Is pricing of dolutegravir equitable? A comparative analysis of price and country income level in 52 countries

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Abstract

Objectives: Differences in marketed prices of antiretrovirals raises questions about the fairness of pricing medicines of significant public health importance such as dolutegravir (DTG). In view of the reduced prices of generically available efavirenz (EFV), there is a need to determine if previous conclusions on DTG's cost-effectiveness need to be re-assessed **Methods:** Lowest list prices of DTG were extracted from national drug price or reimbursement databases for 52 countries. Price was recorded as US\$ per person-year (ppy). We compared the price of DTG to minimum costs of production and reduced prices of EFV, as well as assessed the correlation with gross domestic product (GDP) per capita and HIV epidemic size in three income classification groups ('high', 'upper middle-income', 'lower middle or low-income').

Results: Annual prices of DTG ranged from \$27 per person-year in Georgia to \$20,130 in the USA. Within each income group, there was no observable relationship between DTG prices, GDP per capita and HIV epidemic size. Median price in countries excluded from voluntary licensing agreements (\$8718) was >140 times higher than countries included (\$60). Price of DTG was >500% higher than EFV in many countries. Three full economic evaluations from high-income settings that compared DTG against EFV all used branded drug prices of EFV-based regimens as cost inputs to evaluate DTG's cost-effectiveness.

Conclusions: This study highlights the wide disparity in prices of DTG across countries, even when segregated by similar income levels. The cost-effectiveness of DTG versus EFV should be re-evaluated now that low-cost generic EFV has become widely available.

Keywords: dolutegravir, efavirenz, price, costs, cost-effectiveness

Background

Affordable antiretrovirals have played a pivotal role in increasing global antiretroviral therapy (ART) coverage over the past decade [1]. In 2017, 15.2 million (41%) of the total of 36.7 million people living with HIV (PLHIV) still did not have access to ART [2]. Many countries are also currently still far from reaching the 90-90-90 target [3]. An analysis of HIV treatment cascades in 2016 found that ART coverage was only 12% in Russia, 18% in China and 48% in Brazil [3].

Based on results from the SINGLE trial, the largest head-to-head trial between dolutegravir (DTG) and efavirenz (EFV) in treatmentnaïve patients, DTG showed lower discontinuation rates compared to efavirenz (EFV) (Table 1) [4]. Together with favourable results from several other Phase 3 randomised controlled trials, the World Health Organization (WHO) has recommended DTG as a preferred first line treatment option in HIV-1 positive people since July 2018 [5]. Clinical guidelines from several high-income countries (HICs) have also recommended DTG as the preferred first-line agent, while downgrading efavirenz (EFV) from a preferred option to an alternative treatment option [6–8]. In view of the benefits associated with DTG, there is an increasing global interest in using DTG as part of a strategically preferred universal antiretroviral regimen to accelerate current progress towards the 90-90-90 target [9].

A generic co-formulation of tenofovir/lamivudine/dolutegravir (TDF/3TC/DTG) should become available in 92 low- and lowmiddle income countries at a target price of \$75 per person-year (ppy), according to recent announcements [10]. In these countries, the price of TDF/3TC/DTG should be slightly lower than generic

*Corresponding author: Andrew M Hill, Department of Translational Medicine, University of Liverpool, 70 Pembroke Place, Liverpool L69 3GF, UK. Email: microhaart@aol.com TDF/3TC/EFV [12]. However, this pricing arrangement does not benefit the majority of upper middle-income countries (UMICs) and high-income countries (HICs) where DTG is sold at much higher prices due to ongoing patent restrictions [9]. In particular, several UMICs and HICs in Eastern Europe, South America and South-east Asia with large HIV epidemics have been excluded from the voluntary licensing (VL) agreements [9]. Since the patent for EFV has already expired, it is currently available in many countries as a low-cost antiretroviral due to robust competition between generic manufacturers. For example, in the UK, DTG currently costs \pounds 6,068 ppy [13] compared to \pounds 108 for EFV [14]. The non-nucleoside inhibitor of the retrotranscriptase (NRTIs) used in combination with either DTG or EFV can also be accessed as low-cost generics in most countries (for example ABC/3TC, TDF/FTC or TDF/3TC).

In the SINGLE trial, patients taking ABC/3TC/DTG were less likely to discontinue treatment for adverse events than patients taking TDF/FTC/EFV (Table 1) [4]. However, the risk of virological failure after 3 years was 9% for ABC/3TC/DTG, versus 8% for TDF/FTC/EFV [4]. Therefore, the use of EFV first-line is not associated with an increased risk of virological failure requiring a switch to second-line therapy, when compared to DTG. In most HICs and UMICs where cost of DTG are expected to be much higher, the prevalence of pre-treatment drug resistance (DR) has also declined over the last decade and stabilised at around 10% due to regular viral load testing and pre-treatment genotypic DR testing [14,15]. Given the similar efficacy profile and moderate improvements in tolerability of DTG compared with EFV, the decision to transition from EFV to DTG hinges largely on the cost of each respective treatment option and their financial impact on health systems.

