Dr Andrew Hill

University of Liverpool

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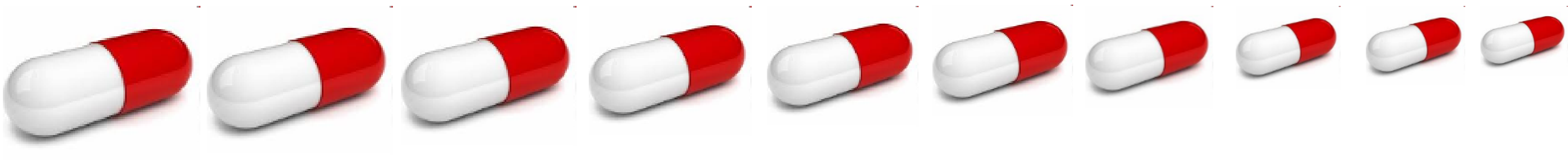
Speaker Name	**Statement**
Dr Andrew Hill	Andrew Hill has received consultancy payments from Gilead, Bristol-Myers Squibb, Janssen and ViiV, not connected with this project.
Date	**April 2015**

Generics – the facts

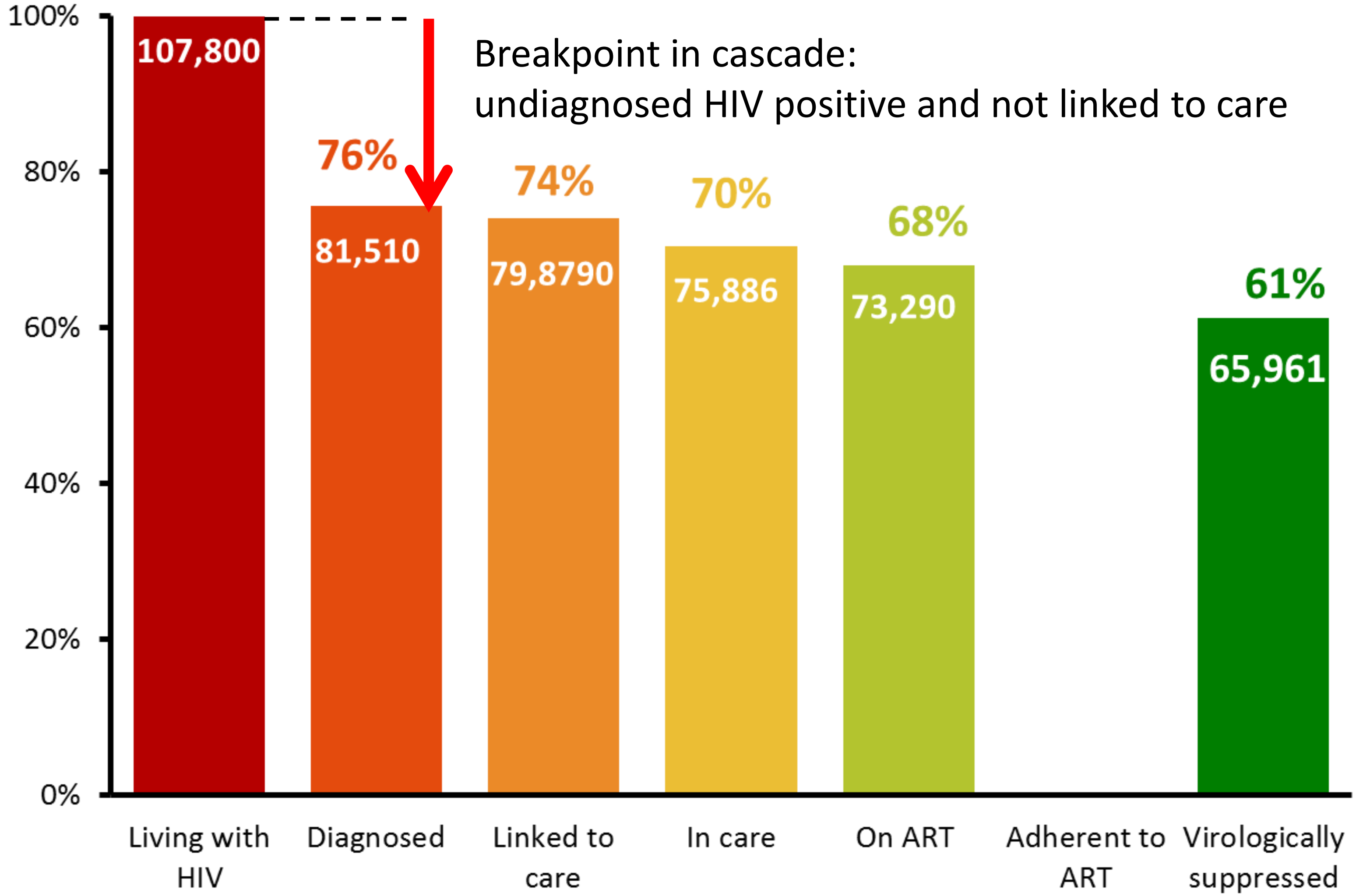


Andrew Hill

