

ORIGINAL ARTICLE

Using an automated decision support tool to improve HIV prescribing: A feasibility study

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Abstract

Objectives: The selection of antiretroviral therapy (ART) regimens for people living with HIV is complex and dependent on individual and clinician-perceived risk factors and preferences. The British HIV Association (BHIVA) advocates cost-effective prescribing and shared decision-making between patients and clinicians. We evaluated the acceptability and potential impact of a prototype multi-patient automated decision support tool (DST) for improving individualized, safe, and cost-effective prescribing.

Methods: We surveyed people living with HIV and clinicians regarding treatment preferences and the acceptability of a DST. We developed a DST to interpret electronic patient record data, using 2022 BHIVA guidelines to identify optimal ART switch options. This was applied to patients prescribed ART between June 2022 and May 2023 in the local HIV service, and potential cost savings were calculated.

Results: Among people living with HIV, 86.7% (144/166) respondents were open to switching to more cost-effective ART. While 94% (15/16) of clinician respondents prioritized lower-cost treatments where possible, only 38% (6/16) reported knowing about ART costs.

Regimen switch options were identified for 274 of 503 people living with HIV meeting the inclusion criteria. Overall, potential cost savings of 28.4% of total ART spend (£26630.25 per month) were calculated if all possible switches to the most cost-effective option identified by the DST were made.

Conclusions: A DST based on BHIVA recommendations and using routinely collected data may be acceptable to patients, useful to clinicians, and could provide significant cost savings. A substantial proportion of people living with HIV in our cohort were open to considering changing their ART based on cost effectiveness.

KEYWORDS

antiretroviral, decision support tool, HIV

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INTRODUCTION

Decisions on antiretroviral therapy (ART) for people living with human immunodeficiency virus (HIV) are multifactorial and complex. Initiation and switching between regimens requires consideration of a number of elements including clinical suitability, availability of medications, and cost as well as a wide range of individual-specific factors including psychological considerations such as medication anxiety and adherence capability, and social determinants such as work schedules and lifestyle. The British HIV Association (BHIVA) guidelines emphasize the importance of cost-effective ART prescribing, recommending the use of ART within the lowest cost bands [1–4] where clinically appropriate. This reflects the growing need to balance high-quality individualized care with good financial governance and sustainability. Additionally, BHIVA advocates for a shared decision-making approach in ART prescribing, ensuring that treatment choices are made collaboratively between people living with HIV and HIV clinicians, a recommendation further supported by the NHS long-term plan [5].

The number of available ART regimens adds to the complexity of prescribing. Currently, there are over 40 ART regimens that can be routinely used in the United Kingdom [2], with 28 regimens that may be suitable in certain circumstances, and an additional four regimens that are currently listed as not routinely commissioned by the NHS [3]. A wide range of factors influence the relative benefits and potential drawbacks of each regimen, including individual needs, comorbidities, previous ART use and known viral resistance, side effects, drug–drug interactions, and biochemical factors such as renal function.

To support decision-making in these complex circumstances, BHIVA has published National ART algorithms to support the initiation, restarting, and switching of ART in people living with HIV [1] guiding evidence-based, cost-effective prescribing practices.

Despite the utility of these algorithms, their application to individual patients is time-consuming and labour-intensive, often requiring cross-referencing individual patient data with guideline information on a per-consultation basis. A publicly available ART decision support tool [6, 7] (DST) is available, but it requires individual patient entry, may be prone to human input error, and does not provide information on the cost-effectiveness of ART regimens in real time or at scale. This gap in the clinical workflow in HIV medication prescribing poses a significant challenge both to prescribers seeking the most appropriate and cost-effective ART regimens and to informed shared decision-making around

ART choices between people living with HIV and clinicians during time-limited consultations.