While the pattern of price variations has previously been demonstrated in second-line antiretrovirals between middle-income countries inside and outside sub-Saharan Africa [15,16], the extent of price disparity of DTG remains unclear at the moment.

Week 144 (FDA snapshot)	DTG-arm	EFV-arm	P value
Viral suppression: pVL <50 copies/mL	71%	63%	0.01
Protocol-defined virological failure: two consecutive $pVL \ge 50$ copies/mL on or after week 24	9%	8%	ns
Discontinuation due to adverse events or death	4%	14%	<0.0001
Failure for reasons other than virological failure or discontinuation due to adverse events or death	16%	15%	ns

The difference in marketed prices of antiretrovirals also raises questions about the fairness of pricing medicines of significant public health importance such as DTG. Compared with EFV-based regimens, DTG-based ones might also be too expensive to be considered cost-effective in HICs and UMICs. Economic evaluations (EEs) conducted in high-income settings have concluded that DTG is a more cost-effective treatment option over EFV, but only at the original patented prices [17–19]. In view of the reduced prices of generically available EFV, the issue of DTG's cost-effectiveness should also be re-assessed. Branded versions of DTG may no longer be cost-effective when compared to low-cost generic EFV.

This study aims to systematically compare the DTG prices across countries of different income levels. We have also compared the DTG price to minimum costs of production and reduced EFV prices in each country to determine if previous conclusions on DTG's cost-effectiveness need to be re-assessed.

Methods

Study design

We have analysed the price of DTG in countries where published information was available. As ex-factory or discounted prices for many countries are confidential, publicly listed prices were used [20]. For countries with data available, list prices of EFV were also gathered for comparison with DTG prices. All prices were recorded as US dollars per person-year (exchanged rates assumed are shown in the Appendix).

Median DTG prices were compared for countries included within and excluded from DTG VL arrangements. Included countries were then divided into three main income groups assigned by the World Bank [21]. Due to lack of data in the low-income group alone and similarity in DTG pricing in low-income and lower-middle income countries due to VL arrangements, both income groups were analysed as a collective group (as LMICs). HICs and UMICs were analysed as separate groups.

Within each income group, the price of DTG in each individual country was compared to its gross domestic product (GDP) per capita in 2016 published by the World Bank [22] and HIV epidemic size, according to UNAIDS [23]. GDP per capita reflects the extent to which the total economic output in a country can be shared by its population [24]. This measure is also of relevance as the tiered pricing system applied for ten LMICs with VL agreements for DTG are based on their GDP [25].

Data sources

Lowest list prices of DTG in over 50 countries were collected from publicly accessible national drug price databases, reimbursement authorities, and WHO Global Price Reporting Mechanism database in April 2018. Additional information was also obtained from press releases, online price comparison tools and email correspondences with various country representatives (price sources can be found in the Appendix). Country statistics on GDP per capita (2016) and the number of PLHIV were extracted from the World Bank database and UNAIDS progress reports respectively [22,23].

Calculation of estimated generic price

To assess the level of price mark-up by the pharmaceutical company, we estimated the generic price of DTG based on a cost-estimation algorithm previously validated for HIV/AIDS, tuberculosis and malaria medicines included in the WHO Essential Medicines List [26]. This algorithm includes the costs of converting raw active pharmaceutical ingredients (API) and excipients into the finished pharmaceutical product as well as taxation and a 10% price mark-up to mimics the real-world profitability margin required to encourage market entry and increase competition between generic manufacturers [26].

Export data of API from India between January 2016 to February 2018 were retrieved from an online database (www.Datamyne. com) that compiles data pursuant to Indian customs regulations [27]. Thereafter, data was averaged to obtain the average price per kilogram of exported API over the timeframe. Per-kilogram prices for each antiretroviral were then input into the cost-estimation algorithm illustrated by Figure 1 [26]. For instance, 18.25 g of API is required for 1 year's supply of DTG at a dose of 50-mg daily. One kilogram of DTG was estimated to cost \$1815. A formulation cost of \$0.01 per tablet followed by a tax rate of 27% and 10% price mark-up were then applied to obtain the estimated generic price of DTG ppy.

Cost inputs used in cost-effectiveness analyses

An electronic search was performed on 11th June 2018 to identify the cost of EFV- and DTG-based regimens used in full EEs on the following databases: MEDLINE, Embase, the Cost-effectiveness analysis (CEA) registry and the Centre for Reviews and Dissemination database. To identify studies from grey literature, search was also conducted on Scopus, Web of Science and Google Scholar. Literature searches were performed using free-text search and subject headings based on the two search concepts 'economic evaluation' and 'dolutegravir', with no restrictions on language and publication date. A full EE is defined as a study that compares both costs (use of resources) and consequences (benefits, outcomes) of alternative treatment options [28].

