

The financial and service implications of splitting fixed-dose antiretroviral drugs – a case study

R Taylor¹, E Carlin¹, Z Sadique², I Ahmed¹ and EJ Adams^{3,4}

Abstract

In 2010/2011, regional commissioners withdrew payment for the fixed-dose combination Combivir, forcing a switch to component drugs. This was deemed clinically acceptable and annual savings of £44 k expected. We estimated the true costs of switching and examined patient outcomes. Information for 46 patients using Combivir was extracted from case notes for each clinical contact in the 12 months pre- and post-switch (clinician seen, tests, antiretrovirals). Post-switch care costs £93/patient more annually versus pre-switch (95% CI £424 to £609), yielding £4278/year more post-switch for all patients. Drug and pathology costs were more expensive post-switch and extra clinical visits required. None of these results were statistically significant. Forty-two per cent of patients switched directly or in the subsequent year to an alternative fixed-dose combination rather than generics. Costs in this group were significantly higher post-switch driven by drug cost. Six patients (13%) reported problems with the switch including confusion around dosing and new side effects. As less-expensive generic antiretroviral drugs become available, it may appear cheaper to switch from fixed-dose combinations to component drugs. However, the additional clinical costs involved may outweigh the initial cost savings of the drugs and switching may cause confusion for some patients, risking loss of adherence.

Keywords

HIV, cost and cost analysis, drug therapy, combination, drug substitution, drugs, generic

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Introduction

The cost of HIV care in the UK was estimated to be £762 million in 2010, and approximately two-thirds of this was spent on antiretroviral (ARV) drugs.¹ These costs are increasing annually, as the cohort of HIV-infected individuals continues to increase in size and age each year.^{1,2} Cost-effective provision of HIV care is therefore vital. With a wide range of ARVs now off-patent, cost savings may be possible if patients switch to cheaper generic versions of these drugs, including fixed-dose combinations (FDCs) to component drugs.

However, unless generic FDCs also become available, there is likely to be increased pill burden associated with switching to generic component drugs. Increased pill burden is known to be associated with poorer adherence³ and poorer self-reported health status.⁴ To date, no randomised trials examining efficacy of branded co-formulations of ARVs with generics have been conducted, so the comparative efficacy is unknown. Mathematic modelling of using a three-pill generic regime in place of a branded combination

performed in the USA suggested a large cost saving, although the authors acknowledge that this confers a small survival disadvantage in their model and may not reflect real-world results.⁵

In July 2010, the HIV Commissioners in the East Midlands region of England stopped reimbursement for the antiretroviral FDC Combivir (Qualie M, personal communication). Instead, they agreed to only pay for the individual components (generic Zidovudine [AZT] licensed in 2008,⁶ which was considerably less

¹Department of Genitourinary Medicine, Nottingham University Hospitals NHS Trust, Nottingham, UK

²Independent Health Economist, London, UK

³Aquarius Population Health, Bristol, UK

⁴School of Social and Community Medicine, University of Bristol, Bristol, UK

Corresponding author:

R Taylor, Department of Genitourinary Medicine, Nottingham University Hospitals NHS Trust, Hucknall Road, Nottingham NG5 1PB, UK.
Email: ruth.taylor@nuh.nhs.uk

expensive than the branded equivalent, plus branded Lamivudine). Although not a first line treatment at the time, a significant number of patients still took Combivir (~9% of all patients on ARVs at that time), either due to reluctance to switch regime or their wish to continue with a regime started during pregnancy. Despite the small numbers, it was deemed by the Commissioners that this change could save an estimated £44,000 annually in our cohort of 800 patients (Qualie M, personal communication). This saving would have represented approximately 1% of the unit's ARV total drug spend. No restrictions were placed on clinicians to avoid switching patients to alternative FDCs.

In this paper, we demonstrate the true costs and potential clinical impact on patients of a policy to switch from a branded FDC to alternate regimens, using the example of Combivir. Results from this case study can inform drug funding decisions.

Methods

Patients and data extraction

Commissioners asked Trusts to stop prescribing Combivir for new patients from April 2010, and to switch patients already on Combivir to component drugs or alternate therapy by July 2010 (Qualie M, personal communication). We retrospectively extracted data from Nottingham University Hospitals NHS Trust's HIV clinic from December 2009 to November 2012. All patients prescribed Combivir on 1 April 2010 were identified via pharmacy records, the date of when they switched from Combivir and data for 12 months prior (baseline) and for 12 months following the switch date were extracted from patient records.