St Stephens AIDS Trust, Chelsea and Westminster Hospital, London, UK

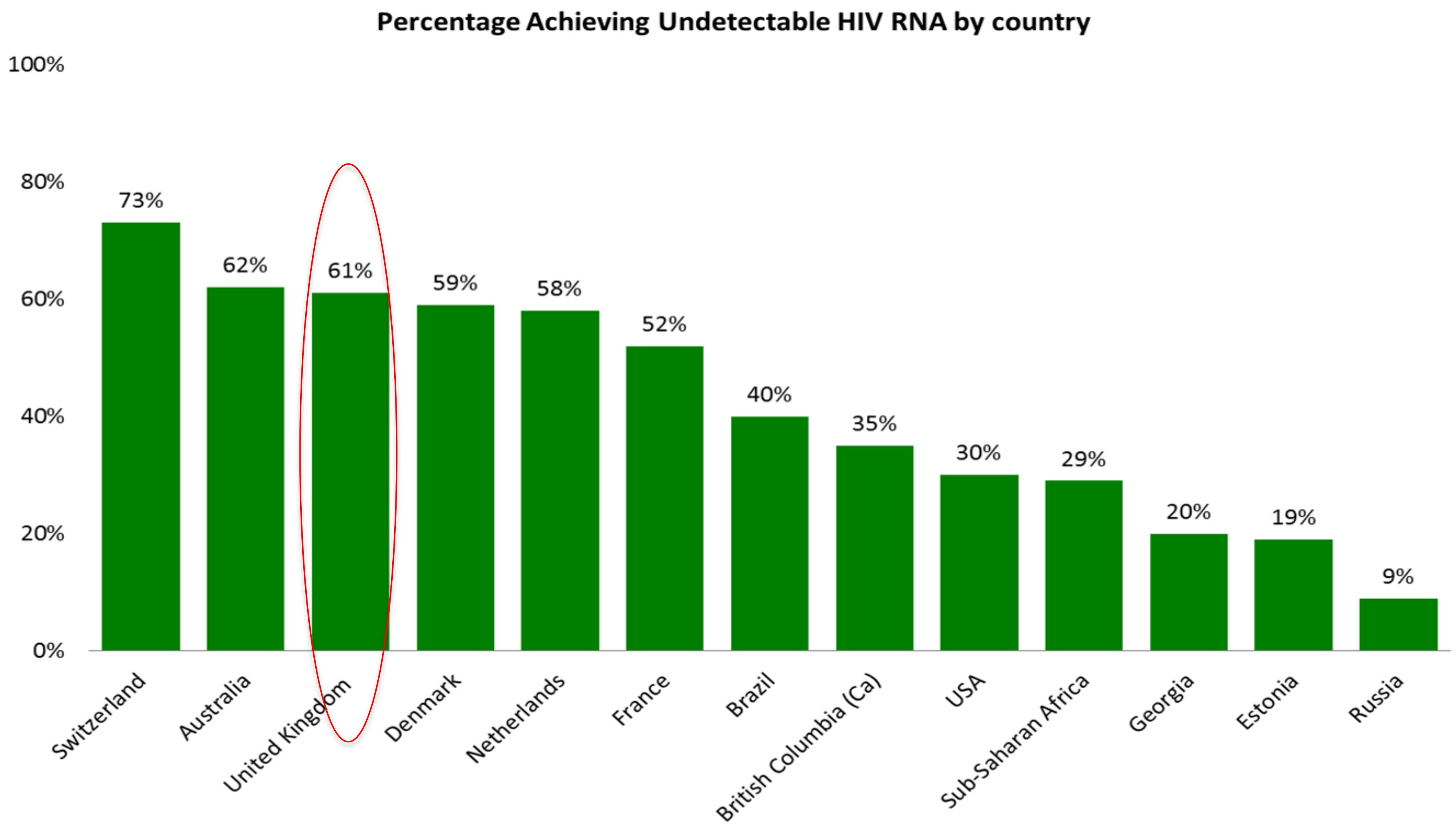
BHIVA Conference, Brighton, UK, 22nd April 2015

Cascade of HIV care – United Kingdom



Reference: Public Health England. *HIV in the United Kingdom: 2013 Report. London: Public Health England.* ; 2013.
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/377194/2014_PHE_HIV_annual_report_19_11_2014.pdf

How does the UK compare to other countries?