Results

The median price of DTG across all 52 countries was \$7920 ppy. The price varied substantially across all countries, ranging from \$27 ppy in Georgia to \$20,130 ppy in the US. The median price of DTG in countries excluded from VL agreements (\$8718) was more than 140 times higher compared to countries which are included (\$60). Similarly, median DTG prices in HICs (\$9164) were much higher than UMICs (\$3285) and LMICs (\$60).

From January 2016 to February 2018, there were 20 shipments exporting 586 kg of API at a total value of \$1,119,338. Based on the cost-estimation algorithm (Figure 1), the estimated generic price was \$42 ppy, which is similar to the price of DTG in countries with the VL. The price of DTG in most HICs and UMICs excluded from the VL agreements is close to 200 times higher than the



Figure 1. Generic price estimation flow chart for dolutegravir 50-mg tablet

estimated generic price. When compared to EFV, the current price of DTG is also more than 100–500% higher in most countries regardless of income group (Table 2).

There was no observable relationship between DTG prices and GDP per capita in all three income groups (Figures 2a–c). The greatest variability in DTG prices was observed in UMICs. For instance, DTG costs \$9656 ppy in Bulgaria compared to \$365 in Brazil, even though its GDP per capita is similar (Bulgaria \$7469 vs Brazil \$8650). In HICs, the price of DTG in USA (\$20,130) is a clear outlier. This price is almost four times higher of that in Canada (\$5267), although their GDP per capita is comparable (US: \$57,638 vs Canada: \$42,349). Excluding the US, the median price of DTG in HICs across varying income levels is stable around \$9042 ppy. In all included LMICs, DTG prices were below \$600, with India and Uganda showing higher prices than the other countries.

Similarly, the HIV epidemic size and DTG prices did not show any correlation in the three income groups. In HICs, for example, Australia has a smaller number of PLHIV and a higher GDP per capita than countries such as France, Germany and UK, but its price of DTG is much lower. In UMICs, although the epidemic size and GDP per capita of Russia and China is similar to Brazil, their DTG prices (Russia \$1871; China \$3854) were more than 5- and 10-fold higher than in Brazil (\$365).

We identified three full EEs with available information on the cost inputs of DTG- and EFV-based regimens used in the economic models (Table 3). All studies were set in high-income settings and used branded drug prices of EFV-based regimens as cost inputs for evaluation of DTG's cost-effectiveness. The cost of TDF/FTC/EFV (Atripla) in Italy by Restelli *et al.* was quoted at branded 2017 price of US\$8736 ppy [19], although generic EFV currently costs US\$788 ppy.

While all three EEs investigated the uncertainty around cost of treatments [17–19,29–31], only two studies assessed a potential reduction in the price of the components in comparator regimens [17,30]. By reducing the price of EFV/TDF/FTC by 20% to illustrate the impact of patent expiry of EFV, Peng *et al.* showed that the incremental cost-effectiveness ratio (ICER) increased by 148% from the base case [30]. Similarly, DTG stopped being a dominant treatment option for treatment-naïve patients when

comparing the combination of generic EFV and Truvada (branded TDF/FTC) in the study by Despiégel *et al.* [17]. However, the price of generic EFV used in the sensitivity analysis was not stated and its impact on the ICER was not explained by the authors [17]. By contrast, the remaining two EEs conducted in France and Italy did not vary the prices of comparator regimens for all analyses [18,19]. Instead, the authors only tested a 10% reduction in price of DTG and varied the cost of subsequent or salvage therapies [18,19].

Discussion

Our comparative price analyses highlight the wide disparity in prices of DTG across countries, even when segregated by similar income levels. The lowest and highest prices of DTG varied between 4 times in HICs and 268 times in UMICs. Our analysis also shows that the prices in countries excluded from VL for DTG were substantially higher compared to prices in countries under the VL agreements which were similar to estimated cost of production. This makes DTG unaffordable in countries excluded from the VL agreements in which people have to pay for their own ART or the public health system needs to treat a large number of PLHIV. This pattern of price differences between higher and lower-income countries is also consistent with findings from previous studies for several other classes of antiretrovirals such as Pls, NNRTIs and NRTIs [15,16].

The prices of DTG seen in HICs and UMICs are likely set by the pharmaceutical company to gain substantial profits from a wealthier subset of the global population. In middle-income countries, with higher incomes and better infrastructure, pharmaceutical companies also claim to adopt a flexible pricing policy that factors in each country's GDP and epidemic size to improve affordability [33]. However, we did not notice any systematic pattern of pricesetting based on GDP per capita or HIV epidemic size.

