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HIV care cost in England: a cross-sectional analysis of antiretroviral treatment and the impact of generic introduction

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Objectives

Reliable and timely HIV care cost estimates are important for policy option appraisals of HIV treatment and prevention strategies. As HIV clinical management and outcomes have changed, we aimed to update profiles of antiretroviral (ARV) usage pattern, patent/market exclusivity details and management costs in adults (≥ 18 years old) accessing HIV specialist care in England.

Methods

The data reported quarterly to the HIV and AIDS Reporting System in England was used to identify ARV usage pattern, and were combined with British National Formulary (BNF) prices, non-ARV care costs and patent/market exclusivity information to generate average survival-adjusted lifetime care costs. The cumulative budget impact from 2018 to the year in which all current ARVs were expected to lose market exclusivity was calculated for a hypothetical 85 000 (± 5000) person cohort, which provided an illustration of potential financial savings afforded by bioequivalent generic switches. Price scenarios explored BNF70 (September 2015) prices and generics at 10/20/30/50% of proprietary prices. The analyses took National Health Service (NHS) England's perspective (as the payer), and results are presented in 2016/2017 British pounds.

Results

By 2033, most currently available ARVs would lose market exclusivity; that is, generics could be available. Average per person lifetime HIV cost was ~£200 000 (3.5% annual discount) or ~£400 000 (undiscounted), reducing to ~£70 000 (3.5% annual discount; ~£120 000 undiscounted) with the use of generics (assuming that generics cost 10% of proprietary prices). The cumulative budget to cover 85 000 (± 5000) persons for 16 years (2018–2033) was £10.5 (± 0.6) billion, reducing to £3.6 (± 0.2) billion with the use of generics.

Conclusions

HIV management costs are high but financial efficiency could be improved by optimizing generic use for treatment and prevention to mitigate the high cost of lifelong HIV treatment. Earlier implementation of generics as they become available offers the potential to maximize the scale of the financial savings.

Keywords: AIDS, antiretroviral therapy, costs and cost analysis, drugs, generic, highly active, HIV

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Introduction

HIV causes a chronic infection that can be controlled by life-long antiretroviral (ARV) use. Reliable estimates of lifetime HIV care costs aid policy decision-making around treatment optimization and HIV prevention strategies such as HIV testing or the offer of pre-exposure prophylaxis (PrEP). Such estimates are challenging to derive because of the complex and changing treatment options, variation in stages of HIV progression, the long time-scale of treatment, and the introduction of generics over time. In the UK, there is open access to free testing for and treatment of HIV infection through the National Health Service (NHS).

In 2016, 96% of the 84 725 persons living with diagnosed HIV infection accessing specialist HIV care in England were receiving ARV treatment (ART) [1]. National spending on HIV specialized services in 2016/2017 was close to £540 million, with slightly more than three-quarters of this total being spent on ART ([2]; A. Duncan, Department of Health, personal communications). The lifetime HIV care cost has been estimated at £360 800 (undiscounted, 2013 values), modelled on men who have sex with men (MSM) aged 30 years and estimated to live for another 41.5 years to reach the age of 71.5 years [3]. This cost was lower (£179 600) when assuming an 80% discount on list price 3 years after ARV patent expiry. The ART regime was based on 2012 British HIV Association treatment guidelines. The analysis used non-ARV HIV care costs derived from cohort data recorded over the years 1996–2008, for persons starting ART with two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a nonnucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) [4]. New ARVs with better side-effect profiles have since been introduced, and patient outcome improvements were observed in the UK Collaborative HIV Cohort (UK CHIC) data over the years 2000–2007 [5]. At the same time, life expectancy in persons living with diagnosed HIV infection has also improved [6]. Given such changes in disease diagnosis and management landscapes, it is prudent to revisit the future resources needed for HIV care, including both ARV and non-ARV costs.

The objectives of this study were to generate a profile of ARV usage patterns for adults aged ≥ 18 years living with diagnosed HIV infection in England, collate details of patent and market exclusivity for currently available ARVs, and model the lifetime cost per person applicable in technology appraisals and annual budget impact analysis at a cohort level for HIV care payers. In the estimates of lifetime cost and annual budget impact, potential

financial savings from switches to bioequivalent generics were considered.

Methods

Data sources and analysis

The HIV and AIDS Reporting System (HARS)

The HIV and AIDS Reporting System (HARS) is a comprehensive HIV surveillance data set for England. It collects quarterly clinical data on all persons seen for HIV care in one of the approximately 170 HIV out-patient clinics in England [7]. Reporting to HARS is 100% complete, including data for all diagnosed HIV-positive persons attending specialist HIV care in England. Data submitted to HARS are de-duplicated using pseudonymous identifiers, in order to generate the cohort of people in care. The latest HARS record for each adult aged ≥ 18 years from 1 January 2016 to 31 December 2016 was extracted. Each record extracted represented a unique person. Variables extracted for this analysis included date of birth, HIV diagnosis date, gender, ethnicity, HIV acquisition route, CD4 count at diagnosis, ART initiation date, ART regime complexity level (first, second or subsequent line, or complex ARV regime) and ARV prescribed. Data completeness was assessed and records with missing or erroneous information (e.g. contradictory HIV diagnosis/ART initiation dates) were excluded from the final analysis of ARV prescription pattern (see Appendix 1 for details).

The 2016 HARS cohort was then stratified by calendar year of HIV diagnosis, from 1981 to 2016, giving 36 subcohorts. Information on type and quantity of ARVs prescribed for each subcohort, including the proportion of those not on ART, was extracted. This provided, for each year living with diagnosed HIV infection (i.e. each subcohort), a different proportional distribution of the various ARVs prescribed.