The costs of HIV treatment in the UK

Every year, the number of people on treatment in the UK rises by 7-10%

Over 100,000 people could be on antiretroviral treatment by 2019

Efforts to find and treat 20-25% undiagnosed patients will increase costs

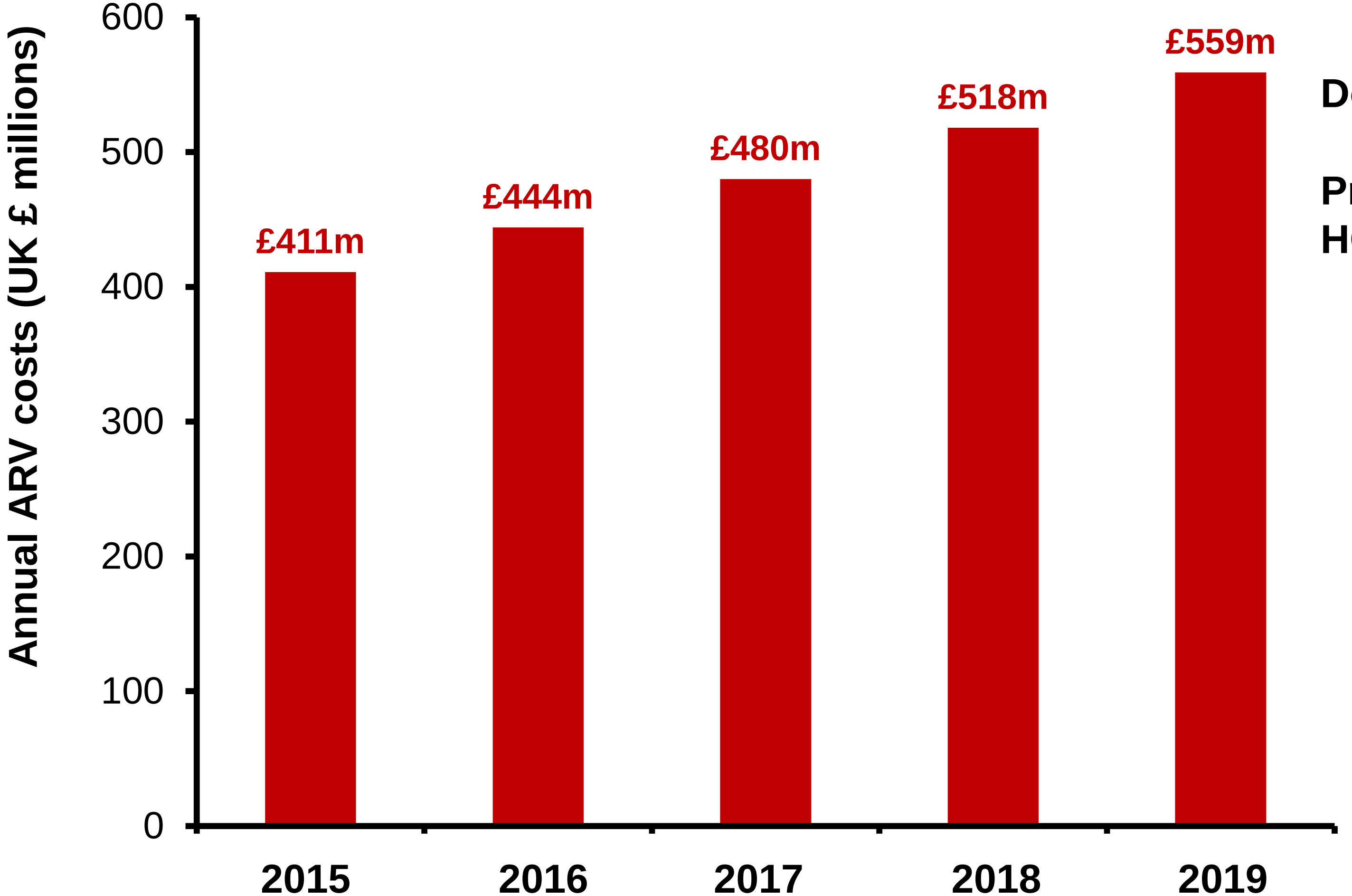
Additional funds needed to cover Pre-Exposure Prophylaxis and HCV treatment

New guidelines for early treatment or even “test and treat” will further increase costs.

There is increasing pressure on the NHS to lower costs.

Projected UK ARV costs, if branded drugs used (8% growth/year)

N on ARVs: 78,000 | 84,000 | 91,000 | 98,000 | 106,000



Does not include:

PreP
HCV treatment

Total NHS spending on medicines, 2014

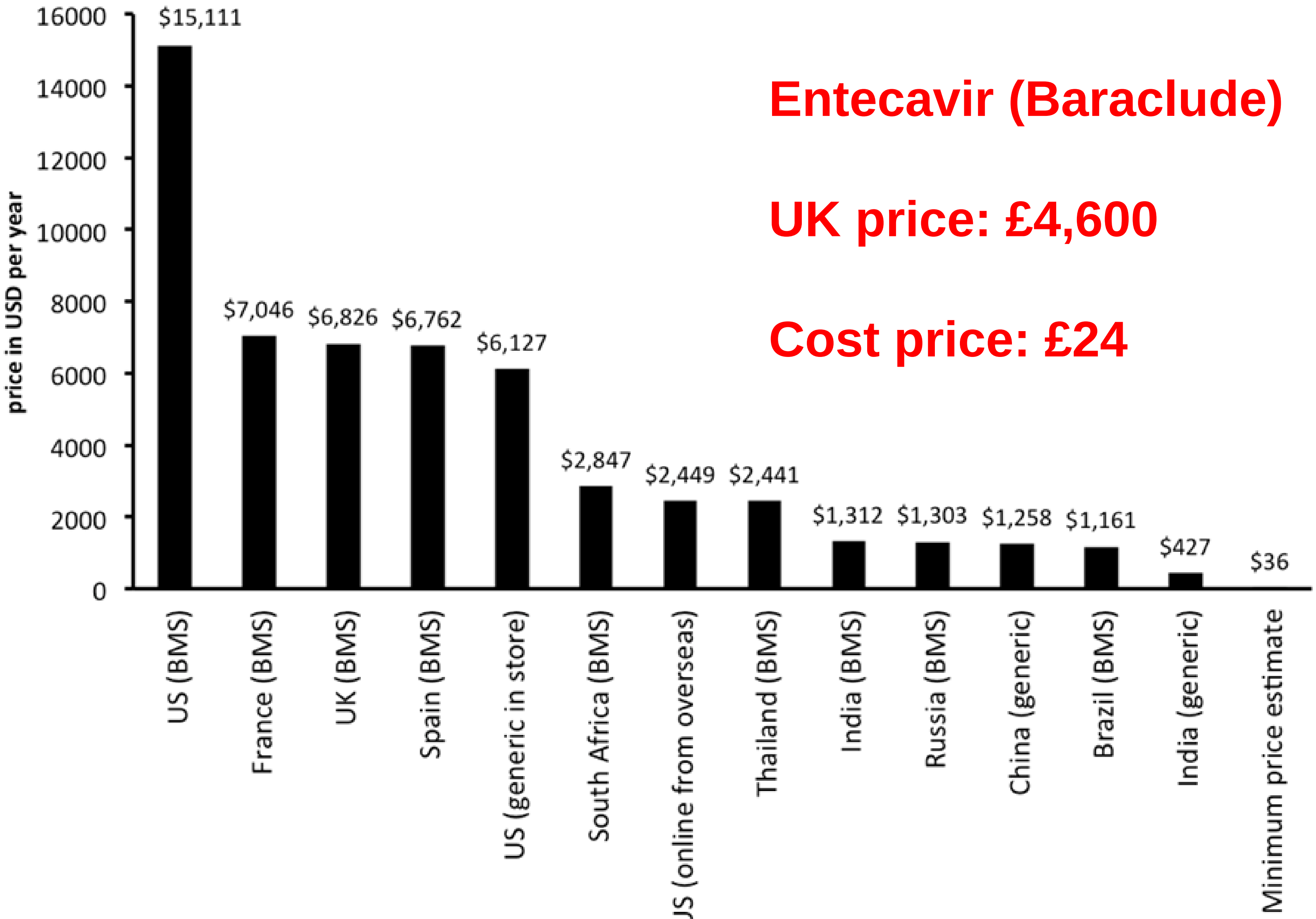
£14.4 billion

Rise of 7.6% on 2013, above inflation

http://www.pharmaceutical-journal.com/news-and-analysis/news/nhs-expenditure-on-prescribed-medicines-up-by-76-with-151-increase-in-hospital-sector/20067182.article#fn_1


Entecavir for Hepatitis B
one year’s supply (0.18g)