For each patient, we recorded data for each clinical encounter (clinic visit or telephone call with clinic personnel). This included clinician(s) seen, pathology tests ordered, ARV medication prescribed, problems and adverse outcomes reported specific to the Combivir switch, HIV viral load (VL) and hospital admissions.

Of the initial 64 patients prescribed Combivir on 1 April 2010, 10 women were on this treatment primarily to prevent mother-to-child transmission of HIV and stopped taking ARVs after delivery. These patients were excluded along with five patients who had no on-going follow-up visits (either lost to follow-up or moved unit) and three whose records were missing. Pregnant patients who remained on ARVs after delivery were included in the analysis.

Costs

The perspective for the analysis was from the health-care provider, and only direct costs were estimated based on healthcare utilisation using a bottom-up methodology.

Resources were considered in three categories: ARV drugs, time with clinical staff and pathology tests. We used local costs from Nottingham University Hospitals NHS Trust for all pathology tests and ARV prices. Trust ARV prices were chosen as negotiated prices can differ from the British National Formulary (BNF)⁷ list prices, and we wanted to accurately estimate the total costs for the Trust. These are not individually reported in this paper as they are commercially sensitive. The authors estimated time spent by each clinical staff member for a standard clinic visit and telephone calls with different members of staff (Table 1). The cost per hour for staff was estimated using the Unit Costs of Health and Social Care.⁸ No inpatient visits were reported.

Table 1. Assumed average duration and costs of clinical consultations.

Clinical consultation categories	Average consultation time (minutes) ^a	Cost per minute (£) ^b	Total estimated cost (£) – face to face	Total estimated cost (£) – telephone consultation ^c
Medical consultant	20	2.7	54.00	13.50
Specialist registrar	30	1.22	36.60	6.10
Nurse ^d	10	0.67	6.70	3.35
Hospital pharmacist	15	0.68	10.20	3.40
Midwife ^e	10	0.67	6.70	3.35

^aSource: Nottingham University Hospital.

^bSource: Curtis.⁸

^cSource: Telephone consultation for any clinician assumed to be 5 min.

^dDay ward nurse.

^eMidwife is assumed to have same unit cost as day ward nurse.

Pregnant patients tend to have more hospital visits and tests.⁹ Four patients were pregnant at some point in the two-year follow-up period. Therefore, visits that were solely related to antenatal care and did not have any HIV specialist input were excluded (e.g. routine antenatal screening), as was the cost of delivery of babies and any resultant inpatient stay.

Analysis

The healthcare utilisation and associated costs were compared for the baseline year on Combivir and the year after switching. We also analysed clinical outcomes in the 12 months before and after switching therapies for each patient:

- Adverse events
- Treatment failure
- Viral load
- Switch to another regimen
- New drug resistance
- Mortality

The difference in pre- and post-switch costs per patient was compared via paired *t*-test.

A sensitivity analysis was undertaken to investigate whether the results were robust to alternative unit costs of ARV drugs in which we used BNF published costs.⁷ A sub-analysis was also completed where we excluded

patients who were switched to another FDC rather than components of Combivir.

Results

Drug regimen

Thirty-two patients (70%) switched from Combivir to single dose equivalents, keeping the same third agent. Three of these had a further nucleoside reverse transcriptase inhibitor (NRTI) switch during the next 12 months onto either Kivexa or Truvada. Thirteen patients were switched off Combivir directly onto another FDC or single tablet regimen.

Healthcare utilisation and costs

Pre-switch and post-switch costs are reported in Figure 1. Costs are similar between both periods, with slightly higher costs post-switch. On average, patients had more visits to clinicians after the switch compared to pre-switch (7.23 [SD 2.97] and 5.07 [SD 3.45], respectively). The average number of pathology tests per year pre-switch was 13.91 (SD 7.92) compared to an average of 17.09 (SD 6.98) pathology tests post-switch.