The ARV types prescribed within each ART regime complexity level (first, second or subsequent line, or complex ARV regime) of the 2016 HARS cohort were also extracted, which gave a proportional distribution of ARV usage pattern within each of the three regimes for the whole cohort.

Cost data

The British National Formulary (BNF) list price for each ARV, based on standard recommended adult (aged ≥ 18 years) oral dosage and frequency, was extracted [8]. BNF70 (September 2015) was used as the reference case cost. Earlier versions [BNF58 (September 2009) and BNF62 (September 2011)] enabled identification of

changes to ARV prices over time, as some generics became available over this period.

Information about patent and other market exclusivity protection such as Supplementary Protection Certificates were accessed via patent information portals in the USA, Europe and the UK [9–11].

Non-ARV costs were calculated from the NHS Improvement reported total spend in England on HIV admitted patient care, out-patient attendances and community contacts (figures provided through Department of Health, personal communications). This total spend, divided by the number of persons seen for care in England [1], provided a crude estimate of the average per person per annum non-ARV cost.

HIV life expectancies

HIV survival probability estimates were updated from previously published work by Public Health England using UK national HIV surveillance data covering the period 2003–2012 [12]. We obtained survival functions for 25 931 persons diagnosed between 2003 and 2007 when they were aged 25–44 years, to reflect average age at diagnosis used in the cost models (see below). The survival function was subsequently extrapolated to age 100 years on the assumption of proportional hazards. Specifically, the average hazard rate in the HIV-positive cohort for the last 5 years of follow-up data was compared to the general population mortality and a constant hazard ratio (proportion hazards) was assumed thereafter. Hence, mortality rates increased with age in proportion to the Office for National Statistics (ONS) mortality rates [13]. The ONS survival function used was generated based on cohort life expectancy projections, starting at the HARS recorded mean age of HIV diagnosis. The overall survival rate and survival rate by HIV acquisition route [MSM, heterosexual or people who inject drugs (PWIDs)] and CD4 count at diagnosis were estimated.

Cost estimation model

Two different approaches (cost models) were used to estimate lifetime HIV care cost. A person entered each model at the HARS recorded mean age at diagnosis. They then moved in yearly time intervals from year of diagnosis to death, adjusted for the probability of survival over time. The models began in calendar year 2018.

Model 1

In the first cost estimation approach (model 1), it was assumed that as a person entered the model from diagnosis, their ARV usage pattern for each year following diagnosis was the same as that recorded in the corresponding

HARS subcohort with the same duration of living with diagnosed HIV infection. For example, the ARV prescription pattern for the subcohort who had lived with diagnosed HIV for 1 year would be used to reflect ARV usage pattern for the first year after HIV diagnosis in the model. Similarly, ARV usage pattern for the HARS subcohort living with diagnosed HIV infection for 2 years would inform the proportion distribution of each ARV use for year 2 of the model, and so on. Thus, each year since diagnosis in the model had a different proportional distribution of ARVs, reflecting changing usage patterns according to duration of diagnosis. This means that the distribution of regimens in model year 30 (calendar year 2054) of people who were diagnosed with HIV infection in 2018 will correspond to the distribution of regimens in 2016 among those who were diagnosed in 1981. As HARS data only contained 36 subcohorts from years 1981 to 2016, ARV patterns of use and cost after 36 years in the model were informed by usage patterns of the final five HARS subcohorts, as long as there were more than five records within each subcohort. Where there were five or fewer records, which occurred in analyses by HIV acquisition route, usage patterns from the 5 years preceding a small subcohort year were used.

Model 2

The second approach to cost estimation (model 2) used the same HARS data to inform when a person entered the model from diagnosis to ART initiation. However, subsequent changes to the ART regime were based on the annual rate of primary ART failure as reported by the UK CHIC cohort study [14]. The annual rate of primary viral rebound was based on data for 16 101 persons who started ART between January 1998 and May 2013 [14]. In those with primary viral rebound following first-line ART, model 2 assumed that the proportional distribution of those given second- or subsequent-line or complex ARV followed the proportional distribution of patients by treatment complexity level as recorded in HARS.

Final output

For each cost estimation model, the ARV usage pattern for each year from diagnosis to death formed the backbone to which cost data were applied. ARV costs were based on BNF70 (September 2015) list prices (price scenario 1). A few generics were available by September 2015, so their BNF list prices could be different from the prices when there was no generic competition. To assess this financial impact of generic introductions, list prices from earlier versions of BNF [BNF58 (September 2009) and BNF62 (September 2011)] were extracted for ARVs that had generics recorded in BNF70 (September 2015).

This enabled a full compilation of ARV prices when only proprietary products were available. Subsequently, a fixed proportional discount was applied to proprietary ARV prices (in the absence of generic competition), beginning 1 year after a proprietary ARV lost market exclusivity. Generic price scenarios explored were prices at 50, 30, 20 and 10% (price scenarios 2–5) of proprietary BNF list prices before generic introduction. However, for an ARV with < 0.05% of total population ARV usage, it was assumed that no generics would be available as a consequence of smaller market size, based on historical observations of generic availability for ARVs that lost market exclusivity [15,16]. A similar assumption was applied when the specific ARV prescribed was unknown, coded as either ART regime complexity level or ARV class.