Entecavir for Hepatitis B
cost per person/year by country

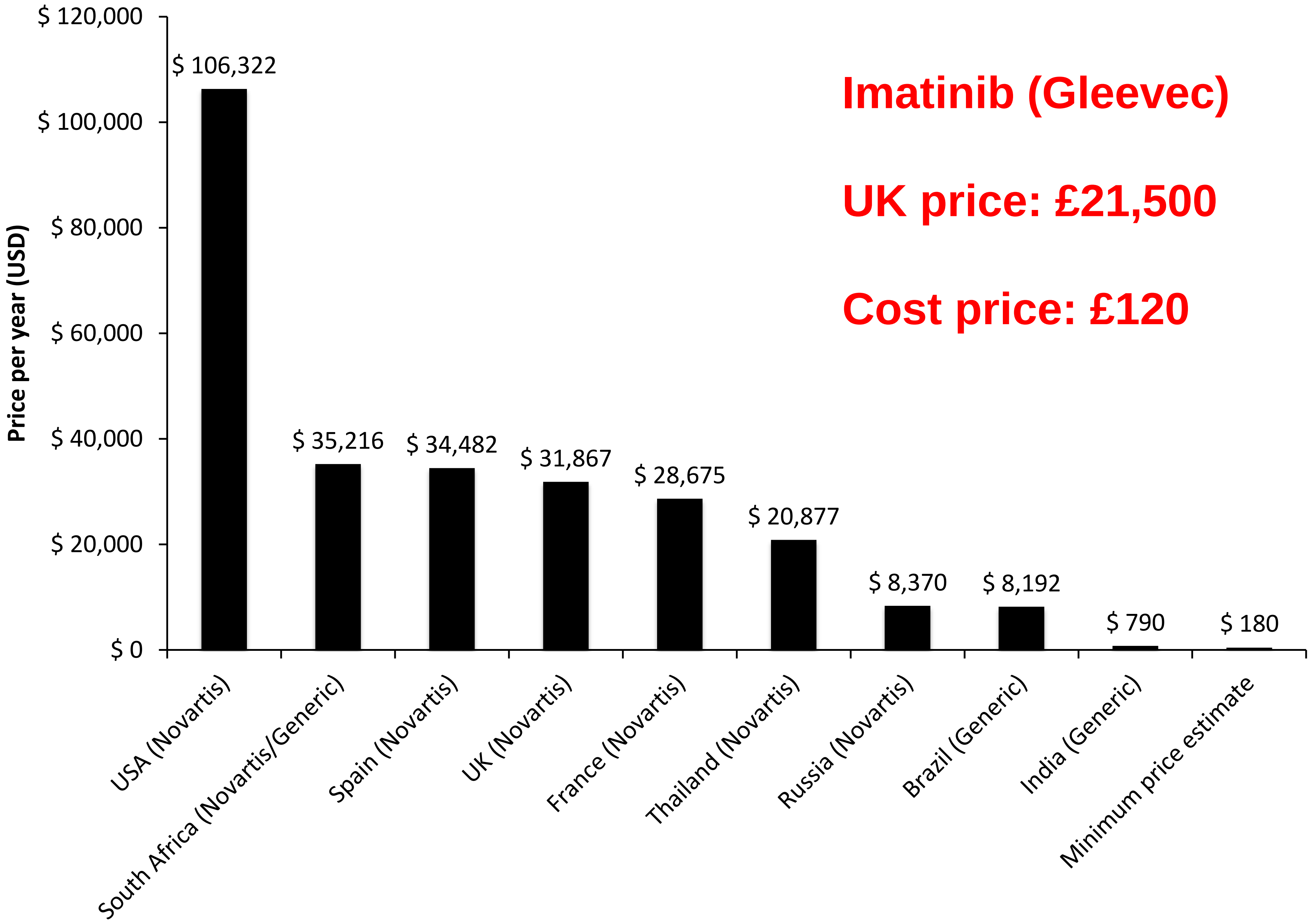


Entecavir (Baraclude)

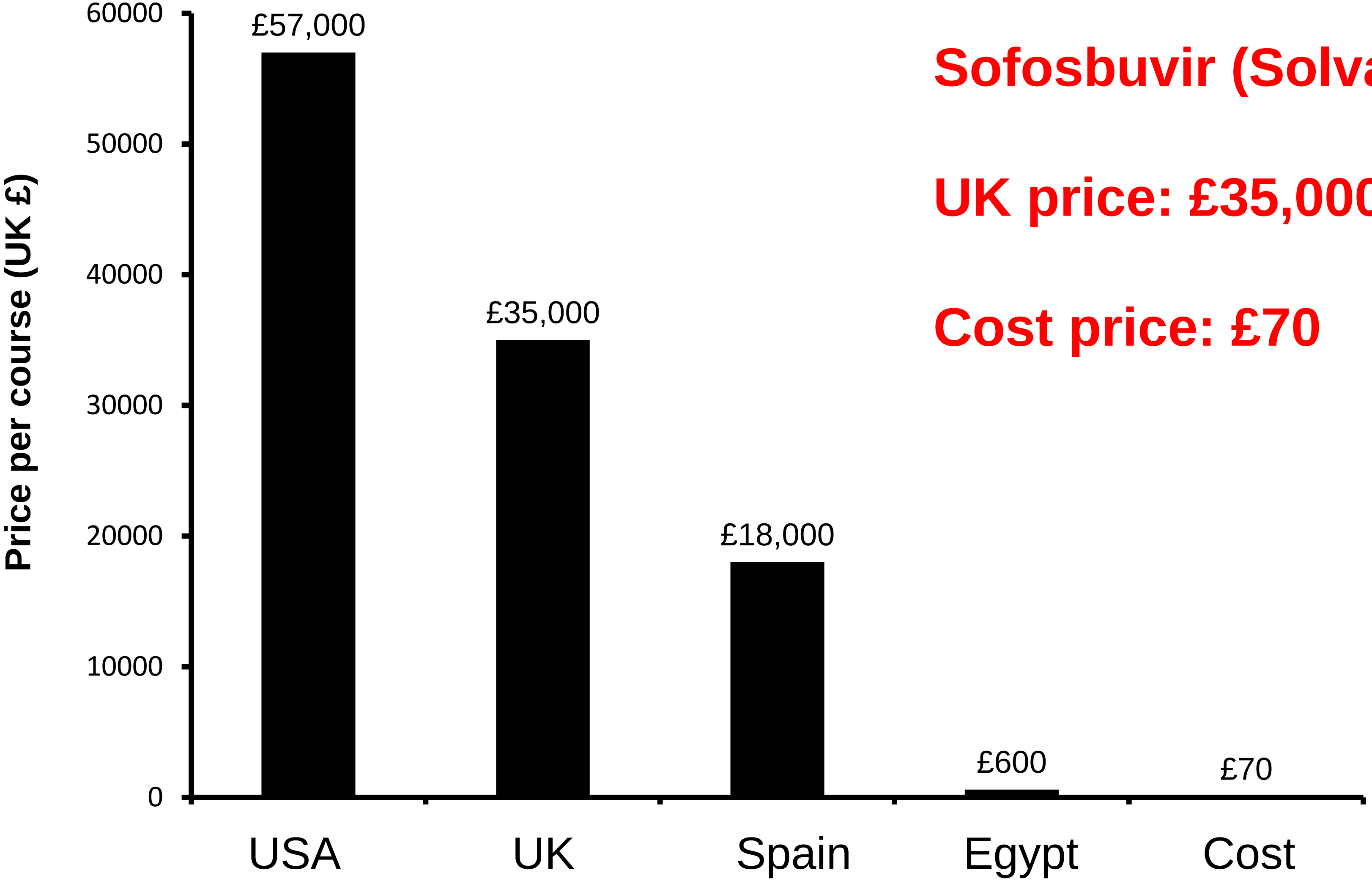
UK price: £4,600

Cost price: £24

Lowest available price for Imatinib (400mg) in selected countries



Sofosbuvir – price for 12 weeks



Sofosbuvir (Solvaldi)

UK price: £35,000

Cost price: £70

How much do HIV drugs cost in the UK?

