THE ROADMAP

SPECIAL EDITION REPORT
DOLUTEGRAVIR

June 2017

I-MAK initiative for medicines access & knowledge

www.i-mak.org

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Abbreviations

General

API	Active pharmaceutical ingredient
FDC	Fixed-dose combination
INSTI	Integrase Strand Transfer Inhibitor
IRIS	Immune Reconstitution Inflammatory Syndrome
LMICs	Low- and middle-income countries
PPPY	Per person per year
TB	Tuberculosis
UMIC	Upper middle-income country
WO	International Patent Publication Numbers
GDP	Gross domestic product

Organizations, Bodies and Companies

CHAI	Clinton Health Access Initiative
DMF	Drug Master File
EMA	European Medicines Agency
GSK	GlaxoSmithKline
I-MAK	Initiative for Medicines, Access & Knowledge
MPP	Medicines Patent Pool
PQm	World Health Organization Prequalification of Medicines
UNAIDS	The Joint United Nations Programme on HIV/AIDS
USFDA	United States Food & Drug Administration
WHO	World Health Organization

HIV

PLHIV	People living with HIV
ISTI	Integrase Strand Transfer Inhibitor
HIV	Human Immunodeficiency Virus
ARV	Antiretroviral
ART	Antiretroviral therapy

ARVs

3TC	Lamivudine
ABC	Abacavir
DTG	Dolutegravir
EFV	Efavirenz
FTC	Emtricitabine
RIL	Rilpivirine
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate

Executive Summary

Clinical Importance

- Dolutegravir (DTG) is a second-generation HIV integrase strand transfer inhibitor that greatly improves upon drugs in its class, and is highly suitable for large treatment programs in low- and middle-income countries.
- WHO HIV treatment guidelines currently recommend DTG as alternative first-line treatment, and for salvage regimens. DTG it is expected to become the preferred first-line treatment pending key data from additional clinical trials and real-life use. DTG is – or will soon be – included in national HIV treatment guidelines from Brazil, Botswana, Cambodia, Kenya, Nigeria, Tanzania, and Zimbabwe.

Cost & Access

- Originator company ViiV has three agreements allowing generic access to DTG: 1) a bilateral agreement that permits Aurobindo to produce generic DTG for 92 countries at a launch price of US$44 per person per year (PPPY); 2) a royalty-free voluntary license to the Medicines Patent Pool (MPP) for pediatric formulations of DTG for supply in 121 countries; and 3) a voluntary license to the MPP for adult formulations of DTG covering 92 countries (royalty-free in 82 countries; 10 countries have a tiered royalty structure).
- Forty-eight upper-middle income countries (UMICs) are excluded from the license; meaning approximately 3.5 million people living with HIV are blocked from accessing generic DTG. UMICs struggle to provide HIV treatment for all who need it because of high prices for the originator drug.
- Reaching production volumes needed to treat over one million people per year (which is likely to happen as early as 2018) could bring the price of generic DTG down to US$28 PPPY, approximately a 35% reduction from the US$44 generic launch price of DTG.

Patents

- DTG has five key International Patent Publication Numbers, which, if granted, would provide ViiV with market monopoly from 2006 to 2031, a duration of 25 years. There is one patent on the main base compound and four secondary patents.
- Based on further prior art searches since the original publication of the ***Roadmap*** report, we revised DTG's base patent strength from strong to medium/questionable, with scope to challenge the patent. We assess DTG's secondary patents all to be of weak strength.

Strategies for Access

- Since excluded countries continue to be unable to negotiate access through licensing agreements, we recommend a shift in strategy to: 1) challenge the base patent as the primary obstacle to generic entry, 2) challenge the secondary patents to remove the five additional years of market monopoly, and/or 3) pursue a coordinated compulsory license strategy, especially in countries in which patent barriers are unlikely to be removed because of lower patentability standards.
- Additionally, we recommend advocates dialogue with their governments to introduce and prioritize DTG using the clinical, cost, and patent information found in this report and that people living in countries excluded from licenses continue to push ViiV to include them, emphasizing the need for affordable, generic-accessible DTG.

Patent Quality Summary

Patent Number	Patent Type	Applicant	Strength of Patent	Explanation
WO 2006/116764	Base	Shionogi & Co Ltd	Medium/ Questionable	DTG is structurally close to prior HIV integrase inhibitor compounds, and the lack of comparative data in the application allows for grounds to challenge the patent on the basis of a lack of inventiveness and therapeutic efficacy.
WO 2010/011812	Prodrug	SmithKline Beecham Corporation	Weak	Various prior art exists that could be used to challenge the inventiveness of this application, while the pharmacokinetic data in the application does not meet the requirements of the therapeutic efficacy test.
WO 2010/068253	Salt/ Polymorph	Shionogi & Co Ltd/ GlaxoSmithKline LLC	Weak	Various prior art exists to show that the claims made in the application are not inventive and also do not meet the therapeutic efficacy test.
WO 2010/068262	Process & Intermediate	GlaxoSmithKline LLC	Weak	Claims related to DTG in this application are not inventive in light of prior patents.
WO 2011/119566	Process	GlaxoSmithKline LLC	Weak	Claims related to DTG in this application are not inventive in light of earlier patents.

INTRODUCTION

Introduction

What is The Roadmap?

In August 2013, the Initiative for Medicines, Access & Knowledge (I-MAK) created ***The Roadmap: The HIV Drug Pipeline and its Patents***, summarizing key clinical, cost, and patent information on important HIV antiretroviral (ARV) medicines in the pipeline. It aimed to help expand access to the next generation of life-saving ARVs in multiple ways, including:

- Helping people living with HIV (PLHIV) and treatment advocates prioritize efforts and make critical advocacy decisions for the coming years.
- Supporting patent offices to strengthen examination of patents for ARVs.
- Assisting generic producers to make decisions about which ARVs to produce, and consequently which patents to challenge and/or which pipeline ARVs to invest in producing.
- Supporting procurement agencies to make decisions within the law regarding what products to purchase and where to source them.
- Providing policy-makers with an evidence base about trends in secondary patenting across this therapeutic class to inform law and policy reform.

To date, stakeholders around the world report that ***The Roadmap*** has been used to inform decisions about whether patents should be granted on key ARVs, including by select local patent offices to assist their examination/raise awareness of the need for stronger examination of these patents.

Since ***The Roadmap*** was published, the need to provide safe, effective, tolerable, and **affordable** HIV treatment has grown more important than ever, given the World Health Organization's 2015 'treat-all' recommendation and the UNAIDS 90-90-90 treatment targets.[1, 2] By 2025, 24.3 million people are predicted to be on first-line HIV treatment.[3] Since the ARV market is continually evolving, stakeholders need up-to-date information to fuel their efforts to increase access.