The final lifetime cost estimate was derived by summing ARV and non-ARV costs across the years since diagnosis, and adjusting for survival probability. Stratifications by HIV acquisition route (MSM, heterosexual or PWID) and CD4 count at diagnosis were performed to assess differences in care cost for different subgroups of patients, but only for model 1, as information was not available to allow such stratification for the other model.

Illustration of the impact on the antiretroviral budget

Finally, a budget impact analysis was conducted to illustrate the impact of switches to bioequivalent generics on the total annual ARV budget of the payer (NHS in England), and the timing and scale of potential savings. An illustrative cohort of 85 000 ($\pm$ 5000) persons was assumed to follow the proportion distribution of ARV usage pattern as reported for the 2016 HARS adult cohort. This gave the quantities required for each ARV, which were subsequently multiplied by ARV prices. Pricing scenarios explored BNF70 (September 2015) list prices, generic prices assuming that they were 10% of proprietary prices (as a minimum pricing scenario), and a combination of 50% proprietary prices and 50% generic prices at 10% of proprietary prices. Cumulative budgets were calculated from calendar year 2018 to the last calendar year in which currently available ARVs were expected to lose market exclusivity. As the budget analysis was carried out for illustrative purposes, the calculations neither account for value added tax (VAT) nor did it consider newly diagnosed persons or deaths.

Application of lifetime HIV cost estimates: a worked example

An exploration of the budget impact for the payer of providing PrEP to 50 000 persons at high risk of infection, assuming an HIV incidence rate of 2 per 100 person-years, was

undertaken. Although PrEP is a prevention tool and differs from the way in which ARVs were used historically to control HIV infection, this example was chosen given the promise and importance of PrEP in tackling the HIV epidemic and the innovative use of technology that it represents. Moreover, given the nature of PrEP delivery under a large-scale public health programme, it was of interest to study the implications of generic availability. This worked example considered PrEP using generic combination ARV (tenofovir disoproxil and emtricitabine) delivered at a cost of 10% of proprietary prices (£433.10, excluding VAT and not accounting for the clinical cost of PrEP provision).

Discounting

All costs are presented in British pounds, 2016/2017 values. Lifetime HIV care costs were discounted at 3.5% and 0% (undiscounted) per annum [17]. Budget impact estimates were undiscounted.

Analysis software

The models were constructed in Microsoft EXCEL 2010. Data management was carried out in STATA version 13.1, StataCorp, TX.

Results

HARS data overview

Over the period 1 January 2016 to 31 December 2016, of the 82 749 adults aged $\geq$ 18 years recorded to have attended HIV specialist clinics in England, 68 801 (83%) had the complete data necessary for the analysis, including date of diagnosis, date of ART initiation, and the ARV prescribed. Assessment of data completeness is presented in Appendix 1. Most individuals had probably acquired HIV infection either through sex between men and women (33 327; 49%) or through sex between men (32 262; 48%). Slightly more than half were of white ethnicity (36 917; 55%), while 23 900 (36%) were of black ethnicity.

The mean population age in 2016 was 46 years [standard deviation (SD) 10.9 years] and the mean time living with diagnosed HIV infection was 10.5 years (SD 6.6 years). Mean age at diagnosis was 36.3 years (SD 10.1 years). A summary overview of the study population is presented in Appendix 1.

Antiretroviral treatment

Around 3.8% of the cohort (2614 of 68 801) were not on ART in 2016, of whom 11% (285 of 2614) were diagnosed

in 2016. Of the remaining 66 187 (96%) on ART, there were about 205 000 individual ARVs recorded (i.e. on average, those on ART were prescribed approximately three ARVs). The most commonly prescribed ARVs in 2016 were tenofovir disoproxil fumarate, emtricitabine, darunavir, efavirenz, lamivudine, abacavir, and newer generation drugs where the specific ARVs prescribed were not explicitly coded (these could be cobicistat, dolutegravir, elvitegravir or tenofovir alafenamide). The proportional distributions of ARVs prescribed are presented in Table 1.

The proportional distribution of ARV classes by duration living with diagnosed HIV infection and by ART regime complexity is shown in Figure 1. Usage of protease inhibitors, a C-C chemokine receptor type 5 (CCR5) chemokine receptor antagonist (maraviroc) or a fusion inhibitor (enfuvirtide) increased with increasing years living with diagnosed HIV infection, as patients moved to complex ART regimes.

Over time, higher proportions of persons diagnosed initiated ART within the first 2 years of diagnosis. For example, 92% of those diagnosed in 2015 and accessing HIV care in 2016 had initiated ART within 2 years, compared with 51% of those diagnosed 10 years earlier (in 2005).

HIV life expectancies

The overall median HIV life expectancy was estimated to be 78 years (Table 2). The estimated number of remaining life years was 1, 2 and 2 years higher when restricted to heterosexuals, MSM, and those with CD4 count ≥ 200 cells/ μ L at diagnosis, respectively, but > 20 years shorter for PWID, compared with overall estimates.

Annual and lifetime HIV care cost

A box plot showing the per person annual ART cost for each of the 36 subcohorts identified in HARS, each representing the corresponding years living with diagnosed HIV infection, is presented in Figure 2. Using BNF70 (September 2015) ARV list prices, the minimum and maximum ART costs per person per annum over the 36 subcohorts were £7173 and £10 017, respectively. Average ARV costs were slightly lower in the first 20 years (average £7687 per year) compared with years 21 to 36 (average £9052 per year). The non-ARV HIV care cost was around £1450 per person per annum pro rata.

The total lifetime HIV care cost calculated using model 1 was £202 300 (3.5% annual discount applied to future values) or £404 300 (undiscounted), while the total generated by model 2 was £193 800 (3.5% discount) or £375 300 (undiscounted).