Staff time costs were higher post-switch, leading to £56 (95% CI £26 to £86) additional cost per patient (Figure 1). Mean drug costs per patient were also

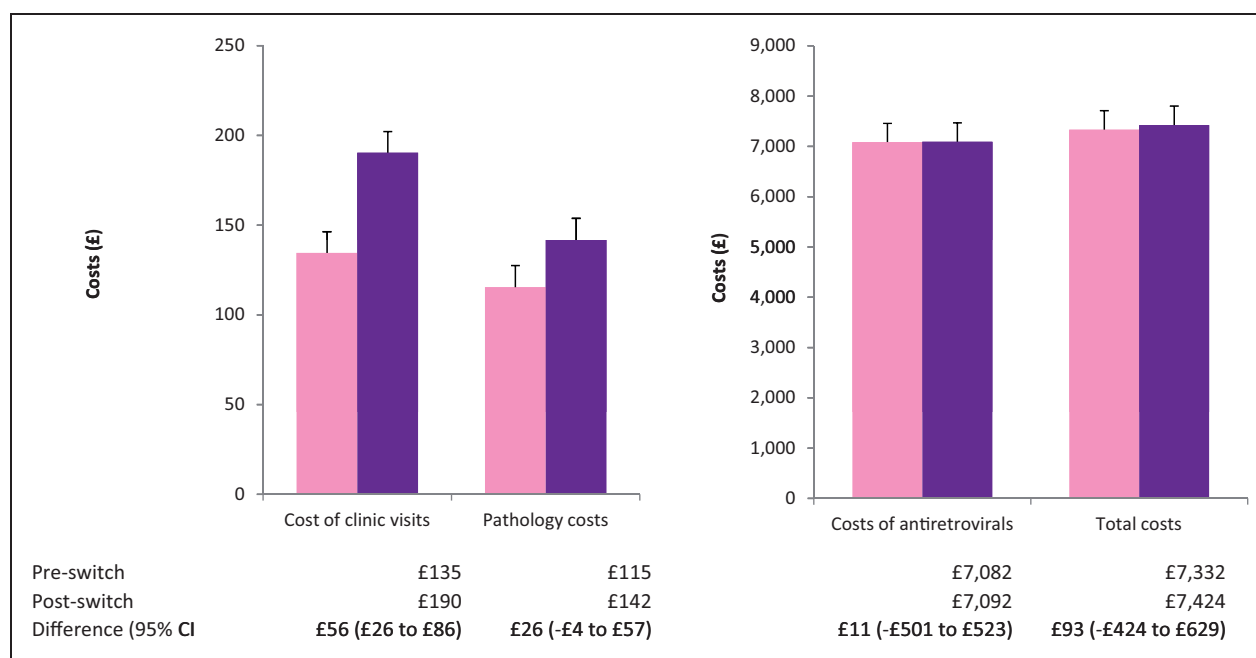


Figure 1. Costs of clinic visits, pathology, antiretroviral drugs and total costs pre- and post-switch.

slightly higher post-switch (£7092 versus £7082) as were the mean pathology costs (£142 versus £115); neither was statistically significant. Annual total cost of care per patient post-switch is relatively more expensive by £93, but the difference in costs is not statistically significant (95% CI £424 to £609). This yields a total increase in costs post-switch in these 46 patients of £4278.

The sensitivity analysis indicates that ARV costs are substantially higher when BNF prices are used compared to Trust prices. With BNF prices, the mean difference of drug costs is £713 greater post-switch (95% CI £334 to £1091) and difference in total healthcare cost is £795 greater post-switch (95% CI £411 to £1178).

A sub-sample analysis of patients who switched onto components of Combivir rather than an alternative NRTI combination shows significant cost savings following the switch, with a reduced annual cost per patient of £742 (95% CI £487 to £998). However, patients who switched to another FDC generated average additional costs per patient post-switch of £1658 (95% CI £570 to £2746).

Patient-reported outcomes

Six patients (13%) reported problems with the switch – five of these had switched directly to single-dose Zidovudine and Lamivudine; one felt he was unable to take the new tablets and switched again two days later, wasting three months of drugs. One patient developed a mild and self-limiting rash. Both of these were patients who had switched to individual Zidovudine and Lamivudine. Four patients contacted the clinic due to confusion about the doses or timings – one of these had taken the incorrect dose of the new medicine for some weeks.

One patient with a history of adherence issues had a VL of 71 copies/uL at the date of the switch, and a detectable VL (411 copies/uL) at one-year post-switch. All other patients maintained a fully suppressed VL at one-year post-switch.

There were no deaths reported. One patient developed an AIDS-defining illness (tuberculosis) in the year after the Combivir switch.

