum, this result implies that the effect was not happening in the pre-post period, and so it can be concluded that the common trend assumption holds.
Difference-in-difference analysis

[Table 3 here]

Table 3 presents the result of difference-in-difference analysis on VPP. The regression result of GLM shows that the ‘Treatment X Post’ term was statistically significant at the 0.1% level for each price. Country dummies were used for fixed effects as aforementioned in the method section and the result is included in appendix 5 due to the large volume. The results of both ex-works prices and incoterms prices in GLM were -0.177 (95% confidence interval: -0.247 to -0.107; p-value<0.001) and -0.213 (95% confidence interval: -0.287 to -0.139; p-value<0.001), respectively. This suggests that VPP has an effect of reducing the ex-works prices of generic Efavirenz by 16.2% and incoterms prices by 19.1%, respectively, after taking the exponential of the interaction term. It is also noted that year dummies were also statistically significant from 2006 to 2013. On the other hand, it can be seen that the magnitude of year dummies is gradually increasing. In 2006, ex-works prices decreased by approximately 29.3% and incoterms prices by 31.8% after taking the exponential of the year 2006 dummy. However, in 2013, the results of GLM regression show that ex-works prices decreased by approximately 88.0% and incoterms prices by 88.3%, compared with when the year is not 2013, after taking the exponential of the year 2013 dummy. Other independent variables were statistically insignificant in GLM.

[Table 4 here]

Table 4 presents the result of bootstrap simulation on the impact of VPP with the standard DID model described in equation 1. An identical interaction term of Treatment X Post in table 3 was used. On the basis of 1,000 times bootstrap re-sampling, this result shows that the coefficient of interaction term of ‘Treatment X Post’ was consistently negative, -0.174 (95% confidence interval: -0.272 to -0.063, p-value<0.001) for ex-works price and -0.217 (95% confidence interval: -0.320 to -0.117, p-value<0.001) for incoterms price, respectively. Based on this result, VPP reduced the mean unit cost of Efavirenz by 16% for ex-works price and by 19% for incoterms price. Bias was as small as 0.0048 for ex-works price and 0.0055 for incoterms price, presenting no substantial difference from the result of GLM model in table 3. Wild cluster bootstrap was conducted separately with the identical model in equation 1, and the result is incorporated in table 4. The P-values based on the wild cluster bootstrap for both ex-works price and incoterms price in table 4 are increased compared with p-values estimated using cluster robust standard error in table 3 (ex-works price: p<0.001; incoterms price: p<0.001). However, the p-values were 0.028 and 0.01, which are still statistically significant at 5% level. In brief, this result of simulation supports the result of the difference-in-difference analysis and the impact of VPP.
Discussion

This study examined the effect of VPP on the procurement prices of ARV. Efavirenz was chosen as a case study given the frequent use of Efavirenz in fixed dose combination (FDC) therapy for HIV. A difference-in-difference (DID) estimator in regression form was used to estimate the effect of VPP. The assumption of a common trend was confirmed with graphs and a regression model using lags and leads of the interaction term. To the best of our knowledge, this is the first study estimating the impact of VPP on ARV procurement prices adopting a formal econometric method.

The analyses found VPP significantly reduced the procurement price of 600mg generic Efavirenz. The coefficient of the DID estimator was significant at the 0.1% level for both ex-works prices and incoterms prices. Simulation using 1,000 times bootstrap re-sampling and p-values calculated by a wild cluster bootstrap strongly supported the results of the DID analysis.

A strong decreasing trend in the ARV price over 8 years was also found. Year dummies were significant for all years aside from 2005. The finding of decreasing ARV costs over 8 years is consistent with the results of Wafula et al. (2013) and with the trend of consistently decreasing ARV prices more widely observed. The median procurement price per treatment year for adult first-line regimens in low- and middle-income countries decreased from $US 499 to $122 between 2003 and 2013 (Perriëns 2014; Perriëns et al. 2014). In 2006, UNITAID was launched to supply drugs at lower prices (Bermudez & Hoen 2010). Also in 2006, Generic FDCs were available to PEPFAR recipients after FDA approval (Waning et al. 2010). Donor funding for HIV increased from $1.6 billion to $8.7 billion largely due to PEPFAR and GFATM from 2002 to 2008 (Kates et al. 2009). The GAVI alliance (GAVI) committed US $500 million for a 5-year period from 2006 to 2010 (Patel et al. 2015). Therefore, the decreasing trend in ARV prices may be associated with increased funding for ARV procurement, the emergence of powerful global donors, and the introduction of generic drugs. These analyses demonstrate that the use of VPP can further reduce drug prices.