Analyses by HIV acquisition route using model 1 suggested marginal differences in estimated total lifetime cost among MSM (£208 300, 3.5% discount; £420 800, undiscounted) and heterosexuals (£199 000, 3.5% discount; £394 900, undiscounted), but much lower cost in PWID (£134 100, 3.5% discount; £201 900, undiscounted), after accounting for different mean ages at diagnosis and survival probability.

Generic introduction

The estimated calendar year of generic availability as ARVs lose market exclusivity are presented in Table 1 and Figure 3. It was estimated that, by year 2033, most of the current ARVs would have lost their market exclusivity protection. Apart from newer generation ARVs, all other ARVs would lose market exclusivity by 2027, and these represent approximately 90% of the market share. Under scenarios exploring generic introductions and assuming prices were 10% or 50% of proprietary ARV prices, lifetime HIV costs discounted at 3.5% (0%) per annum were estimated at £73 300 (£124 100) or £125 100 (£234 600), respectively. These represent lifetime cost reductions of between 42 and 69%, for a 50 to 90% ARV price discount offered by generics. Table 2 presents the estimated lifetime cost by HIV acquisition route and other generic price discount scenarios.

Cumulative antiretroviral budget

Cumulative ARV budget to cover 85 000 (± 5000) persons over 16 calendar years from 2018 to 2033, when all current ARVs were expected to lose market exclusivity, would be £10.5 (± 0.6) billion, £3.6 (± 0.2) billion, or £7.2 (± 0.4) billion, assuming ARV prices at BNF70 (September 2015) prices, at 10% of proprietary prices, or if switches to generics only happened in half of cases, respectively. Figure 3 illustrates when generics were expected to become available and corresponding changes to the ARV budget.

Application of lifetime HIV cost estimates: worked example

Generic ARV (at 10% of the proprietary price) PrEP provision to 50 000 persons at high risk of infection cost £21.6 million a year (excluding VAT). Assuming an HIV incidence rate of 2 per 100 person-years, this could prevent 1000 new HIV infections and avert £29.8 million of HIV care costs in the first 5 years and £124.1 million over a lifetime, both after accounting for generic ARV

Table 1 Number (%) of persons on individual antiretrovirals (ARVs) in 2016 in England ($n = 68\,801^*$), estimated timing of generic availability, and British National Formulary (BNF) 70 (September 2015) list price and proprietary price for each individual ARV

ARV	Proprietary name	Estimated year of generic availability, unless stated otherwise	BNF70 (September 2015) price per person per year (proprietary price, if different)
Where specific ARV prescribed is known			
> 5% of persons prescribed each of these ARVs in 2016			
Abacavir + lamivudine	Kivexa	2019	£3645
Darunavir	Prezista	2020	£5439
Efavirenz + emtricitabine + tenofovir disoproxil fumarate	Atripla	Off-patent [†]	£6488
Emtricitabine + tenofovir disoproxil fumarate	Truvada	2021	£4331
Ritonavir - any dose	Norvir	Off-patent [†]	£2840
Ritonavir boosting dose	Norvir	Off-patent [†]	£473
Tenofovir	Viread	Off-patent [†]	£2488
1%-5% of persons prescribed each of these ARVs in 2016			
Abacavir	Ziagen	2019	£2162
Atazanavir	Reyataz	2019	£3694
Efavirenz	Sustiva	Off-patent [†]	£1251 (£2438)
Emtricitabine	Emtriva	2021 [‡]	£1692
Emtricitabine + rilpivirine + tenofovir disoproxil fumarate	Eviplera	2027	£6403
Lamivudine	Epivir	Off-patent [†]	£669 (£1918)
Nevirapine	Viramune	Off-patent [†]	£2070
Raltegravir	Isentress	2024	£5739
Rilpivirine	Edurant	2027	£2438
< 1% of persons prescribed each of these ARVs in 2016			
Abacavir + lamivudine + zidovudine	Trizivir	2019	£5268
Didanosine	Videx	Off-patent [†]	£1877
Enfuvirtide	Fuzeon	Keep originator price due to small market size	£13 168
Etravirine	Intelence	2024	£3668
Fosamprenavir	Telzir	Keep originator price, off-patent but no generics	£2680
Indinavir	Crixivan	Keep originator price, off-patent but no generics	£2204
Lamivudine + zidovudine	Combivir	Off-patent [†]	£860 (£3654)
Lopinavir	Kaletra	Off-patent [†]	£3475
Maraviroc	Celsentri	2023	£5372
Ritonavir-boosted lopinavir	Kaletra	Off-patent [†]	£3475
Saquinavir	Invirase	Keep originator price, off-patent but no generics	£3059
Stavudine	Zerit	Keep originator price, off-patent but no generics	£1965
Tipranavir	Aptivus	Keep originator price due to small market size	£5369
Zidovudine	Retrovir	Off-patent [†]	£1476 (£2432)
Where specific ARV prescribed is not known			
> 5% of persons prescribed this category of ARVs in 2016			
Newer generation ARVs [§]		2033 [¶]	£4150
< 1% of persons prescribed this category of ARVs in 2016			
First ARV regimen [*]		Keep originator price, specific ARV not known	£7625 (£7907)
Second and subsequent ARV regimens [#]		Keep originator price, specific ARV not known	£7977 (£8226)
Complex ARV [¶]		Keep originator price, specific ARV not known	£10 583 (£10 873)
Other NNRTI ^{††}		Keep originator price, specific ARV not known	£2330 (£2725)
Other NRTI ^{††}		Keep originator price, specific ARV not known	£1927 (£2242)
Other PI ^{††}		Keep originator price, specific ARV not known	£3595
Not known		Keep originator price, specific ARV not known	£4355 (£4434)
Blinded treatment in clinical trials		Keep originator price, specific ARV not known	£0

NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

*Of whom 2614 persons were not on antiretroviral therapy (ART). The list excludes amprenavir (proprietary name Agenerase; coded as used by < 5 persons) and nelfinavir (Viracept; coded as used by eight persons), which have been withdrawn from the market [15]. [†]Assumed generics available from 2018, which is the model first calendar year. [‡]Considered used in combination with TDF in Truvada and the estimated year it became available was the same as the estimated year in which the generic tenofovir disoproxil (any salt form) + emtricitabine combination pill became available. [§]The specific newer generation ARVs could not be determined from the codes available for use under the HIV and AIDS Reporting System (HARS) 2016 (clinics could only code them as "Other drugs"). These drugs included cobicistat, dolutegravir, elvitegravir, tenofovir alafenamide or their combination products with other ARVs; the price was calculated as the average of the cobicistat, dolutegravir and elvitegravir prices. [¶]Actual ARV was unknown (as in note §) but was estimated based on maximum expiry for tenofovir alafenamide. [#]Specific ARV was unknown. The cost was calculated by using a combination of HARS coding for treatment complexity level (first-line, second- or subsequent-line, or complex ART). ^{††}Specific ARV unknown. The cost was calculated from average prices of ARVs within the same class.

Fig. 1 Panel A shows distribution of ARV class by years living with diagnosed HIV; Panel B illustrates distribution of ART regime complexity level (first-, second- and subsequent-line, complex ART, unknown, or not on ART) by years living with diagnosed HIV; Panel C presents distribution of ARV class by ART regime complexity level ($n = 68\ 801$). EI, entry inhibitors; C-C chemokine receptor type 5 (CCR5) antagonist (maraviroc) or fusion inhibitor (enfuvirtide); INTE, integrase inhibitor (raltegravir); NNRTI, nonnucleoside reverse transcriptase inhibitor (efavirenz, etravirine, nevirapine or rilpivirine); NRTI, nucleoside/nucleotide reverse transcriptase inhibitor (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir or zidovudine); PI, protease inhibitor (amprenavir*, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir*, ritonavir, saquinavir or tipranavir). *Amprenavir and nelfinavir have been withdrawn from the market; amprenavir (proprietary name Agenerase, Glaxo Group Limited, Middlesex, UK) was coded as used by fewer than five persons, and nelfinavir (Viracept, Roche Registration Ltd., Welwyn Garden City, UK) was coded as used by eight persons [15].

availability over time and assuming prices were 10% of proprietary prices.

Discussion

The results of our study show that the high overall HIV care costs that accrue over a lifetime can be significantly

lowered by using generic drugs. Patent and market exclusivity information extracted through this exercise show that most currently used ARVs will lose market exclusivity within the next decade. The level of granularity afforded by the comprehensive ARV prescription data captured in HARS, when combined with the patent and market exclusivity information, enabled precise

Table 2 Estimated total lifetime HIV care cost for selected HIV exposure categories and CD4 count at diagnosis, based on differential assumptions around generic discounting, adjusted by mean age at diagnosis and estimated life expectancy

Annual discount rate applied to future values															
Estimated no. of remaining life years from diagnosis			Median estimated HIV life expectancy*	3.50%						0.00%					
				BNF70 prices	Generics at 10% of proprietary prices	Generics at 20% of proprietary prices	Generics at 30% of proprietary prices	Generics at 50% of proprietary prices	BNF70 prices	Generics at 10% of proprietary prices	Generics at 20% of proprietary prices	Generics at 30% of proprietary prices	Generics at 50% of proprietary prices		
Model 1	Overall†	35	43	78	£202.3K	£73.3K	£88.3K	£103.2K	£125.1K	£404.3K	£124.1K	£156.5K	£188.9K	£234.6K	
	CD4 < 200 cells/µL at diagnosis	39	40	79	£201.7K	£72.4K	£87.5K	£102.4K	£124.0K	£387.3K	£118.2K	£149.7K	£181.0K	£225.7K	
	CD4 ≥ 200 cells/µL at diagnosis	35	45	80	£206.2K	£76.0K	£91.1K	£106.1K	£129.1K	£417.4K	£131.0K	£164.1K	£197.1K	£246.5K	
	MSM	35	44	79	£208.3K	£77.2K	£92.4K	£107.6K	£130.1K	£420.8K	£130.9K	£164.5K	£175.9K	£217.3K	
Model 2	PWID	34	20	54	£134.1K	£55.5K	£64.7K	£73.4K	£85.7K	£201.9K	£74.4K	£89.1K	£103.2K	£123.3K	
	Heterosexuals	36	45	81	£199.0K	£71.1K	£86.0K	£100.8K	£123.5K	£394.9K	£121.8K	£153.6K	£164.5K	£206.4K	
	Overall	35	43	78	£193.8K	£70.2K	£84.6K	£98.9K	£123.0K	£375.3K	£119.0K	£148.7K	£178.4K	£228.1K	

*Median HIV life expectancy calculated based on assumptions of proportional hazards in HIV-positive persons compared with Office for National Statistics (ONS) survival estimates, which were derived using cohort life expectancy projections. †Ratio of antiretroviral:nonantiretroviral costs under different price scenarios: British National Formulary (BNF) 70 (86:14), and generics at 10% of proprietary prices (49:51), 20% of proprietary prices (61:39), 30% of proprietary prices (68:32) and 50% of proprietary prices (75:25).

explorations of changes to HIV care cost over time, under various price discount scenarios. The budget impact illustration highlights the potential scale of financial savings to the payer with generic use, potentially reaching £500 million of savings in a single year by year 2021, under the assumption that generic versions of ARVs that have lost market exclusivity become available at 10% of the proprietary price. This illustrates the importance of the speed at which switches to bioequivalent generics need to happen to realize these financial efficiency savings. The methods used to construct the two models were straightforward and their outputs were comparable.