Why did we create the Special Edition Report?

In order to provide key information updates for prioritized ARVs, I-MAK created ***The Roadmap Special Edition Report on Dolutegravir*** (DTG). This report expands on the information provided in the original ***Roadmap*** to equip stakeholders with current clinical, cost, and patent information to inform decision-making about the best strategies to expand currently limited access to DTG, a second-generation, best in class HIV integrase strand transfer inhibitor that greatly improves upon drugs in its class and is highly suitable for large treatment programs in low- and middle-income countries. Current World Health Organization (WHO) HIV treatment guidelines recommend DTG as alternative first-line treatment.[1] DTG is expected to become the preferred first-line treatment as key data become available from additional clinical trials and real-life use.

What information is included in this report?

- *Clinical Drug Information:* Overview, clinical relevance for resource-limited settings, side effects, knowledge gaps, and status in treatment guidelines.
- *Cost and Access Information:* Timeline of key events related to market access, production costs and potential savings, generic supplier landscape, generic accessible countries, price references, and future developments to watch for.
- *Patent Information:* Detailed patent information including international patent publication numbers and validity analyses focusing on legal requirements for inventive step and/or therapeutic efficacy.
- *Strategies for Access:* Recommended strategies to expand access to DTG.

We appreciate any feedback you have on this report. Please take this survey to let us know how we can make this and future reports more useful to you: https://goo.gl/forms/YmFJ11LvkBh8aeil1.

CLINICAL DRUG INFORMATION

Dolutegravir Clinical Drug Information

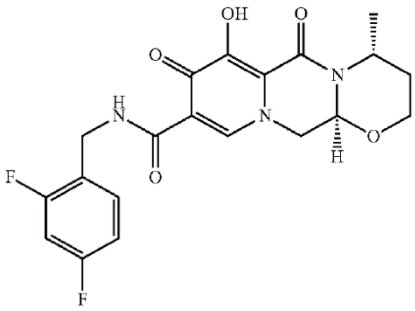
US brand name:
- Tivicay®
- Also sold as Trimeq® in a fixed-dose combination with ABC and 3TC

Proprietor:
- ViiV Healthcare (GlaxoSmithKline/Pfizer/ Shionogi)

Drug class:
- Integrase strand transfer inhibitor

Status:
- US Food and Drug Administration (USFDA) approved for adults and adolescents over 12 years old who weigh more than 40kg in August 2013
- European Medical Association (EMA) Marketing Authorization application approved January 2014
- Aurobindo Pharma Limited (generic) USFDA tentative approval September 2016
- USFDA approved 10mg and 25mg DTG tablets for children ages 6 to less than 12 years old who weigh at least 30kg in June 2016

COMPOUND STRUCTURE



KEY HIGHLIGHTS

- A potent, once-daily pill that can be taken with or without food.[4]
- Improved tolerability and reduced side effects over full-dose (600 mg) EFV.[5] (See *Common Side Effects*)
- A high barrier to resistance, meaning that people can stay virally suppressed on DTG-based treatment for a longer time.[5, 6,7,8]
- Safe and effective for HIV-positive people who are treatment-naive or treatment-experienced.
- There is no cross-resistance between DTG and EFV. This means that DTG will be effective in people with resistance to EFV, and vice versa. These drugs could be used sequentially in first-and second-line HIV treatment regimens in settings with low background prevalence of EFV resistance.
- Daily dose of 50 mg does not require boosting; in the absence of patent barriers, it could be produced at low cost and easily co-formulated.[9]
- A low propensity for drug-drug interactions.

CLINICAL RELEVANCE FOR RESOURCE-LIMITED SETTINGS

There are many practical reasons why DTG is suited for resource-limited settings, which are supported by patient-centered and public health perspectives:

Durability

- People are likely to stay on first-line treatment with DTG longer given its high barrier to resistance. This will result in fewer switches to expensive, less tolerable second-line regimens. This is especially important in countries where treatment options and access to viral load monitoring and resistance testing are limited.
- DTG is more tolerable than normal-dose EFV.[5] Although DTG also causes central nervous system side effects, a study of people who switched from EFV to DTG because of these side effects reported that they had significant improvement in abnormal dreams, dizziness, depression, anxiety and better quality of life.[10]

Affordability

- DTG's low dose (50mg/day) means it could be mass-produced at a low cost while remaining profitable for generics manufacturers.[9] DTG's dose is 12x less than EFV (600mg); when produced at scale, the annual cost for DTG is likely to be significantly lower than that of EFV.
- DTG can be used as the backbone of first-line antiretroviral therapy (ART), especially in settings where resistance to EFV is common. Because there is no cross-resistance between EFV and DTG, these drugs could be used sequentially. Using EFV in second-line ARV regimens could significantly decrease the cost of HIV treatment.

Convenience for people living with HIV and treatment programs

- The low dose of DTG facilitates co-formulation into one pill. Fixed-dose combinations (FDCs) simplify procurement, lower the risk of prescribing, dispensing, and user errors and suboptimal treatment due to drug stock outs.[11]
- DTG can potentially be used in first-line, second-line, and salvage regimens (although current WHO HIV treatment guidelines recommend DTG as an alternative first-line option and for third-line/salvage regimens); using the same ARV for first-line and salvage treatment simplifies procurement.
- DTG can be taken with many other commonly used drugs, including hormonal contraception, methadone and buprenorphine, and antifungals.
- Ongoing studies suggest that DTG may be appropriate for use in maintenance therapy when combined with only one additional ARV, which could reduce side effects and decrease expense of HIV treatment. More research is needed before this approach can be recommended.

DTG IN TREATMENT GUIDELINES

In 2015, the WHO HIV treatment guidelines included new recommendations for DTG, both as an alternative first-line treatment option and as part of third-line treatment.[1] DTG is expected to become a WHO preferred first-line treatment option if safety, effectiveness and dosing during pregnancy, breastfeeding, and in conjunction with rifampicin-based tuberculosis (TB) treatment are confirmed by clinical trials.[12] DTG is – or will soon be – included in national HIV treatment guidelines from Brazil, Botswana, Cambodia, Kenya, Nigeria, Tanzania, and Zimbabwe.[9,13]

COMMON SIDE EFFECTS

DTG is considered to be a safe and tolerable drug. Discontinuation rates from side effects have been low in clinical trials (2%).[14] The most common side effects from DTG-based treatment are headache and insomnia; rash, diarrhea, and nausea were reported in ≤2% of study participants.[4] Serious side effects – severe allergic reaction and liver enzyme elevations, especially in people co-infected with viral hepatitis – have been reported in clinical trials, although these were rare.