Discussion

Our case study indicates that although there were cost savings predicted for switching patients from a proprietary FDC ARV to component drugs including generics, this was based on drug cost alone and did not account for all of the associated healthcare costs. We show what may happen as other proprietary FDCs come off-patent and are available as generic versions, or if there is a decision to move patients from FDCs to

individual components as part of cost-efficiency savings.

Sub-analysis indicates that for patients switching directly to Zidovudine and Lamivudine plus a third agent, and remaining on this regime for one year, there are significant savings in the total healthcare costs. However, the savings in this group are considerably less than initially predicted based on drug costs alone. The increased input from clinicians and the resultant increase in pathology tests in the 12 months post-switch, plus the actual costs to the department of the new drug prescriptions, negates any large savings.

In addition, over one-quarter of patients (29%) did not end up going onto the generic combinations as was initially intended, but were switched directly to an alternative FDC. Another six others (13%) subsequently switched in the following year. This could be due to various reasons, including reluctance to increase pill burden or about side effects, particularly regarding the use of Zidovudine. Analysis of this subset of patients showed that the subsequent healthcare costs at one year are significantly higher in this group, mainly driven by drug costs. It could be argued that unless all FDC combinations were proscribed, this pattern of switch to alternative FDCs in some patients is likely to be similar in other units.

Whilst the use of Zidovudine as part of the NRTI backbone is no longer recommended routinely in the British HIV Association (BHIVA) Treatment Guidelines unless in special circumstances,¹⁰ some patients may still require it (e.g. pregnancy, resistance profile) or prefer to remain on a regime that they are comfortable with. The use of other NRTI/NRTI-NNRTI combinations is standard practice¹⁰ and as such similar issues will arise when other drugs in these combinations become available as generics. Specific reference to the use of generic drugs is made in the European AIDS Clinical Society (EACS) guidelines¹¹ and suggests that they may be used when available, but only when they replace the same drug and do not break a recommended FDC.

It has been shown that ARV consisting of the so-called single tablet regimens are associated with significantly better adherence and lower risk of hospitalisation compared to patients using ARVs consisting of three or more pills per day.¹² Additionally, with an increasingly aging HIV population² and recognised prevalence of polypharmacy in the HIV cohort,¹³ the total pill burden for an individual patient may be significantly higher than just their ARVs. There is a perceived adherence benefit associated with even small reductions in pill burden (e.g. from five to three pills a day),^{4,14} and a large survey of HIV-positive individuals indicated that patients prefer regimes which involve few pills and once-daily dosing.^{14,15}

Further work has shown improvements in ARV adherence when patients are given an FDC as all or part of their regimes.¹⁶

A Spanish HIV unit found similar results to ours. All FDCs were withdrawn for financial reasons and patients were switched to generics, yet there were additional costs to the hospital mainly related to adverse events and additional staff costs.¹⁷

The limitations of our study included several missing patient records, and possible bias due to assumptions about clinician time and resultant health cost. However, as the same time periods and costs were assigned pre- and post-switch it is unlikely that this would have affected results. Patient follow-up was only done for one year post-switch. The increased clinician input and pathology may be concentrated around the period after the switch; surveying patients for longer than one year may show that costs regressed to the mean. However, using drug costs alone during the one year period indicates that the cost saving is still non-significant.

We were unable to collect completely accurate data on all patient-reported problems due to the retrospective nature of the study, and had to rely on case notes. We may have underestimated any patient anxiety or uncertainty about the new regime, or issues not recorded at the time by the clinician. We were also unable to add in dispensing costs to our analysis.

When extrapolating these data it should also be noted that the withdrawal of payment for Combivir may have acted as a catalyst for switch to newer drugs in the form of alternative FDCs, and the removal of older agents such as AZT from regimes. It is unclear as to what extent similar prescribing behaviour would follow, if more modern FDCs were restricted.

Choosing the right ARVs for patients will become more challenging as new drugs (including new and generic FDCs) become available and fiscal pressures increase. Whilst switching to generic drugs may appear to be a solution to reducing spend on ARV drugs, it may not be cost saving when all associated expenditure is considered. This case study has shown that switching is likely to generate additional healthcare costs. Basing purchasing decisions on drug costs alone does not take account of a more complex clinical picture. All fiscal factors must be considered when making ARV commissioning decisions with the aim of providing not only good patient treatment but also saving money. We would expect our local results to be applicable to other HIV clinics across the UK and internationally.