Although switching ARVs from proprietary products to bioequivalent generics should be straightforward, any switches must consider patient and clinician acceptability, how switches may impact adherence to treatment, and the availability and stability of the generic supply chain. Patients newly starting ART could be offered a generic ARV, provided that it is clinically appropriate [18].

If savings from switching to bioequivalent generics are used for HIV prevention, this could further reduce future financial costs to the health care system, as shown in the worked example of PrEP provision.

The lifetime costs estimated in this paper are slightly higher than previously published estimates [3]. Potential reasons for differences could be the type of ARV considered, the survival functions used, and differences in non-ARV HIV-related costs considered. This study used

the most comprehensive ARV surveillance data available in England and based HIV survival projections on the latest published survival data [12], which generated median HIV survival estimates that were similar to other published evidence for the UK [6]. However, non-ARV cost used a pro rata national estimate and did not account for differences in management cost by disease stage. Work is on-going to use HARS data on treatment complexity to determine the standard tariff paid to providers by NHS England for HIV clinical care provision [19]. When these become available, the data could be used to provide improved accuracy of these cost calculations.

In addition, the current study findings are likely to be overestimates of the true costs to the payer, as BNF list prices were used instead of actual prices paid by NHS England. Actual prices are usually lower following regional contract negotiations, but these remain commercial-in-confidence information [2]. Nevertheless, actual procurement prices will probably change over time, depending on market size and competition. For example, the proprietary price of lamivudine 300 mg was £1918 per annum but subsequently reduced by > 93% as generics became available, based on a June 2018 BNF update search [8]. Although recent prices paid for generics are available through the Drugs and Pharmaceutical Electronic Market Information Tool (eMIT), these have not been used as, at the time of analysis, generic market prices had only become available for four ARVs

Fig. 2 Box plot showing the median, interquartile range, and outlier per person annual antiretroviral therapy (ART) cost for each of the 36 subcohorts as recorded in the HIV and AIDS Reporting System (HARS) ($n = 68\,801$). Each subcohort represents a different year since diagnosis.

Fig. 3 Illustration of total annual antiretroviral (ARV) budget to cover 85 000 ($\pm$ 5000) persons per annum, not adjusted for new diagnoses or survival over time. TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; EFV, efavirenz; ZDV, zidovudine; 3TC, lamivudine; ddl, didanosine; LPV/r, ritonavir-boosted lopinavir; NVP, nevirapine; RTV, ritonavir; SQV, saquinavir; FPV, fosamprenavir; d4T, stavudine; IDV, indinavir; ABC, abacavir; ATV, atazanavir; DRV, darunavir; TPV, tipranavir; MVC, maraviroc; ETR, etravirine; RAL, raltegravir; RPV, rilpivirine; T20, enfuvirtide.^aHARS coding in 2016 for tenofovir did not discriminate between the disoproxil prodrug and the alafenamide prodrug. Assumed to be mostly tenofovir disoproxil, the patent for which has expired before 2018, and for which generics are available (tenofovir disoproxil in different salt forms); ^bPatents for SQV (saquinavir), FPV (fosamprenavir), d4T (stavudine), and IDV (indinavir) have expired but there is currently no generics registered for use in the UK; ^cAssumed no generics would be available upon patent expiry for T20 (enfuvirtide) and TPV (tipranavir) due to small market size (<0.05% market usage); ^dAlthough patent and market exclusivity protection for FTC (emtricitabine) has expired before 2018, there is no generic emtricitabine available in the UK market. Thus, assumed FTC (emtricitabine) is used with TDF (tenofovir disoproxil fumarate), the combination product Truvada[®] currently has market exclusivity protection until February 2020, pending legal challenge of the supplementary protection certificate for Truvada[®]; ^eCould be either cobicistat, dolutegravir, elvitegravir, tenofovir alafenamide or their combination products with other ARVs; price calculated as average of cobicistat, dolutegravir, and elvitegravir prices; patent expiry estimated based on maximum expiry for tenofovir alafenamide.

(efavirenz, lamivudine, nevirapine and zidovudine). As the market stabilizes over time, future analysis should take into consideration prices reported through eMIT.

Another limitation of this study is that it assumed no substantial changes to HIV management or a person's remaining lifetime risk of HIV infection after diagnosis. They were also projected to live with HIV, from the average diagnosis age of 35 years, for the next four decades (median). Such extrapolations into the future carry significant uncertainties. For example, recent evidence suggests

possible changes to ART regimes, with the use of two ARVs instead of three achieving comparable clinical outcomes [20]. It is also unknown whether or when an HIV cure, or at least a strategy enabling prolonged ARV interruption, could become available. Mortality in those living with HIV was assumed to be proportional to that of the general population, which implies a high mortality rate in men and those aged $\geq$ 70 years. At older ages, mortality from other causes may become more comparable to that in the general population, resulting in a longer life

expectancy than that assumed here. In particular, HIV survival among PWID was substantially lower than that in other risk groups, as a consequence of the high mortality rates at younger ages being extrapolated throughout their lifetime via the proportional hazard assumption. This approach does not account for changes in injecting drug use behaviour and corresponding risks over the remaining lifetime, or changes in the relative hazards of injecting-associated risks compared with other-cause mortality.