Central nervous system side effects from DTG-based treatment include dizziness, insomnia, nervousness, depression, anxiety, mood changes, and rarely, psychosis. Recently, in "real-world" data, poor tolerability of DTG has led to discontinuation rates of 16%, far higher than in clinical trials: these and other side effects led to higher than expected rates of treatment discontinuation, especially in women, people over 60 years of age, and people using ABC (which is co-formulated with DTG and 3TC).[15,16] More research on risk for, frequency, and potential causes of these side effects is needed, especially in populations who were underrepresented in clinical trials.

KNOWLEDGE GAPS AND PROGRESS FILLING THEM

Data is still needed on DTG use during pregnancy, breastfeeding, and rifampicin-based TB treatment. The recent reports of treatment discontinuations from DTG-containing treatment regimens due to intolerance must also be better understood. More information will become available from clinical trials and in countries where DTG is being rolled out as first-line treatment, including:

- Plans for a trial relevant to LMICs are underway; it will compare two DTG-based regimens to the WHO preferred first-line regimen.[17]
- A trial of DTG-based treatment in pregnant women and their infants is planned.
- Ongoing trials are looking at twice-daily DTG (or DTG vs. EFV) during rifampicin-based TB treatment, and safety and efficacy of DTG during treatment for multi-drug resistant TB.

Studies are exploring treatment with DTG and one other drug, mostly in people with acute or early HIV infection, or people on treatment who have an undetectable viral load.[18, 19, 20] Using less drugs in a "drug-sparing strategy" could save millions of dollars, but a substantial amount of evidence on this approach is needed to support changes in treatment guidelines.

Dolutegravir is active against HIV-2, but clinical data are limited and trials are needed in people who are INSTI-naive and INSTI-experienced.

ALERT
Integrase Inhibitors and Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) can occur after starting HIV treatment, usually when the CD4 cell count is low. As the immune system recovers, IRIS can cause a person to become ill from pre-existing infections, such as TB and hepatitis B.

A recent review of real-life data from two European cohorts found that people with a CD4 cell count of <200 cells/mm^3 who started INSTI-based HIV treatment were more than twice as likely to develop IRIS than people starting other ARVs.[21, 22] This might be because INSTIs lower HIV viral load more rapidly than other antiretrovirals.[21, 23] Most clinical trials of INSTIs studied people with higher CD4 cell counts, and were not conducted in places where TB co-infection is common among PLHIV. More information on incidence and management of IRIS is needed, especially in resource-limited settings where TB is prevalent.

COST AND ACCESS INFORMATION

Cost and Access Information

DTG MARKET ACCESS TIMELINE

August 2013	USFDA approves Tivicay® (DTG 50mg)
January 2014	EMA approves Tivicay® (DTG 50mg)
Early 2014	ViiV Healthcare and Aurobindo Pharma Limited sign a licensing agreement that allows Aurobindo to supply DTG 50mg in 92 licensed countries, following completion of required local regulatory approval processes.[24]
April 2014	ViiV grants two voluntary licenses to the Medicines Patent Pool (MPP) for adult and pediatric formulations of DTG.[25] (See *Licensing Agreements*)
November 2015	CHAI, UNITAID, and UNAIDS announce agreement for DTG and DTG/TDF/3TC FDC with supply partner Aurobindo that set a launch price of US$44 per person per year (PPPY) for single-dose DTG, a price that is comparable to EFV.[26]
December 2015	WHO announces inclusion of DTG as a recommended alternative first-line treatment regimen in combination with TDF+FTC (or 3TC).[1]
April 2016	ViiV extends its license to the MPP to cover all lower-middle income countries. (See *Licensing Agreements*)
June 2016	ViiV announces a public tender agreement with the Ministry of Health of Botswana to supply DTG 50mg to the country for first-line treatment as part of its 'Treat All' program. This was the first time that DTG was made available to a national health program in sub-Saharan Africa, and reportedly the largest tender agreement ever secured by ViiV Healthcare in the African sub-continent.[27]
June 2016	USFDA approved 10mg and 25mg DTG tablets for children ages 6 to less than 12 years old who weigh at least 30kg.
September 2016	Aurobindo Pharma Limited is the first generic company to receive tentative approval from the USFDA for its 50mg DTG formulation.
November 2016	The MPP announces that two of its generic manufacturing partners – Mylan and Cipla – were the first to submit their DTG 50mg formulations to the WHO Prequalification of Medicines (PQm) Programme for review and approval.
December 2016	ViiV announces an agreement to supply Tivicay® to Brazil in what is the largest tender agreement to date for Tivicay®. 100,000 PLHIV are expected to receive Tivicay® by the end of 2017 at an agreed price of about US$558 PPPY – reducing the price by 70%. However, this price is still much higher than if Brazil procured generic DTG from either local or international sources.[13, 28]

LICENSING AGREEMENTS

The following license agreements indicate where generic DTG should be accessible:

- ***Bilateral agreement:*** Aurobindo Pharma Limited can produce generic DTG for 92 countries at a launch price of US$44 PPPY.[26]
- ***License agreement with the MPP for Pediatric Formulation:*** A royalty-free voluntary license to the Medicines Patent Pool (MPP) for pediatric formulations of DTG for supply in 121 countries.
- ***License agreement with the MPP for Adult Formulation:*** The agreement originally included all low-income, all least-developed, and all sub-Saharan African countries by MPP generic supply partners. Extending the agreement to all lower-middle income countries in April 2016 added an additional 35 countries, including four countries with patents: Armenia Moldova, Morocco, and Ukraine. In total, the voluntary license covers 92 countries (royalty-free in 82 countries; 10 countries have a tiered royalty structure, see below).[25]