In addition, it was found that HIV prevalence was not associated with drug prices. This is consistent with Danzon et al. (2013) and Wirtz et al. (2009). Transaction volume was not associated with the drug price. This too is consistent with results from Wirtz et al. (2009). They found that transaction volume does not have an effect on the price reduction using GPRM data. This fact confirms that GPRM data do not support our common assumption that large procurement volume reduces procurement prices. Generic competition was not statistically significant and again, this is consistent with results from Danzon et al. (2013) and is plausible because there is little incentive to reduce ARV prices in generic markets.

While VPP may improve access to HIV drugs, it is difficult to say whether or not improved procurement arrangements have the ability to strengthen the health systems of low and middle income countries more generally. It has been pointed out that the long term dependence of principal recipients (PR) countries on external funding bodies can weaken the health systems of these countries (The World Bank(WB) and GAVI Alliance 2010). On the contrary, PR countries could turn this challenge into an opportunity if they use the experience to develop the capacity to forecast, budget and plan independently.
Mills (2014) argued that the strengthening of public systems of supply such as transport infrastructure could be an alternate solution for improving drug supply. In particular, a landlocked country may need additional time for transportation from the nearest port (GFATM 2011). This argument suggests that improving drug procurement processes may be an important starting point but would not be sufficient to improve drug access without a concurrent expansion of public facilities and qualified health to ensure those drugs reach the patients most in need (Mills 2014). Thus while VPP may not strengthen health systems more broadly, health systems strengthening seems a necessary precursor to maximising the gains of a VPP scheme.

The quality of the data used in the study has been continuously improved through the use of rigorous data management and updating with new information. This includes; Individual transactions in GPRM showing a price of US$0 and duplications being removed (World Health Organisation 2013), missing data being replaced with updated price data compared to the previous version of the dataset a few years ago, the recent inclusion of Incoterms prices in the dataset (World Health Organisation 2013), and the fact that GFATM periodically report the transaction prices so that the data is constantly updated. Moreover, as procurement services agents (PSA) rather than recipient countries have the responsibility for data entry (GFATM 2014), data is transparently managed. However, these data do not have components of retail prices such as mark-up. Therefore, analysis of retail drug prices would not be possible with this dataset.

The strengths of this study are, firstly, that it used the International Chamber of Commerce standard trade definition (Incoterms) price as a dependent variable. The majority of studies on procurement prices could not consider the Incoterms prices due to data unavailability. However, excluding Incoterms can strongly bias the results regarding procurement prices because procurement processes include the variable cost of freight and shipping. This study attempted to reduce this bias by employing Incoterms price as the dependent variable. Secondly, this study is based on the recently updated GPRM data. The update made this data richer compared with the previous version of GPRM data; hence, the analysis carried out in this study did not have to rely on multiple imputation (MI) to supplement missing data. Thirdly, adopting fixed effects to GLM by including country dummies, which work as subject-specific slopes, this study tried to control endogeneity arising from time-invariant unobservables such as national policies. Instrumental variables were not used in this study as it was hard to find an appropriate instrument for the procurement price of ARVs, especially the price of Incoterms, given the scarcity of literature on the procurement prices of ARVs. However, this study attempted to reduce the endogeneity caused by omitted variables (Cameron & Trivedi 2005) by including a proxy variable of generic competition such as the number of manufacturers and by using a fixed-effects model.

A few limitations of these analyses should be noted. Firstly, this analysis targeted only one ARV, Efavirenz. Therefore, the given result needs to be carefully interpreted and may not be generalizable to other types of drugs. Further research expanding the result of this study to other ARVs will be needed. Secondly, the timeline of analysis was limited to 2013 due to data unavailability, even though VPP is still being implemented.
Conclusion

This study provides robust economic evidence about the effect of voluntary pooled procurement on antiretroviral drug prices and highlights a clear agenda for further work in this area. Voluntary pooled procurement significantly reduced the price of 600mg generic Efavirenz between 2009 and 2013. Voluntary pooled procurement can be a potentially effective strategy for the reduction in HIV drug prices and the improvement of technical efficiency in HIV drug procurement. Future work should aim to explore a more generalizable or multi-context analysis of the impact of voluntary pooled procurement. It would also be possible and potentially worthwhile, to carry out a difference-in-difference analysis on a basket of various HIV drugs rather than focusing on a single drug such as Efavirenz as in this study.

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