The higher prices of DTG seen in countries in these HICs and UMICs may be a result of ineffective price negotiations due to incomplete information. For instance, policymakers who lack complete information about the cost of production or the price neighbouring countries pay may end up paying many times more than others may end up paying many times more than others [32]. Procurers are unlikely to accept high DTG prices if they are

Country	DTG price per person-year (US\$)	EFV price per person-year (US\$)	Price increase (%): DTG <i>vs</i> EFV price	Country	DTG price per person-year (US\$)	EFV price per person-year (US\$)	Price increase (%): DTG vs EFV price
	High-income	e countries			Upper middle-in	come countries	
United States	\$20,130	\$3507	474%	Bulgaria	\$9656	\$1154	737%
Latvia	\$11,872	\$788	1407%	Croatia	\$8867	\$2322	282%
Denmark	\$11,056	\$2284	384%	Serbia	\$7807	\$2750	184%
Japan	\$10,908	\$5127	113%	Lebanon	\$7765	\$1129	588%
Cyprus	\$10,725	\$2625	309%	Peru	\$5658	\$722	684%
Israel	\$10,559	\$2723	288%	Turkey	\$5204	\$906	474%
Germany	\$10,541	\$2806	276%	China	\$3854	\$1152	235%
Czech Republic	\$10,306	\$2218	365%	Colombia	\$3285	\$47	6889%
Iceland	\$10,099	\$3667	175%	Argentina	\$2682	\$420	539%
Switzerland	\$9972	\$3574	179%	Mexico	\$2629	\$143	1738%
Austria	\$9618	\$2538	279%	Russia	\$1871	\$146	1182%
New Zealand	\$9548	\$555	1620%	Belarus	\$1181	\$24	4821%
Hungary	\$9343	\$3851	143%	South Africa*	\$835	\$29	2779%
Belgium	\$9282	\$1243	647%	Brazil	\$365	\$365	0%
Netherlands	\$9164	\$1883	387%	Cuba	\$57	\$21	171%
Greece	\$9083	\$1678	441%	Lower middle and low-income countries			es
France	\$9045	\$1778	409%	India*	\$538	\$321	68%
Lithuania	\$9040	\$825	996%	Uganda*	\$269	\$29	828%
Luxembourg	\$9020	\$1289	600%	Ukraine*	\$69	\$29	138%
Oman	\$8718	\$1035	742%	Equat*	\$60	\$35	71%
Slovenia	\$8630	\$1545	459%	Uzbekistan*	\$60	\$33	82%
United Kingdom	\$8495	\$155	5381%	Cambodia*	\$60	\$29	107%
Norway	\$8179	\$3228	153%	Armenia*	\$45	\$37	22%
United Arab Emirates	\$8033	\$5629	43%	Georgia	\$27	\$39	-31%
Bahrain	\$7500	\$5256	43%				
Italy	\$7350	\$788	833%				
Australia	\$6540	\$2211	196%				
Chile	\$6338	\$931	581%				
Canada	\$5267	\$336	1468%				

Country	Annual drug prices (US\$)				
	Prices cost-effe ana	used in ctiveness lysis	Prices in 2018		
	DTG + 2 NRTIs	EFV + 2 NRTIs	DTG	EFV	
Canada [17]	\$12,419	\$12,134	\$5267	\$336	
Italy [19]	\$13,081	\$8736	\$7350	\$788	
United States [30]	\$28,455	\$24,983	\$20,130	\$3507	

aware that minimum production costs of DTG could be as low as \$42 ppy, with economies of scale. In Georgia, where the price of DTG was lower than estimated cost of production, this was likely achieved due to donation program from international donor Organizations and may not reflect of actual prices.

Confidential agreements on drug prices also prevent purchasers from making accurate international price comparisons to guide pricing decisions [20]. In some countries, prices are also set according to established cost-effectiveness thresholds based on GDP per capita [33] or average monthly wages [34] which indicate purchasers' maximum willingness to pay for a drug [35]. This may result in a highest possible price that meets the threshold level, with significant budgetary impact [35].

Furthermore, as the entry of generic EFV has lowered its off-patent drug price, the price difference with DTG has become significantly pronounced as shown in our comparative price analysis. The cost inputs used in the identified EEs, all of which were funded by pharmaceutical companies, did not accurately reflect medication prices in the marketplace. Therefore, if cost inputs for the EEs are updated, this may potentially change the ICERs and hence, DTG might not be cost-effective as previously described.

Generic drug entry of standard of care comparators such as EFV in cost-effectiveness studies are a major source of uncertainty. Yet, researchers only varied the price of DTG by 10–20% but kept



Figure 2. Relationship between DTG price, GDP per capita and HIV epidemic size (by income group)

the price of study comparators constant in most EEs [17–19]. Although Despiégel *et al.* stated that DTG stopped being the dominant strategy when compared to a cheaper combination of generic EFV and Truvada (branded TDF/FTC), the extent of price reduction associated with the use of generic EFV in the SA is unclear [17].

Strengths and limitations

In the comparative price analysis, we used publicly available list prices of DTG and EFV which might not be reflective of

actual prices paid by governmental reimbursement Organizations. Often, purchase prices negotiated are lower than the drugs' list prices due to confidential discounts or rebates [20]. However, considering most countries negotiate a similar discount rate, between 20% and 30% [37], the price difference between countries is unlikely to differ greatly even if using available list prices. Furthermore, we did not differentiate between generic and branded prices of EFV when comparing to DTG. This was limited by the information available, in which some countries only provided prices of either branded or generic EFV. Nevertheless, this study shows that price of EFV, regardless of being generic or branded, was substantially lower compared to DTG in most countries.