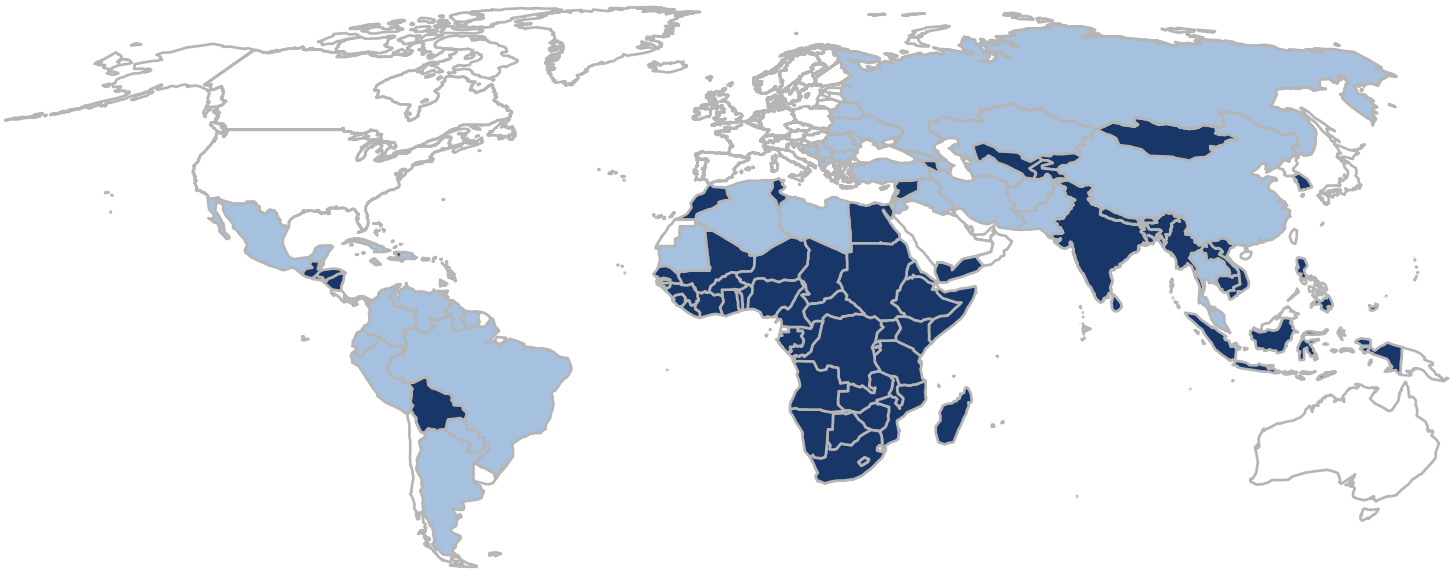
ViiV created a royalty obligation for sales of generic product into the public market for ten specific lower-middle income countries included in its adult formulation license agreement. The royalty rates are tiered (see *Figure 1*) and based on the gross domestic product (GDP) of the specific country, and generic suppliers pay royalties directly to ViiV.

Viiv's inclusion of 92 countries in the licenses is an important step towards bringing lower cost generic DTG to communities who need them. However, 48 upper middle-income countries are excluded from ViiV's MPP license, and **approximately 3.5 million people with HIV are living in upper middle-income countries excluded from the license** (See *Appendix A*). These countries must negotiate directly with ViiV for price and terms by which they can access DTG.

Figure 1: Tiered Royalty Rates in the ViiV-MPP License

Countries	Royalty
Tier 1: Philippines, India, Vietnam, Moldova	5%
Tier 2: Egypt, Indonesia, Morocco, Armenia, Ukraine	7.5%
Tier 3: Turkmenistan	10%

Figure 2: Countries Included and Excluded from ViiV's MPP License



Included in licensing agreements to make generic DTG available

Upper middle-income countries excluded from licensing agreements to make generic DTG available

From Global Price Reporting Mechanism (GPRM) data; accessed 1/23/17

GENERIC SUPPLIER LANDSCAPE

Figure 3 summarizes the current landscape of generic suppliers of DTG. As of September 2016, DTG has been sub-licensed to nine companies: Cipla, Desano, Emcure, Hetero Labs, Laurus Labs, Lupin, Micro Labs, Mylan, and Strides;[25] Aurobindo has a separate licensing agreement.

Aurobindo is the only generic supplier of single-dose DTG that has achieved approval from a stringent regulatory authority (USFDA) that allows them to sell into the public markets funded by international donors. Three companies have submitted for WHO PQm for single-dose DTG and are currently under assessment; an unknown supplier has also submitted for approval of the TDF+3TC+DTG fixed-dose combination.[29] Drug Master Files (DMFs) filed with the USFDA also indicate a readiness to participate in the DTG market; 11 companies have submitted DMFs for DTG and are ready to manufacture an active pharmaceutical ingredient (API) under good manufacturing practice with a validated process, meeting all requirements for inclusion in a marketing application for a finished product.

In sum, there is no shortage of eligible generic suppliers to produce DTG once regulatory approvals have been met. Given the timeline of prequalification, it is anticipated that additional generic suppliers could be approved by WHO during 2017 or early 2018.

Figure 3: Generic Supplier Landscape

Level	Companies	Notes
Level 1 *Has met regulatory requirements and is active in the marketplace*	• **Aurobindo** (tentative approval September 2016)	The first and currently only supplier to have gained product approval from a stringent regulatory authority (USFDA) and is eligible to supply product to public markets.[24]
Level 2 *Has submitted application for final formulation*	• **Cipla** (Submitted November 2016) • **Mylan** (Submitted November 2016) • **Undisclosed** supplier(s)	Three suppliers (Cipla[a] and Mylan in Nov 2016[30], and an undisclosed supplier) have submitted to WHO PQm for approval of single-dose 50mg, and one for the TDF+3TC+DTG fixed-dose formulation (undisclosed);[29] none have received approval. The undisclosed supplier(s) are very likely one (or two) of the nine MPP sub-licensees.
Level 3 *Has submitted documentation for manufacturing API*	• **Aurobindo** (Submitted October 2014) • **Mylan** (Submitted November 2015; December 2016) • **Shanghai Desano** (Submitted February 2016) • **Cipla** (Submitted March 2016; February 2017) • **Hetero** (Submitted May 2016) • **Larus** Labs (Submitted September 2016) • **LEK** (Submitted December 2016) • **MSN** (Submitted December 2016) • **Micro Labs** (Submitted January 2017) • **Macleods** (Submitted January 2017) • **Lupin** (Submitted 2017)	Eleven companies have submitted DMFs for DTG to the USFDA.[31] All 11 DMFs are "active", meaning that the DMF was found acceptable for filing administratively, and all are Type II: Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product.

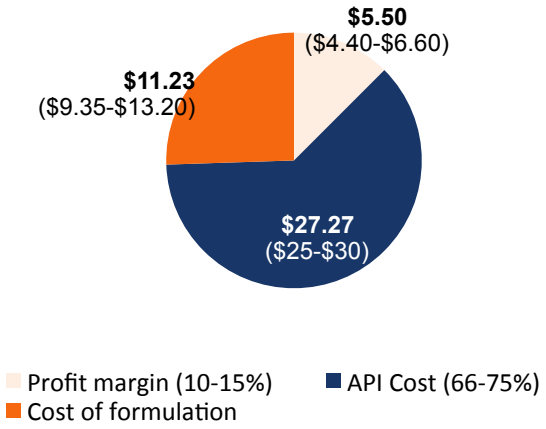
[a] Cipla's one sale of DTG to Belarus in 2016(see *Figure 7*) may indicate that the company has received WHO prequalification approval already for its generic version, however this cannot be substantiated at the time of this report.