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Conflict of interest

RT has received funding from Gilead to attend a conference to present preliminary results, EA has received funding from St Georges NHS Trust, Terrence Higgins Trust, the Office for Sexual Health and Pathway Analytics for research relating to the cost of HIV, EC has received payments for conferences and lectures unrelated to this work from ViiV, Bristol Myers Squibb, Gilead, Abbot, Pfizer.

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References

1. House of Lords. *No vaccine, no cure: HIV and AIDS in the United Kingdom*. London: HMS, 2011, <http://www.publications.parliament.uk/pa/ld201012/ldselect/ldaids/188/18802.htm> (accessed 18 March 2014).
2. Health Protection Agency. HIV in the United Kingdom: 2012 report, 2013, <http://www.hpa.org.uk/Publications/InfectiousDiseases/HIVAndSTIs/1211HIVintheUK2012/> (accessed 18 March 2014).
3. O'Connor JL, Gardner EM, Mannheimer SB, et al. Factors associated with adherence amongst 5295 people receiving antiretroviral therapy as part of an international trial. *J Infect Dis* 2013; 208: 40–49.
4. Gianotti N, Galli L, Bocchiola B, et al. Number of daily pills, dosing schedule, self-reported adherence and health status in 2010: a large cross-sectional study of HIV-infected patients on antiretroviral therapy. *HIV Med* 2013; 14: 153–160.
5. Walensky RP, Sax PE, Nakamura YM, et al. Economic savings versus health losses: the cost-effectiveness of generic antiretroviral therapy in the United States. *Ann Intern Med* 2013; 158: 84–92.
6. Medicines and Healthcare Products Regulatory Agency. *Public assessment report. Decentralised procedure zidovudine 100mg capsules, hard zidovudine 250mg capsules, hard*. UK/H/1086/01-02/DC UK licence numbers: PL 20532/0100-0101 Aurobindo Pharma Limited. London: MHRA, 2008, <http://www.mhra.gov.uk/home/groups/l-unit1/documents/websitesresources/con025677.pdf> (accessed 18 March 2014).
7. British Medical Association and the Royal Pharmaceutical Society of Great Britain. *British national formulary 59: March 2010*. London: Pharmaceutical Press, 2010.
8. Curtis L. *Unit costs of health & social care: 2010*. Canterbury: Personal Social Services Research Unit, 2010, www.pssru.ac.uk (accessed 18 March 2014).
9. Taylor GP, Clayden P, Dhar J, et al. British HIV association guidelines for the management of HIV infection in pregnant women 2012. *HIV Med* 2012; 13(suppl 2): 87–157.

10. Williams I, Churchill D, Anderson J, et al. British HIV association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012. *HIV Med* 2012; 13(suppl 2): 1–85.
11. European AIDS Clinical Society. *European AIDS clinical society guidelines*. Report no. 6.2. Paris: European AIDS Clinical Society, 2012, <http://www.pssru.ac.uk/project-pages/unit-costs/2011/index.php> (accessed March 2014).
12. Sax PE, Meyers JL, Mugavero M, et al. Adherence to antiretroviral treatment and correlation with risk of hospitalization among commercially insured HIV patients in the United States. *PLoS One* 2012; 7: e31591.
13. Marzolini C, Elzi L, Gibbons S, et al. Prevalence of comedICATIONS and effect of potential drug-drug interactions in the Swiss HIV cohort study. *Antivir Ther* 2010; 15: 413–423.
14. Moyle G. The assessing patients' preferred treatments (APPT-1) study. *Int J STD AIDS* 2003; 14(suppl 1): 34–36.
15. Kauf TL, Davis KL, Earnshaw SR, et al. Spillover adherence effects of fixed-dose combination HIV therapy. *Patient Prefer Adherence* 2012; 6: 155–164.
16. Maitland D, Jackson A, Osorio J, et al. Switching from twice-daily abacavir and lamivudine to the once-daily fixed-dose combination tablet of abacavir and lamivudine improves patient adherence and satisfaction with therapy. *HIV Med* 2008; 9: 667–672.
17. Homar F, Lozano V, Martinez-Gomez J, et al. Cost analysis of HIV treatment and drug-related adverse events when fixed-dose combinations of antiretrovirals (FDCs) were stopped, versus continuation with FDCs. *Health Econ Rev* 2012; 2: 16.