Applications and implications

This study highlights the critical need for greater transparency in the prices of antiretrovirals, including back-end discounts and rebates for purchases and payers. Although DTG has shown an improved safety profile in randomised controlled trials, it is still necessary to assess how much higher the price of DTG should be compared to the current reduced price of EFV. Pharmaceutical companies like Gilead and GlaxoSmithKline have been posting growing sales figures and accumulated over \$200 billion from HIV drug sales during the past 15 years [38]. As such, there is no justification for prices of DTG to remain significantly above current reduced prices of EFV or its estimated generic price.

Expanded international price comparisons and generic price estimation may empower government price negotiations and support cost-effectiveness calculations [26]. Given the potential of the WHO GPRM and Global Fund Price and Quality Reporting database to provide a good source of market intelligence on international prices, countries should in principle use reported prices from other countries as a benchmark to negotiate lower prices of DTG. Similarly, knowledge of realistic research, development and production costs can act as a form of price control mechanism to set ceiling prices [26]. For instance, any manufacturer who submits a government tender in South Africa is requested to provide a breakdown of drug price into API, formulation, packaging and profit margin components [39].

As the exact timing of generic entry and level of price reduction is subject to variation, these should also be incorporated in the economic models as part of SAs [40]. Studies have found that drug prices fall approximately by 40% after 2 years of generic drug entry [41]. This failure to consider and accurately incorporate the impact of generic drug entry may therefore result in an underestimation of DTG's incremental cost-effectiveness ratio, and thus overstate its true economic benefit [40]. DTG might even be considered cost-effective for immediate use in HICs or UMICs when comparators are initially expensive but lose its cost--benefit ratio in the long term when generic comparators become available at a later date [40].

Nevertheless, the impact of generic drug entry has been found to be largely ignored in literature if generic versions of study comparators are not available at the time of the study [40]. As more antiretrovirals are close to patent expiration, it is therefore becoming increasingly important for future pharmacoeconomic studies on new drugs to incorporate the impact of generic drug entry into their economic models to provide more accurate projections of their cost-effectiveness to quide policy decisions.

Although DTG is considered a better clinical option for patients in high-income settings, a multiple-tablet regimen of available generic EFV and TDF/FTC tablets at a fraction of that cost may also be considered as an adequate short-term solution to improve ART coverage to more patients before a cheap fixed-dose combination containing DTG becomes available. This is given the similar efficacy profile and moderate improvements in tolerability of DTG compared with EFV, as well as similar efficacy and safety outcomes between multiple-tablet regimens and branded single-tablet fixed-dose combination [43]. With the patent expiration for TDF/FTC expected around 2021 [44], this could also potentially pave the way for a generic FDC available in highincome settings, thereby reducing both cost and pill burden simultaneously.

Conclusion

Our comparative analysis of international prices shows that DTG might not be cost-effective for use, especially in UMICs and HICs where prices of DTG are high. Cost differences between antiret-rovirals will continue to impact HIV care delivery in the near future as more antiretrovirals become available as generic for-mulations. While we continue to advocate for more resources to treat people with HIV, we need to identify opportunities for lowering drug prices so that these resources can be better utilised to deliver HIV services essential to the continuum of care in low, middle, and high-income countries.