CURRENT GENERIC PRICE & ESTIMATED PRODUCTION COSTS

At this time, and with the lack of import-export data and low volume demand, the best means of estimating the current API production price of DTG API is by projecting backwards from the finished product pricing (e.g. Aurobindo's launch price of US$44). Broadly, the total costs of generic DTG are driven by two variables (see *Figure 4*):

- The profit margin, which are generally 10 to 15% for a generics supplier of a new HIV product. Applying this generalized percentage to Aurobindo's launch price of US$44 PPPY, we estimate profit margins for DTG range from US$4.40 to US$6.60 of the generic price.
- The cost of the API, which constitutes approximately two-thirds to three-quarters of the final generic formulation price.[32] Therefore, we estimate API costs of DTG using Aurobindo's generic launch price range from US$25 to US$30.

Figure 4: Average Drug Component Costs for DTG

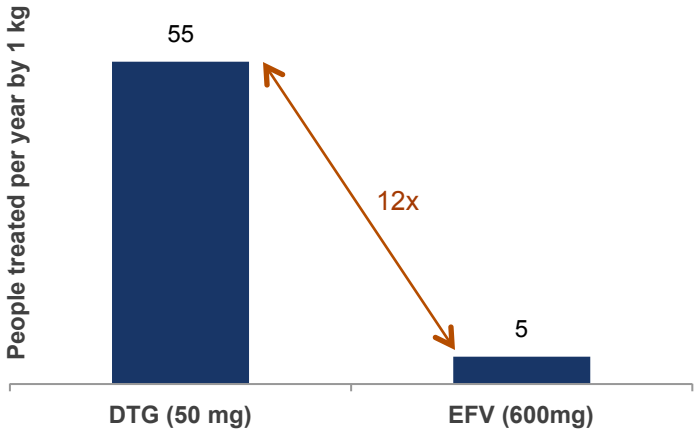


The corresponding range of API costs for DTG per kilogram given 10 to 15% profit margins is estimated to be approximately US$1,353 to US$1,627. APIs constitute the bulk of a drug's price and are done at volume in tonnage. Therefore decreases in API cost ultimately can make the final cost of a drug significantly lower, as discussed in the next section.

DTG's low-dosage means more patients can be treated with the same amount of API.

For example, 12 times as many PLHIV can be treated with DTG than with the same amount of EFV (see *Figure 5*). While the low-dosage feature of DTG is advantageous from a production standpoint (small amounts of drug can treat large number of PLHIV), it also means that in order to realize optimal API cost, there needs to be a comparatively large scale-up of PLHIV treated.

Figure 5: Number of patients treated by 1 kilogram of DTG vs. EFV



POTENTIAL PRICE OF DTG

Experts in chemical drug synthesis have estimated that it is possible to reduce the cost of DTG API from its current 'low-volume' level to about US$800/kg. It is estimated that this would require volumes to treat over one million people, which is likely to happen as early as 2018 as more countries adopt the 2015 WHO guidelines and DTG replaces EFV.[9] Additionally, if more countries included DTG in their clinical guidelines, volume-driven cost decreases in DTG might not occur sooner, but might result in more substantial API price reductions.

Figure 6 summarizes the potential cost savings that could be realized with reaching production volumes of DTG for one million PLHIV. In sum, about 18,000 kilograms of API would need to be produced, likely split amongst three to five suppliers. **The final DTG price (with profit margins) could likely be about US$28 PPPY, about a 35% reduction from Aurobindo's launch price of generic DTG 50mg.**

Figure 6: Targeting a 50% decrease in API costs

Total target patients on DTG	**1,000,000**
Corresponding API needed (kilograms)	**18,250**
Average volume (kg) produced by each supplier	
3 suppliers in the market	6,083
4 suppliers in the market	4,563
5 suppliers in the market	3,650
Current formulation cost (85-90% of current US$44 generic reference price)	US$37.40 – US$39.60
Current API cost component (66-75% of formulation)	US$25.00 – US$30.00
Maximum potential reduction in API cost (50%)	US$12.50 – US$14.85
Target formulation costs	US$27.50 – US$29.50
Total % decrease in formulation cost	33 – 38%

Truly optimal pricing of APIs used for ART has only come historically when LMIC demand reached several hundred tonnes/year. This volume demand may never be realized with DTG, as treating every person living with HIV with DTG – 37 million people[33] – would only require about 690 tonnes of API/year. This is a third of the current annual volume demand for EFV, which is about 2,000 tonnes/year for the 10 to 11 million people estimated to be on treatment in 2016.[9]

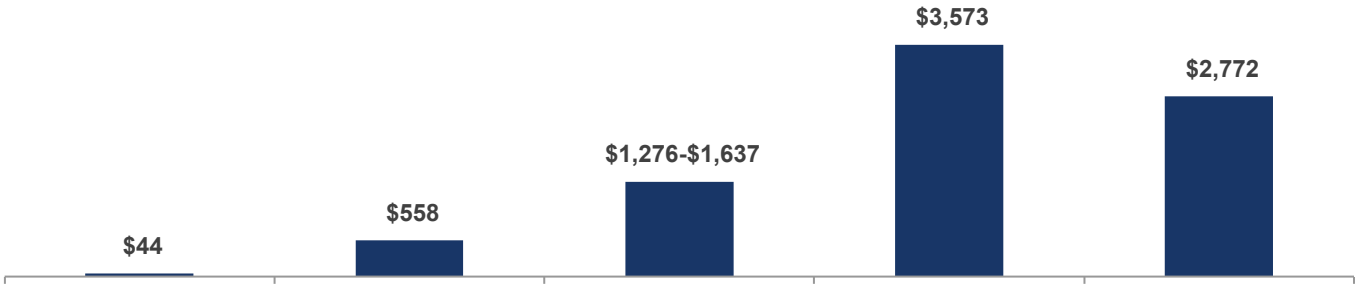
Fixed Dose Combinations

DTG-based FDCs could be affordable in countries where patents have expired or have not been granted or filed, or where voluntary licenses permit this. A generic, fixed-dose combination of DTG/3TC/TAF (a less toxic, lower-dose formulation of tenofovir)[34] could be produced for US$60 PPPY;[35] an FDC containing DTG/TAF/FTC could be available for US$85 PPPY, by 2018/2019. Generics manufacturers are working to obtain FDA approval for a one-pill, once-daily FDC of TDF/3TC/DTG in 2017.[17]

PRICE REFERENCES

Given that generic DTG was only recently approved for public market purchasers and very few countries have adopted DTG into their formal treatment guidelines, there is limited information available on the prices that have been paid for DTG. To date no countries have received the Aurobindo launch price of US$44. In UMICs excluded from the license, the price of DTG is remains high – US$1,200 to US$3,500 PPPY. Purchase volumes are small and therefore, only a small proportion of PLHIV are being treated.