UK prices per person-year: £ Sterling

Drug/price	NHS List	Low-income countries
Tenofovir	£2880	£34
FTC	£1956	£22
Abacavir	£2136	£140
3TC	£1608	£18
Efavirenz	£2400	£30
Nevirapine	£2040	£23
Rilpivirine	£2400	£30
Darunavir/r	£3600	£450
Atazanavir/r	£3636	£150
Raltegravir	£5652	£422

Sources: BNF 2014, Clinton Foundation 2013, MSF 2014

Patented versus generic drugs

If drugs are still on patent, pharmaceutical companies can negotiate prices with NHS based on value (cost per QALY, NICE evaluation)

Basic drug patents last for 20 years. Additional “evergreen” patents can extend the time when only pharmaceutical companies can sell drugs.

There are “evergreen” patents on co-formulations of drugs, which can last for over 10 years after the patents on the individual drugs have expired.

Drug prices can be discounted, below list price (typically 30%)

After patent expiry, drugs can then be sold by generic companies as well.

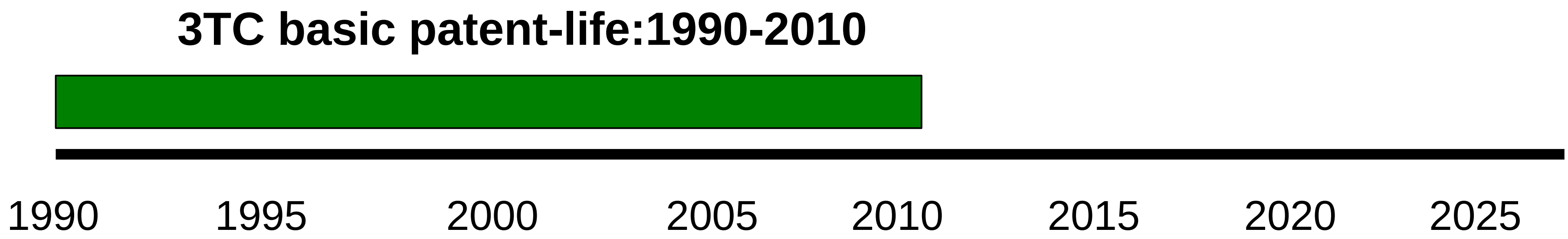
Their prices are normally at least 80% lower than the discounted prices.

3TC patent: February 1990

Prime Minister
Margaret Thatcher

Number 1 Album
Phil Collins

The original 20-year patent life of 3TC






“Evergreen patenting” of 3TC

3TC basic patent-life:1990-2010
1990-2010

ZDV/3TC
2013

1990 1995 2000 2005 2010 2015 2020 2025






“Evergreen patenting” of 3TC

3TC basic patent-life:1990-2010
1990-2010

ZDV/3TC
2013

ABC/3TC
2019

1990 1995 2000 2005 2010 2015 2020 2025

“Evergreen patenting” of 3TC

3TC basic patent-life:1990-2010
1990-2010

ZDV/3TC
2013

ABC/3TC
2019

ABC/3TC/DTG
2029

1990 1995 2000 2005 2010 2015 2020 2025










Patent Expiry dates: 2015-2029

11 years (2015-2026) when many drugs are available as individual generics, but co-formulated versions are still on patent

2015: ZDV, 3TC, NVP, EFV, RTV – already generic

2016: ABC, LPV/r

2017: TDF, ATV/r, DRV/r

2019: ABC/3TC (Kivexa)

2021: ETR

2024: TDF/FTC (Truvada)

2025: Raltegravir

2026: TDF/3TC/EFV (Atripla), TDF/FTC/RPV (Complera),

2029: ABC/3TC/DTG (Triumeq), TAF/FTC/ELV/c

Ref: Medecins Sans Frontieres 2014: Untangling the web of ARV price reductions

How much could generic HIV drugs cost?

UK prices per person-year: £ Sterling

Drug	List price (NHS)	-30% (Discount)	-80% (Generic)	Date
Tenofovir	£2880	£2016	**£403**	2017
FTC	£1956	£1369	**£274**	now (3TC)
Abacavir	£2136	£1495	**£300**	2016
3TC	£1608	£1126	**£225**	now
Efavirenz	£2400	£1680	**£336**	now
Nevirapine	£2040	£1428	**£286**	now
Rilpivirine	£2400	£1680	-	2023
Darunavir/r	£3600	£2520	**£504**	2017
Atazanavir/r	£3636	£2545	**£509**	2017
Raltegravir	£5652	£3956	-	2025

Sources: BNF 2014, Clinton Foundation 2013, MSF 2014

When generic ARVs become available, what will be the value of STRs?