Acknowledgements

Conflicts of interest and source of funding

None

References

- Clinton Health Access Initiative. ARV market report. The state of the antiretroviral drug market in low- and middle-income countries, 2016–2021. 2017. Available at: https://clintonhealthaccess.org/content/uploads/2017/09/2017-ARV-Market-Report_Final-2.pdf (accessed May 2018).
- UNAIDS. Fact sheet Latest statistics on the status of the AIDS epidemic. Available at: www.unaids.org/en/resources/fact-sheet/ (accessed: May 2018).
- Levi J, Raymond A, Pozniak A et al. Can the UNAIDS 90-90-90 target be achieved? A systematic analysis of national HIV treatment cascades. BMJ Global Health 2016; 1: e000010
- 4. Walmsley S, Baumgarten A, Berenguer J et al. Brief report: dolutegravir plus abacavir/ lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: week 96 and week 144 results from the SINGLE randomized clinical trial. J Acquir Immune Defic Syndr 2015; **70**: 515–519.
- World Health Organization. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidance. Available at: www.who.int/hiv/ pub/guidelines/ARV2018update/en/ (accessed August 2018).
- British HIV Association. British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals 2016. 2016. Available at: www. bhiva.org/documents/Cuidelines/Monitoring/2016-BHIVA-Monitoring-Guidelines. pdf (accessed May 2018).
- European AIDS Clinical Society (EACS). *Guidelines Version 9. October 2017*. Available at: www.eacsociety.org/files/guidelines_9.0-english.pdf (accessed May 2018).
- Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. 2017. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf (accessed July 2018).
- World Health Organization. Policy brief: transition to new antiretrovirals in HIV programmes. 2017. Available at: http://apps.who.int/iris/bitstream/ handle/10665/255888/WHO-HIV-2017.20-eng.pdf?sequence=1 (accessed May 2018).
- Médecins Sans Frontières Access Campaign. Untangling the web of antiretroviral price reductions. 2016. Available at: www.msfaccess.org/sites/default/files/ HIV_report_Untangling-the-web-18thed_ENG_2016.pdf (accessed May 2018).
- UNITAID and Medicines Patent Pool. Patents and licenses on antiretrovirals: a snapshot. 2014. Available at: https://medicinespatentpool.org/uploads/2017/07/ ARV-Snapshot_April2014Rev.pdf (accessed May 2018).
- Hill A, Barber M, Gotham D, Fortunak J, Nath S, Pozniak A. Generic treatments for HIV, HBV, HCV, TB could be mass produced for <\$90 per patient. *IAS 2017*. July 2017. Paris, France. Abstract TUAD0104.
- British National Formulary. Dolutegravir: medicinal forms. Available at: https:// bnf.nice.org.uk/medicinal-forms/dolutegravir.html (accessed July 2018).
- Gov.uk. Drugs and pharmaceutical electronic market information tool (eMIT). Available at: www.gov.uk/government/uploads/system/uploads/attachment_data/ file/671991/eMIT_national_201706.xls (accessed July 2018).
- Simmons B, Hill A, Ford N et al. Prices of second-line antiretroviral treatment for middle-income countries inside versus outside sub-Saharan Africa. J Int AIDS Soc 2014; 17(4S3): 19604.
- Ford N, Ananworanich J, Ruxrungtham K et al. Is the pricing of antiretrovirals equitable? Analysis of antiretroviral drug prices in 20 low- and middle-income countries. *IAS 2013*. June 2013. Kuala Lumpur, Malaysia. Abstract WELBD05.
- Despiegel N, Anger D, Martin M et al. Cost-effectiveness of dolutegravir in HIV-1 treatment-naive and treatment-experienced patients in Canada. Infect Dis Therapy 2015; 4: 337–353.
- Pialoux G, Marcelin A-G, Despiegel N et al. Cost-effectiveness of dolutegravir in HIV 1 tratmost eventioned (TE) patients in Erange PloS One 2015; 10: e0145825
- HIV-1 treatment-experienced (TE) patients in France. PloS One 2015; 10: e0145885.
 Restelli U, Rizzardini G, Antinori A et al. Cost-effectiveness analysis of dolutegravir plus backbone compared with raltegravir plus backbone, darunavir+ritonavir plus backbone and efavirenz/tenofovir/emtricitabine in treatment naive and experienced HIV-positive patients. Ther Clin Risk Manag 2017; 13: 787–797.
- Vogler S, Zimmermann N, Habl C et al. Discounts and rebates granted to public payers for medicines in European countries. Southn Med Review 2012; 5: 38–46.
- World Bank. World Bank Country and Lending Groups. Available at: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-andlending-groups (accessed July 2018).

- World Bank. GDP per capita (current US\$). Available at: https://data.worldbank. org/indicator/NY.GDP.PCAP.CD (accessed July 2018).
- UNAIDS. Countries. Available at: www.unaids.org/en/regionscountries/countries (accessed July 2018).
- UNICEF. Definitions: economic indicators. Available at: www.unicef.org/infobycountry/stats_popup7.html (accessed May 2018).
- Initiative for Medicine Access and Knowledge (I-MAK). The Roadmap. Special edition report: dolutegravir. 2017. Available at: www.i-mak.org/wp-content/ uploads/2017/06/I-MAKRoadmapSEReportDTG20170619F.pdf (accessed May 2018).
- Hill AM, Barber MJ, Gotham D. Estimated costs of production and potential prices for the WHO Essential Medicines List. BMJ Global Health 2018; 3: e000571.
- 27. Descartes Systems Group Inc. *Datamyne*. Available at: www.datamyne.com/ (accessed April 2018).
- Drummond MF, Sculpher MJ, Claxton K et al. Methods for the Economic Evaluation of Health Care programmes. 4th edn. Oxford: Oxford University Press; 2015.
- Keeling N, Crumby A, Nunna S. Cost-effectiveness of once daily dolutegravir versus twice daily raltegravir as first-line antiretroviral therapy in HIV-infected adults in the United States. *Value Health* 2014; 17: A274.
- Peng S, Tafazzoli A, Dorman E *et al.* Cost-effectiveness of DTG+ABC/3TC versus EFV/TDF/FTC for first-line treatment of HIV-1 in the United States. *J Med Econ* 2015; 18: 763–776.
- Zheng A, Kumarasamy N, Huang M et al. The cost-effectiveness and budgetary impact of a dolutegravir-based regimen as first-line treatment of HIV infection in India. J Int AIDS Soc 2018; 21: e25085.
- Ramani S V, Urias E. Access to critical medicines: when are compulsory licenses effective in price negotiations? Soc Sci Med 2015; 135: 75–83.