The budget impact illustration presented in this paper used a static cohort size and did not capture the uncertainty of changing disease incidence, impact of prevention strategies, long-term mortality, long-term treatment options and ARV prices. Such quantities could have probabilistic distributions attached to them, but the range of uncertainty is currently unknown. If the population size changes, or if the treatments being used change in cost, this will proportionally affect the total budget. Nonetheless, the objective of the current exercise was to highlight the scale of financial savings with which bioequivalent generics offer to the payer. Setting a constant figure enabled presentation of the impact of simple discounts on the overall budget.

Finally, this study only explored scenarios of direct reductions in ARV prices as generics become available and assumed switches to bioequivalent generics. It did not consider options whereby patients on established ART regimes had their ARV components changed to another ARV within the same class on the basis of cost [2]. It also did not consider other forms of commercial discounts offered by proprietary ARV manufacturers to counter lower prices offered by alternative generic ARVs within the same class or those that form part of a combination product.

In conclusion, high overall lifetime HIV management costs were consistently generated by the two models presented in this paper. The study also illustrates the magnitude of potential financial savings when generics become available and are prescribed. Consideration of the potential to transfer some of the financial savings to HIV prevention strategies such as PrEP offered further insights into options that may be used to achieve improved financial efficiency through a balanced optimisation of generic use for treatment and prevention. It must be acknowledged that there remains uncertainty around the availability of generics, their prices and future changes in disease management options. For the present, HIV infection remains a long-term condition, and policy prioritization should ensure timely generic switches and prevention of new infections, which will result in a corresponding curbing of spending on lifetime care.

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Appendix 1

Data cleaning of the HIV and AIDS Reporting System (HARS) dataset

The last recorded observation for each person seen for HIV care in England over the period 1 January 2016 and 31 December 2016 was extracted, giving a total of 82 749 observations from adults aged ≥ 18 years. Each observation represented a unique person. Each patient

was identified through a matching algorithm which took into account a variety of demographic data e.g. soundex code (scrambled form of surname), date of birth, gender and residency information. Patient information was linked over time and a unique identifier assigned to each patient, this allowed effective monitoring when individuals switch clinics. The possibility of a person not being linked when they switch clinic and therefore having more than one record is rare.

Data completeness was assessed and observations with missing or erroneous information about ARV type used, clinic geographical region, date of HIV diagnosis and ART initiation were excluded from the final analysis. Details of the steps considered when excluding these observations are explained below.

Assess data completeness

- (1) Data completeness and data quality for each variable of interest was assessed; details are presented in Table A1. For each variable, observations with completed fields were checked to ensure there was no erroneous information in the complete observations. These are noted alongside Table A1. After excluding observations with missing or erroneous dates of diagnosis or ART initiation, HIV clinic location, and

Table A1 Data completeness for each variable of interest ($N = 82\,749$ adults aged ≥ 18 years); complete observations excludes unknown values

Variable	Complete observations (n)	Complete observations ($n/N\%$)
Year of birth	82 749	100
Gender	82 749	100
Year of diagnosis*	82 749	100
Years living with diagnosed HIV*	82 749	100
HIV clinic location	82 421	100
Ethnicity	81 640	99
Exposure route (risk category)	81 101	98
Year of ART Initiation†	80 484	97
ART regime complexity level‡	72 827	88
ARV1 code§	72 827	88
First CD4+ count	67 594	82

*Exclude diagnoses coded as occurring before 1981 or after 2016, the same apply for years living with diagnosed HIV as this was calculated from year of diagnosis; †Exclude two observations whereby the year of ART initial was before 1981; ‡This has been cleaned to be consistent with ARV codes, where there was a code for ARV but ART regime complexity recorded patient "not on ARV" or "missing", changed to "on ART, regimen unknown"; $n = 8890$ observations were coded as "on ART, regimen unknown"; §This has been cleaned to be consistent with ART regime complexity, where there was a missing code for ARV but ART regime complexity recorded patient as on first-, second- or subsequent-line or complex ART or "not on ARV", updated ARV1 codes according to ART regime complexity; $n = 6489$ observations were recoded as first-line ART regime ($n = 575$), second- or subsequent-line ART regime ($n = 1515$), complex ART regime ($n = 63$), and not on ART ($n = 4336$) from 16 411 observations with missing values, leaving 9922 observations with missing values.

missing ARV codes, the final dataset used for the analysis included 68 801 (83% of 82 749 persons).

- (2) Summary overview of key variables generated from complete observations used in analysis and the incomplete/excluded observations were compared. These are shown in Table A2 (Part a and Part b – two parts to make readable). There appeared to be no major differences in the key variables used for the analysis. Attendance frequency is lower for the incomplete observations, although this variable was not used in the cost models.

Survival extrapolations

Figure A1 shows the ONS cohort life expectancies and HIV survival function extrapolated based on the assumption of proportional hazards of HIV mortality rates compared with ONS mortality rates (see main text for details). Life expectancies were estimated from HARS recorded

mean age of HIV diagnosis. HIV mortality rates were stratified by risk categories.