Single pill
£4500 - £7400/year*

TDF/FTC/EFV: £4500

TDF/FTC/RPV: £5200

TDF/FTC/ELV/c: £7400

ABC/3TC/DTG: £6700

Three pills
<£1000/year

Generic ABC or TDF

Generic 3TC

Generic EFV or PI/r

***Prices include 30% discount from NHS list price (BNF)**
Sources: BNF 2014, generic company prices

Outcomes for co-formulated ARVs versus individual tablets in nine randomised trials (n=2,568)

Endpoint	Absolute difference (95% C.I.) FDC versus individual drugs	p value
Virological Failure (HIV RNA >400 c/mL)	-1.3% (-2.8%, +0.2%)	p=0.09
Development of HIV drug resistance	5/1100 (FDC) vs 0/538 (Control)	n.s.
Discontinuation for adverse events	+1.2% (-0.3%, +2.6%)	p=0.11
HIV RNA <50, Switch=Failure*	+2.6% (-0.04%, +5.2%)	p=0.05
Adherence >95%	+5.0% (1.4%, +8.7%)	p=0.007

All differences were within the 10% non-inferiority margin set by regulatory authorities.

*Switch = failure endpoint dominated by discontinuations with HIV RNA <50 copies/mL

Hill et al. Glasgow HIV conference, November 2014 [oral presentation]

Assumptions for generics model

1. 72,000 people on treatment in the UK in 2014,

   - rises 8% per year to >100,000 in 2019, in line with previous years

2. Pharmaceutical companies sell drugs to NHS at 28% discount from list price

Home care delivery is used for 70% of patients

3. Generic drugs are 80% cheaper than NHS prices. Immediately after patent expiry, people switch from branded to generic HIV drugs

4. Generic approvals:

   2014: 3TC, EFV, ABC, NVP, ZDV

   2016: ABC, LPV/r

   2017/8: TDF, DRV/r, ATV/r

5. Drugs remaining on patent: integrase inhibitors, ETR, RPV (15% use)

Two options for generics model

Option 1 – Use only patented, co-formulated drugs.

- no generic drugs are used
- Pharmaceutical company prices remain stable from 2014 to 2019
- dolutegravir introduced at a similar price to branded efavirenz
- average pill count = 2.3 / day

Option 2 – 100% switch to generic drugs in the year of patent expiry

Only change is generic substitution

2014: 3TC, EFV, ABC, NVP, ZDV

2016: ABC, LPV/r

2017/8: TDF, DRV/r, ATV/r

Average pill count would rise to 3.5/day (increase of 1.2 pills/ day).

HOWEVER – SOME GENERIC CO-FORMULATIONS MAY EMERGE

Switches to generics: 2015-2019

TDF/3TC or ABC/3TC + generic EFV stays as the first-line recommendation

2015

Switch from FTC to generic 3TC

Systematic switch from Atripla to TDF + generic 3TC + generic EFV

2016

Switch from patented to generic ABC

2017-9

Switch to generic tenofovir

Generic PIs introduced: ATV/r and DRV/r

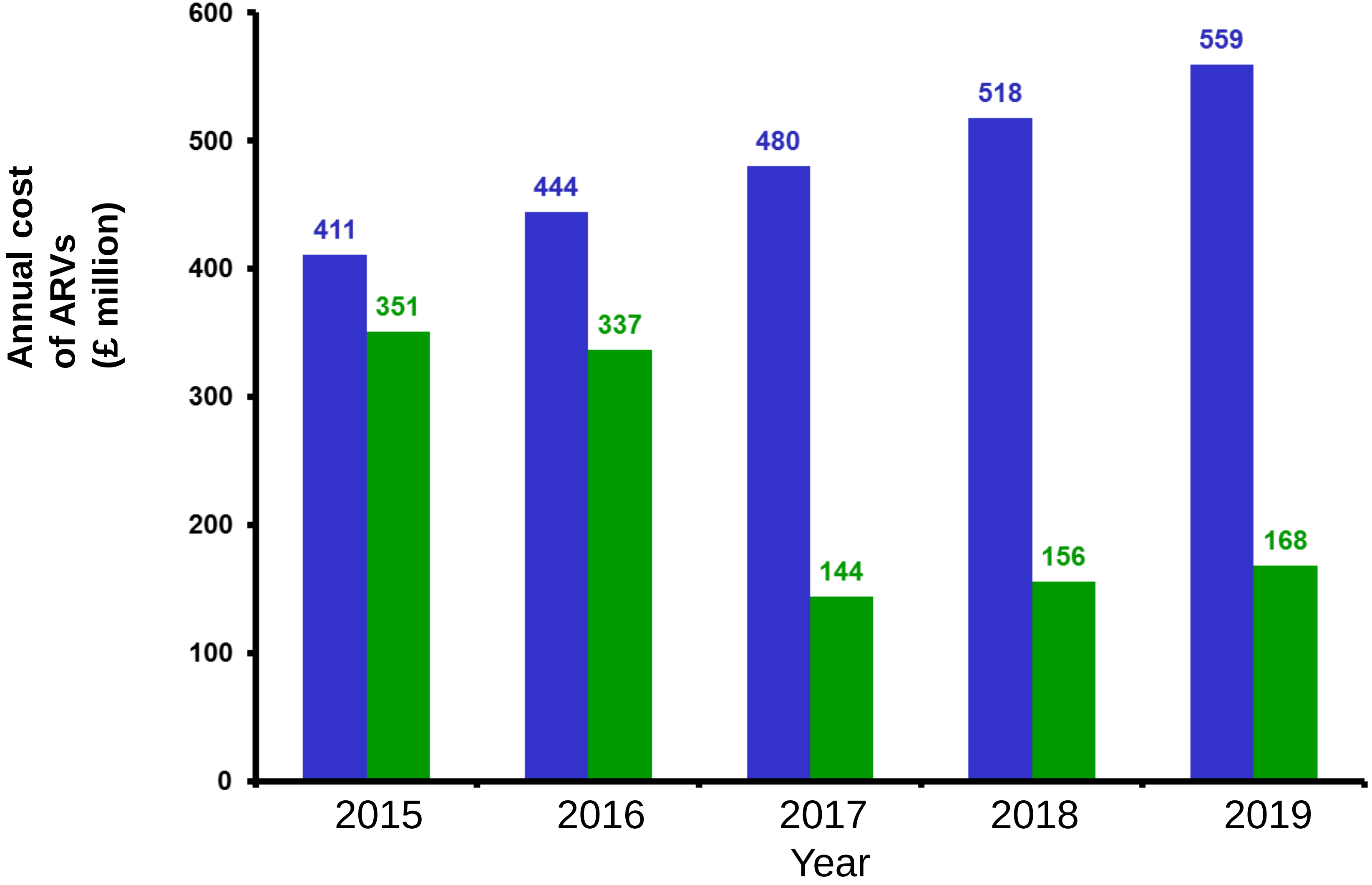
Integrase, etravirine or rilpivirine used for toxicity switching (15%)