- Jakubiak-Lasocka J, Jakubczyk M. Cost-effectiveness versus cost-utility analyses: what are the motives behind using each and how do their results differ? A Polish example. Value Health Regional Issues 2014; 4: 66–74.
- Skoupá J, Annemans L, Hájek P. Health economic data requirements and availability in the European Union: results of a survey among 10 European countries. *Value Health Regional Issues* 2014; 4: 53–57.
- Iyengar S, Tay-Teo K, Vogler S et al. Prices, costs, and affordability of new medicines for hepatitis C in 30 countries: an economic analysis. PLoS Med 2016; 13: e1002032.
- Gianotti N, Poli A, Galli L *et al*. Efficacy and safety of switching from branded to generic antiretrovirals in virologically suppressed HIV-infected patients. *PLoS One* 2017; 12: e0182007.
- Morgan SG, Vogler S, Wagner AK. Payers' experiences with confidential pharmaceutical price discounts: a survey of public and statutory health systems in North America, Europe, and Australasia. *Health Policy* 2017; 121: 354–362.
- Statista. Selected top AIDS drugs worldwide based on revenue from 2014 to 2016 (in million U.S. dollars). Available at: www.statista.com/statistics/273434/revenueof-the-worlds-most-important-aids-drugs/ (accessed July 2018).
- Republic of South Africa National Department of Health. HP09-2016SD: The supply and delivery of solid dosage forms to the department of health for the period 1 August 2016 to 31 July 2018. 2016. Available at: www.health.gov.za/ tender/docs/contracts/HP092016SDContractCircular.pdf (accessed July 2018).
- Shih Y-CT, Han S, Cantor SB. Impact of generic drug entry on cost-effectiveness analysis. *Medical Decision Making* 2005; 25: 71–80.
- Berndt ER, Aitken ML. Brand loyalty, generic entry and price competition in pharmaceuticals in the quarter century after the 1984 Waxman-Hatch legislation. Int J Econ Business. 2011; 18: 177–201.

Appendix: price source and exchange rate assumed for each country

Country	Price source	Website	Exchange rate assumed
Argentina	Fundación Huésped (Huésped Foundation)	Email correspondence	N.A (price given in USD)
Austria	Österreichische Sozialversicherung (Austrian Social Security)	http://www.hauptverband.at/oeko/?portal=hvb	1 EUR = 1.22 USD
Australia	Pharmaceutical Benefits Scheme (PBS)	http://www.pbs.gov.au/pbs/home	1 AUD = 0.78 USD
Bahrain	National Health Regulatory Authority	http://www.nhra.bh/SitePages/View.aspx?PageId=42	1 BHD = 2.65 USD
Belgium	National Institute for Sickness and Disability Insurance	http://www.inami.fgov.be/SiteCollectionDocuments/ liste-specialites-prices-20180501.pdf	1 EUR = 1.22 USD
Brazil	Ministry of Health	Email correspondence	N.A (price given in USD)
Bulgaria	National Council on Prices and Reimbursement of Medicinal Products	http://portal.ncpr.bg/registers/pages/register/list- medicament.xhtml	1 BGN = 0.60 USD
Canada	Régie de l'assurance maladie du Québec (RAMQ)	http://www.ramq.gouv.qc.ca/SiteCollectionDocuments/ liste_med/liste_med_2018_04_03_en.pdf	1 CAD = 0.78 USD
Chile	K@iros Chile	http://cl.kairosweb.com/index.php	1000 CLP = 1.7 USD
China	315Jiage (Drug Price 315)	https://www.315jiage.cn/x-MianYiLi/208712.htm	1 CNY = 0.16 USD
Colombia	Ministry of Health and Social Protection	https://www.minsalud.gov.co/salud/MT/Paginas/ termometro-de-precios.aspx	1000 COP = 0.36
Croatia	Croatian Health Insurance Fund	http://www.hzzo.hr/zdravstveni-sustav-rh/trazilica-za- lijekove-s-vazecih-lista	1 HRK = 0.16 USD
Cyprus	Ministry of Health, Pharmaceutical Services	https://www.moh.gov.cy/moh/phs/phs.nsf/dmlpricelist_gr/dmlpricelist_gr?OpenDocument	1 EUR = 1.22 USD
Czech Republic	State Institute for Drug Control	http://www.sukl.eu/modules/medication/search.php	1 CZK = 0.048 USD
Denmark	Danish Medicines Agency	https://www.medicinpriser.dk/Default.aspx	1 DKK = 0.16 USD
Germany	Medizinfuchs.de	https://www.medizinfuchs.de/	1 EUR = 1.22 USD
Greece	Ministry of Health	http://www.moh.gov.gr/articles/times-farmakwn/ deltia-timwn	1 EUR = 1.22 USD
France	Ministre des Solidarités et de la Santé (Minister of Solidarity and Health)	http://base-donnees-publique.medicaments.gouv.fr/index. php	1 EUR = 1.22 USD
Hungary	National Health Insurance Fund Manager	http://www.neak.gov.hu//data/cms1019079/DRUG_LIST_ FOR_INTERNATIONAL_PRICE_COMPARISON_20180212.xls	1 EUR = 1.22 USD
Iceland	Pricing Committee	http://www.lgn.is/gogn/icelandic_medicine_price_04_2018. xls	1000 ISK = 9.8 USD
India	National Pharmaceutical Pricing Committee	http://nppaimis.nic.in/nppaprice/pharmasahidaamweb.aspx	1 INR = 0.015 USD
Israel	Ministry of Health	https://www.health.gov.il/Subjects/Finance/DrugPrice/ Pages/default.aspx	1 ILS = 0.28 USD
Italy	Ministry of Health	http://www.salute.gov.it/imgs/C_17_pubblicazioni_2696_ allegato.pdf	1 EUR = 1.22 USD