Figure 7: Dolutegravir Reference Prices (PPPY for 50mg)



92 countries in bilateral license

Launch price agreed by Aurobindo in November 2015.

NOTE: It is not clear if the Aurobindo ceiling price is contingent upon minimum patient volumes, and could be higher for initial product introductions.[26]

Brazil

Price negotiated by ViiV and Brazil's Ministry of Health for supply of branded DTG to 100,000 patients in 2017.[13]

Belarus

From two sales to Belarus: 2015 (GSK) for 16 patients at US$1276 and 2016 (Cipla) for 17 patients at US$1637.[36]

Argentina

From one purchase in Aug. 2016 between GSK SA and the National Ministry of Health for 582 patients.[37]

Ukraine

From one purchase between GSK and the Institute of Epidemiology and Infectious Diseases by Gromashevskiy for 6 patients of DTG in December 2016.[38]

WHAT TO WATCH FOR

1) The Botswana tender: This is the first public market tender of DTG in sub-Saharan Africa and for significant volumes. Watch for the final price to be at/below the US$44 reference price established by Aurobindo, particularly because it may just be Aurobindo and perhaps ViiV – via an API supply agreement from Desano – competing for the tender.

2) Further price reductions as additional generics receive regulatory approval: The approval by WHO PQm of the four pending submissions for DTG (3 single-dose and one fixed-dose), expected by the end of 2017, will introduce the first generic competition to Aurobindo. Expect prices in public market tenders to drop below the US$44 reference price once competition begins. How quickly and how much lower will be the key things to watch for.

3) Other countries adopting DTG into national first-line treatment guidelines: Following WHO officially including DTG as an alternative first-line ART treatment regimen (in combination with TDF+FTC or 3TC), Botswana[39] and Brazil[40] were among the first to incorporate DTG into their own national treatment guidelines in December 2015. Watch for other countries to follow suit, thereby expanding DTG beyond the early-adopter countries and continuing toward the goal of one million people treated per year that will significantly reduce the costs of DTG.

4) Negotiations between ViiV and other upper-middle income countries: ViiV's access policy for upper-middle income countries (those that are generic-inaccessible markets) is to continue with direct bilateral negotiations with government officials. The deal with Brazil for US$558 PPPY for 100,000[13,27] PLHIV is one known point of reference. Other bilateral negotiations should be monitored for their outcomes.

5) Fixed-dose combinations of DTG being developed: Generic suppliers have the right (through the MPP or bilateral agreements with ViiV) to develop fixed-dose combinations that contain DTG. The first of these is the alternative first-line regimen recommended by WHO: TDF+(FTC or 3TC)+DTG. Aurobindo is working towards submitting a one-pill, once-a-day TDF+3TC+DTG combination with the FDA that could be available later this year or early-2018. While Aurobindo is near certain to be the first supplier to submit this DTG combination, look for others to follow.

An interesting long-term development is the combination of DTG+RIL as effective first-line ART. ViiV has initiated trials of DTG+RIL. The daily dose of DTG+RIL would be only 75 mg/day (50 mg DTG and 25 mg RIL). The potential pricing of this combination would potentially be below US$50 PPPY if used at large scale for treating several million PLHIV.

PATENT INFORMATION

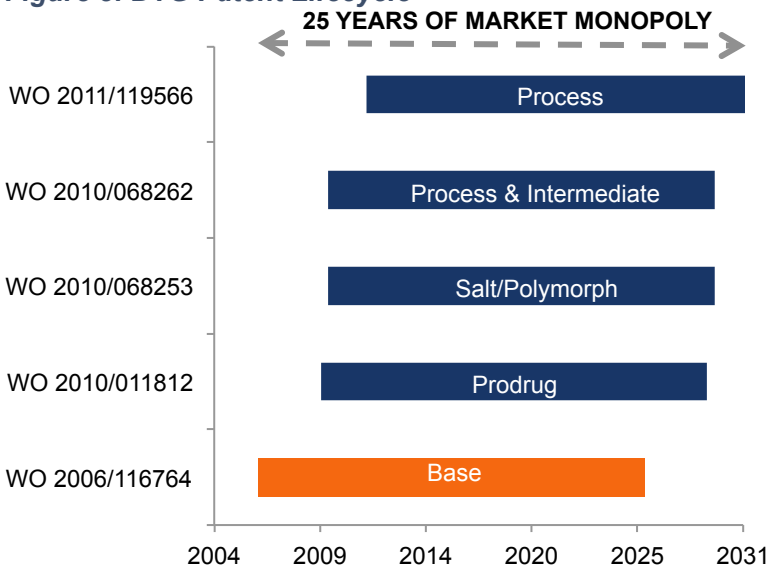
Patent Information

DTG PATENT LIFECYCLE

DTG has five key International Patent Publication Numbers (WO), which, if granted, would provide ViiV with a market monopoly from 2006 to 2031, **a duration of 25 years**. There is one patent on the main base compound that expires in 2026, and four secondary patents that could be used to extend the patent life of DTG to 2031.

Chemical name for DTG
(4R, 9aS)-5-hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a, 10-hexahydro-2H-1-oxa-4a,8a-diaza-antracene-7-carboxylic acid 2,4-difluoro-benzylamide.

Figure 8: DTG Patent Lifecycle



METHODOLOGY FOR ASSESSING PATENT STRENGTH

The strength of a drug's patents can help inform the strategies that are pursued to provide access. For example, compulsory licensing may be the better strategy for drugs with strong underlying patents in countries, which are typically excluded from voluntary licenses. Patent oppositions would be more appropriate for drugs with weak and medium strength patents.

In order to assess patent strength, our team of lawyers and scientists analyzed each of the patents from the patent landscape for DTG and the available prior art. We determined through this process that patents on DTG fell into one of three basic categories:

- ***Weak***: Considerable prior art, common knowledge, and/or data to challenge the patent for lack of inventive step and/or on the grounds of lacking efficacy
- ***Medium/Questionable***: Prior art and data raise questions on inventiveness and/or efficacy, but further analysis of comparative data is required
- ***Strong***: Little or no prior art suggesting the patent falls into the above categories.