Additional options (not included in base case analysis):

Switch to PI+3TC, generic NVP, dose optimisation, TDF-ABC switching

Predicted annual NHS costs of ARVs, 2015-2019

Option 1, patented: total cost of ARVs 2015-2019 = £2.41 billion
Option 2, generics: total cost of ARVs 2015-2019 = £1.16 billion
Potential saving = £1.25 billion



2015: Use of PI/r + 3TC (maintenance)

TDF/FTC/ATV/r
£5412/year


BMS ATV/r


Gilead TDF/FTC

ATV/r + 3TC
£2496/year


BMS ATV/r


Generic 3TC

Same switch for
LPV/r and DRV/r

Sources: BNF 2014, generic company prices

Savings by switching from 2NRTI/PI/r to PI/r+3TC

Three randomised trials – no difference in efficacy

Clinical trial	Treatment arms	Follow up time + inclusion	HIV RNA <50 Dual therapy	HIV RNA <50 Triple therapy
GARDEL	LPV/r + 3TC vs LPV/r+2NRTIs	48 weeks Naïve	189/217 (87%)	169/209 (81%)
Ole	LPV/r + 3TC vs LPV/r+2NRTIs	48 weeks Switch	108/118 (92%)	110/121 (91%)
SALT	ATV/r + 3TC vs ATV/r+2NRTIs	48 weeks Switch	112/134 (84%)	109/139 (78%)

Additional savings of £100 million, if introduced (20% switch)

Avoid toxicity of TDF, TAF or ABC

Potential outcomes:

Larger savings:

1. Competition between generic suppliers – lower prices.
2. Generic nevirapine (not included in base-case analysis)
3. More use of home delivery
4. Large-scale switch to PI/r + 3TC as maintenance therapy
5. Dose optimisation: EFV, DRV/r, ATV/r – small additional reductions in price, but regulatory approvals needed

Smaller savings:

1. Slower uptake of generic drugs. Generics not available at time of patent expiry.
2. Limited number of generic suppliers – 80% reduction in price not achieved.
3. Patients / clinicians unwilling to switch from co-formulations to generics

Conclusions

Switching from patented to generic antiretrovirals could save in the region of £1.25 billion in NHS drug costs over the next 5 years (2015-2019).

This switch in treatment would involve the average HIV-positive person increasing their pill count from 2.3 to 3.5 per day. May be less if generic companies can make alternative co-formulations

This money could be used to fund other much needed HIV programmes, such as HIV prevention or the treatment of HCV co-infection.

The benefit of fixed dose combinations over individual generic pills has not been proved in randomised clinical trials, despite large differences in costs.

Generics and the NHS

Companies which have invested in Research and Development should be rewarded with appropriate value-based prices for their new medicines, after NICE evaluation. However, evergreen patenting should be closely monitored – not all inventions are equally useful.

After patent expiry, medicines should be provided at generic prices as close to their cost of production. There needs to be active switching to generics to maximise savings.

When a generic medicine is available, the cost-effectiveness of all existing patented medicine should be re-evaluated. Existing prices may no longer be justified.

This strategy could lead to huge savings from the current £14.4 billion annual NHS medicines budget.

Thanks to:

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British HIV Association
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21st Annual Conference of the British HIV Association (BHIVA)

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21–24 April 2015

The Brighton Centre, Brighton, UK