Country	Price source	Website	Exchange rate assumed
Japan	Ministry of Health, Labour and Welfare	http://www.mhlw.go.jp/topics/2018/04/dl/tp20180418- 01_01.pdf	1000 JPY = 9.2 USD
Latvia	State Agency of Medicines	https://www.zva.gov.lv/zalu-registrs/	1 EUR = 1.22 USD
Lebanon	Ministry of Public Health	https://moph.gov.lb/en/Pages/3/3010/pharmaceuticals#/ en/view/3101/drugs-public-price-list-	1000 LBP =0.66 USD
Lithuania	Ministry of Health	http://sam.lrv.lt/lt/veiklos-sritys/farmacine-ir-kita-su-tuo- susijusi-veikla/vaistu-ir-medicinos-pagalbos-priemoniu- kompensavimas/nekompensuojamieji-vaistai	1 EUR = 1.22 USD
Luxembourg	La Caisse nationale de santé (National Health Fund)	http://cns.public.lu/content/dam/cns/legislations/ texte-coordonne/med-comm/1804-liste-comm.pdf	1 EUR = 1.22 USD
Mexico	Gob.mx	https://www.gob.mx/cms/uploads/attachment/file/ 243931/MEDICAMENTOS_ANTIRRETROVIRALES_2017.pdf	1 MXD = 0.053 USD
The Netherlands	National Health Care Institute (Zorginstituut Nederland)	https://www.medicijnkosten.nl/databank	1 EUR = 1.22 USD
New Zealand	Pharmaceutical Management Agency	http://www.pharmac.govt.nz/HMLOnline.php	1 NZD = 0.72 USD
Norway	Norwegian Medicines Agency	https://www.legemiddelsok.no/sider/default.aspx?f=Han;Mt l;Vir;ATC;Var;Mar;Mid;Avr;par;gen	1 NOK = 0.13 USD
Oman	Ministry of Health	https://www.moh.gov.om/en/web/dgpadc/-2	1 OMR = 2.60 USD
Peru	Ministry of Health	http://observatorio.digemid.minsa.gob.pe/#	1 PEN = 0.31 USD
Saudi Arabia	Saudi Food and Drug Authority	https://www.sfda.gov.sa/en/drug/search/Pages/default. aspx?PageIndex=1&sm=human	1 SAR = 0.27 USD
Russia	State Register of Medicines	http://grls.rosminzdrav.ru/pricelims.aspx	1 RUB = 0.02 USD
Serbia	Serbian Republican Health Insurance Fund	http://rfzo.rs/index.php/osiguranalica/lekovi-info/ lekovi-actual	100 RSD = 0.99USD
Slovenia	Public Agency of the Republic of Slovenia for Medicinal Products and Medical Devices (JAZMP)	http://www.jazmp.si/fileadmin/datoteke/seznami/SFE/ Cene/cene_2007hist.html	1 EUR = 1.22 USD
South Africa	South African Medicine Price Registry	http://www.mpr.gov.za/PublishedDocuments.aspx	1 ZAR = 0.08 USD
Switzerland	Federal Office of Public Health	http://www.spezialitaetenliste.ch/ShowPreparations.aspx	1 CHF = 1.02 USD
Turkey	Turkish Medicine Guide	https://www.ilacrehberi.com/	1 TRY = 0.24 USD
United Arab Emirates	Department of Health	https://www.haad.ae/haad/tabid/1328/Default.aspx	1 AED = 0.27 USD
United Kingdom	British National Formulary	https://bnf.nice.org.uk	1 UKP = 1.40 USD
USA	GoodRx	https://www.goodrx.com	NA (price given in USD
Others	WHO Global Price Reporting Mechanism	http://apps.who.int/hiv/amds/price/hdd/	NA (price given in USD