In this report, the strength of a patent is based on whether a drug product meets legal requirements for inventiveness and/or therapeutic efficacy.

Inventiveness: In determining whether a drug is inventive by legal standards, we have adopted the standard approach of whether the invention claimed in a patent application would have been obvious to a person skilled in the field given the prior art available. Included in this assessment are practices that would be considered common general knowledge to a person in the art.

Efficacy: Here we employ the legal standard of the Indian Supreme Court, as set out in its April 2013 decision in Novartis AG vs. Union of India & Others. We also focus on India because it is the home to the leading generic ARV producers.

PATENT QUALITY ASSESSMENT SUMMARY

Based on further prior art searches since the original publication, we **revised DTG's base patent strength from strong to medium, with scope to challenge**. At the time of writing The Roadmap, it appeared that the structure of DTG appeared to differ from earlier integrase inhibitors, suggesting inventiveness and efficacy, necessitating further evaluation. Our research for this report found HIV integrase inhibitor compounds that are structurally close to the base compound for DTG exist in the prior art. As a result, the prior art identified suggests that there are grounds for arguing that base compound of DTG is not inventive and does not meet the efficacy test.

We assess DTG's secondary patents to all be of weak strength. A key secondary patent application for DTG relates to its prodrug. Substantial prior art exists on prodrug techniques, and as such this application appears to lack inventive step. With respect to efficacy, there is no data in the patent application to suggest that the prodrug improves oral delivery or the therapeutic efficacy of DTG.

Other relevant secondary patents identified in the landscape relate to processes, intermediate compounds, salt and polymorphic forms of DTG. There is a significant amount of prior art available to suggest all these patents lack inventive step. In the case of the patent covering the salt and polymorphic forms of DTG, it does not appear to meet efficacy standard.

Main Compound Patent: WO 2006/116764
Shionogi & Co Ltd

PATENT QUALITY: MEDIUM/ QUESTIONABLE

Is it inventive?

- This application discloses the compound DTG as Example Y-3 on page 116. DTG is specifically claimed in claim 32 on page 267.
- WO 2006/116764 was filed on 28 April 2006. This application claims priority from two earlier applications dated 28 April 2005 and 27 October 2005. A review of the priority applications shows that DTG is not disclosed. Accordingly, the priority rights for this application are not validly claimed and the effective date of the application should be 28 April 2006.
- A review of the prior art shows that HIV integrase inhibitor compounds that are structurally close to DTG already existed. Compounds 377 and 378 of US Publication No. 20050054645 (or EP1544199) disclose a nitrogen-containing fused ring compound having the same diketo acid moiety as DTG. Compounds 270 to 273 of WO 2005/118593 also disclose bicyclic compounds and a diketo acid moiety as found in DTG.
- Given that there is no data provided in the application for DTG that shows any advantage over these prior art compounds, it can be argued that it is only an alternative HIV integrase inhibitor with no inventiveness.
- In the event that the slight structural difference between DTG and the compounds disclosed in US Publication 20050054645 or WO 2005/118593 is considered inventive, it is possible to counter this view by adopting a combination of prior art.
- Suggested prior art combinations that show the slight structural differences in DTG would be obvious in light of US Publication No. 20050054645 in combination with either EP1297834 or US Patent Publication No. 2006079517. Alternatively, WO 2005/118593 in combination with US Publication No. 20050054645 can be used to show the obvious nature of the compound DTG.

Is there efficacy?

The application for DTG fails to provide comparative efficacy data with the known compounds disclosed in US Publication 20050054645 or WO 2005/118593. As DTG should be considered a derivative of these earlier compounds, data showing therapeutic efficacy over these existing forms would be required in order for it to be considered an invention. At the time of filing the application, this data has not been provided and accordingly the requirement for therapeutic efficacy is not met.

Prodrug Patent: WO 2010/011812 **PATENT QUALITY:** WEAK

SmithKline Beecham Corporation

Is it inventive?

- This application claims ester prodrugs, tautomeric forms (e.g. enantiomers and isomers), and salts of DTG. The esters are formed via the hydroxyl group on the tricyclic ring.
- A series of potential esters are disclosed. It is not known whether any of the prodrugs claimed in this application are clinically relevant at this stage. There is the possibility that one of these prodrugs may be used as part of a 3 month prophylaxis treatment for high-risk persons or be used for switching to a different product as the base patent comes closer to expiry.
- Prodrugs have been widely used in the ARV field for a number of other compounds including TDF where disoproxil esters (TD) and phosphoramidate (TAF) have been used. The advantages offered by prodrugs are well known and this would appear to be an obvious approach for delivery of any new antiretroviral compound.
- Various prior art exists that could be used to challenge the inventiveness of this application, including US Publication No. 20050054645, WO 2006116764, US Publication No. 2007072831, and US Publication No. 20060116356.
- Similarly, obtaining tautomeric forms and salts of a compound is common general knowledge for which substantial prior art exists.

Is there efficacy?

The prodrug claimed in this application would be considered a new form of the known substance DTG (see WO 06/116764 above).

As filed, the data provided in the application indicates that the prodrug leads to high plasma levels of DTG as compared to the base compound. The data also shows that the concentration of the prodrug is less than 24 ng/ml, indicating cleavage of the prodrug in an efficient manner. As none of this pharmacokinetic data meets the requirements of the therapeutic efficacy test, the patent should not be considered an invention.

Process & Intermediate Patent: WO 2010/068262 **PATENT QUALITY:** WEAK
Glaxosmithkline LLC

Is it inventive?

- This application claims a process for intermediate compounds. The particular process claimed is to create aldehyde methylene, or hydrated or hemiacetal methylene attached to a heteroatom of a 6 membered ring without going through an olefinic group and without the necessity of using an osmium reagent.
- WO 2006/11674, US Patent No. 5688815, US Patent No. 7211572, CA 2379370, and EP0768302 are all relevant prior art for showing that the process claimed in this application would have been obvious and, therefore, not inventive.

Is there efficacy?

The efficacy test is not applicable to patent applications that claim a process.

Salt/Polymorph Patent: WO 2010/068253 **PATENT QUALITY:** WEAK
Shionogi & Co Ltd/Glaxosmithkline LLC

Is it inventive?

This application is directed at 3 different inventions.