Cost data

Non-ARV care cost

Itemisation of non-ARV HIV specialist care cost, England, year 2016–17 (personal communications, Department of Health, summary data provided by NHS Improvement using reference costs i.e. average unit costs to NHS providers for defined services provision, represents cost to the provider)

	Estimated total cost (£ million); 2016–17
Admitted patient care	14.4
Outpatient attendances	104.6
Community contacts	3.7
Total	122.7

Table A2 Summary overview of HARS 2016 observations for all adults aged ≥ 18 years, stratified by observations with complete values for variables of interest (dates of diagnosis and ART initiation, and ARV codes; $n = 68\ 801$) and those with incomplete observations ($n = 13\ 948$)

(a*)						
HIV exposure category	No. (%) of observations		Mean (SD; IQR) age at diagnosis; unit: years		Mean (SD; IQR) years living with diagnosed HIV	
	Complete observations	Incomplete observations	Complete observations	Incomplete observations	Complete observations	Incomplete observations
Overall	68 801	13 948	36.3 (10.1; 29–42)	36.2 (10.1; 29–42)	10.5 (6.6; 5–14)	10.4 (7.0; 4–15)
MSM	32 262 (46.9%)	6783 (48.6%)	35.6 (10.0; 28–42)	35.4 (9.5; 28–41)	10.6 (7.5; 5–15)	10.7 (7.6; 4–16)
Hets	33 327 (48.4%)	6354 (45.6%)	36.9 (10.1; 30–43)	37.2 (10.1; 30–43)	10.5 (5.6; 6–14)	10.6 (6.1; 6–15)
MTCT	222 (0.3%)	139 (1.0%)	22.9 (7.5; 18–25)	20.2 (3.9; 18–21)	5.0 (3.9; 2–7)	3.9 (2.6; 2–5)
PWID	1210 (1.8%)	191 (1.4%)	34.9 (8.1; 29–40)	35.1 (8.1; 29–41)	12.0 (8.3; 5–17)	10.8 (7.9; 4–15)
Blood products	519 (0.8%)	94 (0.7%)	35.9 (11.9; 26–43)	39.3 (14.7; 26–51)	13.4 (9.5; 5–19)	11.4 (8.3; 4–18)
CD4+<200 at diagnosis [†]	15 945 (27.7%)	2545 (25.2%)	39.1 (10.4; 32–45)	38.4 (10.1; 31–45)	9.9 (5.5; 6–14)	10.8 (6.0; 6–15)
CD4+ $\geq$ 200 at diagnosis [†]	41 541 (72.3%)	7563 (74.8%)	35.2 (10.1; 28–41)	35.3 (9.9; 28–41)	9.5 (6.2; 4–13)	8.8 (6.0; 4–13)
(b*)						
HIV exposure category	No. (%) of all diagnoses [†] of very late diagnoses		Ethnicity			
			White (%)		Black (%)	
	Complete observations	Incomplete observations	Complete observations	Incomplete observations	Complete observations	Incomplete observations
Overall	15 945 (28%)	2545 (25%)	36 917 (55.2%)	6534 (49.2%)	23 900 (35.7%)	5086 (38.3%)
MSM	4880 (18%)	877 (17%)	27 575 (86.6%)	5052 (76.4%)	1469 (4.6%)	532 (8.0%)
Hets	10 297 (37%)	1567 (34%)	8000 (24.2%)	1257 (20.1%)	22 049 (66.6%)	4415 (70.6%)
MTCT	68 (34%)	23 (32%)	37 (17.1%)	07 (5.1%)	150 (69.1%)	108 (78.8%)
PWID	263 (28%)	25 (23%)	1034 (86.1%)	160 (85.1%)	65 (5.4%)	10 (5.3%)
Blood products	117 (33%)	11 (24%)	271 (52.8%)	58 (62.4%)	167 (32.6%)	21 (22.6%)
CD4+<200 at diagnosis [†]	15 945 (100%)	2545 (100%)	6559 (41.5%)	905 (36.3%)	7741 (49.0%)	1294 (51.9%)
CD4+ $\geq$ 200 at diagnosis [†]	0 (0%)	0 (0%)	24 406 (59.5%)	3886 (52.8%)	12 774 (31.1%)	2441 (33.2%)
					3870 (9.4%)	1031 (14.0%)
					3.4 (2.3)	3.5 (2.3)
					3.6 (2.4)	3.6 (2.4)
					3.2 (2.1)	3.2 (2.1)
					3.7 (2.6)	3.7 (2.6)
					102 (8.5%)	18 (9.6%)
					75 (14.6%)	14 (15.1%)
					1507 (9.5%)	294 (11.8%)
					3.4 (2.3)	3.4 (2.3)
					3.5 (2.3)	3.5 (2.3)
					2.7 (2.1)	2.8 (2.1)
					2.7 (2.0)	2.7 (2.0)
					2.4 (1.7)	2.4 (1.7)
					3.7 (2.5)	2.8 (2.1)
					3.4 (2.4)	3.2 (2.7)
					2.6 (2.0)	2.6 (2.0)

*Table broken down to two parts to make readable; †CD4+<200 at diagnoses represented very late diagnoses; ‡Excluded attendances above 14 times a year (99th percentile).

Figure A1 ONS cohort life expectancies [1] and estimated HIV survival (from mean age at diagnosis*, overall and by risk category) [2], assuming proportional hazards of HIV mortality rates compared with ONS mortality rates. *Mean age at diagnosis by risk category as follows: overall (35 years); CD4+<200 at diagnosis (39 years); CD4+≥200 at diagnosis (35 years); MSM (35 years); PWID (34 years); heterosexuals (36 years). [Colour figure can be viewed at wileyonlinelibrary.com]