- Claims 1 and 2 are directed to an alternative synthetic process for making DTG. The prior disclosures in WO 2006/116764, US Patent No. 6919351, and WO 2006/066414 makes the process claims of this application obvious and not inventive.
- Claim 11 of the application is an independent claim that relates to a brominated intermediate compound that does not appear to have any relevance to DTG. Accordingly this report does not provide an analysis of whether the claim is inventive.
- Claims 14 to 29 cover salt forms of DTG, in particular a sodium salt and its crystalline forms. There is a substantial amount of prior art that can be relied upon to show that obtaining a salt and polymorphic form of a compound is routine and not inventive. Relevant prior art to challenge these claims would include WO 2006/116764, Berge et al, Pharmaceutical Salts (1977) and Gould PJ, Salt Selection for Basic Drugs (1986).

Is there efficacy?

The claims of this application directed to the salts and polymorphic forms do not show any enhancement in the therapeutic efficacy of the compound DTG. As a result, these claims of the application would not be considered inventions under the efficacy test.

Process Patent: WO 2011/119566 **PATENT QUALITY:** WEAK
Glaxosmithkline LLC

Is it inventive?

This application relates to alternative synthetic routes for manufacturing DTG and its intermediates.

The process claimed in this application would be considered obvious and not inventive in light of the disclosures made in WO 2006/116764, US Publication No. 20060019996, US Patent No. 4524149, and WO 2010011819.

Is there efficacy?

The efficacy test is not applicable to patent applications that claim a process.

STRATEGIES FOR ACCESS

Strategies for Access

Since DTG appeared to be a stronger patent and is a priority drug, since the publication of ***The Roadmap*** advocates have spent over three years working to ensure that ViiV created an inclusive access program and/or licensing geographical scope, that have the broadest possible reach across LMICs.

However, further work needs to be done to increase access to DTG, especially since upper middle-income countries continue to be unable to negotiate access through licensing agreements. We therefore recommend a shift in strategy; the following recommendations are not mutually exclusive and can be planned together:

- ***Consider challenging the base patent*** – the primary obstacle to generic entry – based on the revised evidence available since The Roadmap was released. Further prior art research has determined that it is medium strength, and therefore has scope to challenge. Prospects of success would depend on local standards of patentability.
- ***Challenge the secondary patents*** to remove the additional five years of market monopoly and open the generic market by 2026. The secondary patents are particularly weak and are universally challengeable as determined by this assessment.
- ***Coordinate a global effort on compulsory licenses***, especially in countries where patent barriers are unlikely to be removed because of lower patentability standards.
- ***Continue to push ViiV to be included in licensing agreements***, emphasizing the need for affordable, generic-accessible DTG. Advocates should also prioritize equipping themselves on equitable royalty structures in advance of negotiations.
- ***Dialogue with governments to introduce and prioritize DTG*** using the clinical, cost, and patent information found in this report.

ANNEX A

Annex A

Countries Included and Excluded from ViiV's MPP License

Excluded Countries

COUNTRY	PLHIV
Albania	
Algeria	8,800
America Samoa	
Argentina	110,000
Azerbaijan	11,000
Belarus	35,000
Belize	3,600
Bosnia and Herzegovina	
Brazil	830,000
Bulgaria	
China	850,000
Colombia	150,000
Costa Rica	10,000
Cuba	22,000
Dominica	
Dominican Republic	68,000
Ecuador	29,000
Fiji	700
Georgia	9,600
Grenada	
Guyana	7,800
Iran (Islamic Republic of)	73,000
Iraq	
Jamaica	29,000
Jordan	
Kazakhstan	23,000
Lebanon	2,400
Libya	
Macedonia	200
Malaysia	92,000
Maldives	100
Marshall Islands	
Mexico	200,000
Montenegro	
Palau	
Panama	17,000
Paraguay	17,000
Peru	66,000
Romania	16,200
Russian Federation	
Serbia	3,000
St Lucia	
St Vincent and the Grenadines	
Suriname	3,800
Thailand	440,000
Turkey	
Turkmenistan	
Venezuela (Bolivarian Republic of)	110,000
TOTAL	**3,238,200**

UNAIDS 2015 data[41] used where available; CIA World Fact Book[42] was used as a second source.

Included Countries

COUNTRY	PLHIV
Afghanistan	6,900
Angola	320,000
Armenia	3,600
Bangladesh	9,600
Benin	69,000
Bhutan	600
Bolivia (Plurinational State of)	18,000
Botswana	350,000
Burkina Faso	95,000
Burundi	77,000
Cambodia	74,000
Cameroon	620,000
Cape Verde	3,200
Central African Republic	120,000
Chad	170,000
Comoros	
Congo	446,600
Democratic Republic of the Congo	370,000
Djibouti	9,400
Egypt	11,000
El Salvador	20,000
Equatorial Guinea	
Eritrea	14,000
Ethiopia	
Federal States of Micronesia	
Gabon	47,000
Gambia	21,000
Ghana	270,000
Guatemala	55,000
Guinea-Bissau	
Guinea	120,000
Haiti	130,000
Honduras	20,000
India	2,100,000
Indonesia	690,000
Côte d'Ivoire	460,000
Kenya	1,500,000
Kiribati	
Kosovo	
Kyrgyz Republic	8,100
Lao People's Democratic Republic	11,100
Lesotho	310,000
Liberia	30,000
Madagascar	48,000
Malawi	980,000
Mali	120,000
Mauritania	14,000
Mauritius	8,200
Moldova	18,000
Mongolia	<500
Morocco	24,000
Mozambique	1,500,000
Myanmar	220,000
Namibia	210,000
Nepal	39,000
Nicaragua	9,900
Niger	49,000
Nigeria	3,228,600
North Korea (Democratic People's Republic of Korea)	
Pakistan	100,000
Papua New Guinea	40,000
Philippines	42,000
Rwanda	200,000
Samoa	
Sao Tome and Principe	1,000
Senegal	46,000
Seychelles	
Sierra Leone	51,000
Solomon Islands	
Somalia	30,000
South Africa	7,000,000
South Sudan	180,000
Sri Lanka	4,200
Sudan	56,000
Swaziland	220,000
Syria Arab Republic	900
Tajikistan	16,000
Timor-Leste	
Togo	110,000
Tonga	
Tunisia	2,600
Tuvalu	
Uganda	1,500,000
Ukraine	220,000
United Republic of Tanzania	1,400,000
Uzbekistan	33,000
Vanuatu	
Viet Nam	260,000
West Bank and Gaza	
Yemen	9,200
Zambia	1,200,000
Zimbabwe	1,400,000
TOTAL	**29,170,700**

UNAIDS 2015 data[41] used where available; CIA World Fact Book[42] was used as a second source.

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