To address this, we sought to develop an automated, multi-patient DST (ART_switch1) which proactively applies current BHIVA guideline recommendations for clinical safety, efficacy, and tolerability alongside current cost-effectiveness data to a local patient cohort database within the security of the hospital computer system, leveraging existing electronic patient record (EPR) data to generate individualized ART recommendations. Where potential ART regimen switch options are identified by the ART_switch1 tool, this proactive approach would enable discussion between a dedicated ART pharmacist and people living with HIV prior to a routine scheduled consultation to allow for informed and efficient shared decision-making during the consultation itself.

Our focus was to develop a tool that enables greater shared decision-making around ART regimens while ensuring that treatment decisions are both clinically sound and as cost-effective as feasible, but we recognize the potential for such a tool to face resistance from end-users if it does not align well with user needs and preferences, particularly in regard to maintaining strict confidentiality. We therefore developed ART_switch1 to be a non-commercial tool, based on Microsoft Excel already installed on NHS Trust IT systems, and using only locally stored data. This study aims to determine if such an automated multi-patient DST would be acceptable to people living with HIV and clinicians, and its feasibility in optimizing ART prescribing in a cost-effective manner using existing EPR data.

METHODS

This project was registered as a quality improvement project at South Tees Hospitals NHS Foundation Trust (#625) and did not require further ethical approval. All analysis using individual identifiable information was performed only on NHS computers within the South Tees Trust IT network.

Separate digital surveys for clinicians and people living with HIV were developed using Microsoft Forms. A link to the people living with HIV survey, consisting of nine questions that could be answered on a mobile device, was sent by text message to all adult people living with HIV from the South Tees HIV service who had previously consented to text message contact. The survey aimed to explore several key areas, including current involvement in treatment decisions, preferences for clinical guidance versus autonomous choice, desire for information about treatment options and costs, and willingness to consider medication changes (for list of questions see Table S1).

The clinician survey was sent to all HIV, virology, and infectious disease consultants and specialist trainees in the region via email and/or text message. No identifiable information was collected from either survey. The survey aimed to establish the acceptability and potential value in using digital tools to aid prescribing (Table S2a,b). We did not record sexual preference or ethnicity as part of the survey due to privacy concerns and limitations of the groupings obscuring differing outcomes within and between groups.

To perform the ART switch analysis, standardized data elements were extracted from HIV and AIDS Reporting Service (HARS) forms exported from the local digital sexual health patient information system (Inform Health Limited, Skegness) using Microsoft Excel. HARS forms are completed routinely at HIV outpatient visits across the United Kingdom. The following data were extracted: Name, Date of Birth, NHS number, Responsible Clinician, HIV type, HIV Viral Load, CD4+ T-cell count, HLA-B*5701 status, AIDS-defining Illnesses, Concurrent Infection with Viral Hepatitis or Tuberculosis, Concurrent Care under Psychiatry, Current Pregnancy, Persistent Viraemia on ART, and Current Severe Unstable HIV-Associated End-Organ Disease (liver and renal disease secondary to advanced HIV). Data validation checks were performed to identify missing or inconsistent values and renal function data (eGFR), and any missing data was added manually.

All medications prescribed in the local HIV outpatient clinic between 01 June 2022 and 31 May 2023 were analyzed and matched to the validated HARS dataset. Current ART regimens were extracted from prescription data, with non-ART medications removed, and costed using data from the local outpatient pharmacy (obtained with permission) correct as of 01 June 2023. If multiple ART regimens were prescribed during the indicated period, only the most recent was included. This exported, validated, and matched cohort-level dataset was then analyzed as a single batch.

As the ART_switch1 tool is based on the BHIVA 2022 antiretroviral guidelines [4], its use is limited to the individuals the guideline applies to, namely adults living with HIV-1 infection. For the purposes of this study, individuals in situations where ART choices were likely already very limited, such as those with unstable disease or complex comorbidities, where algorithmically generated ART choices based on HARS data were deemed less likely to add value, were not included. Therefore, the inclusion criteria for this study were adults aged ≥ 18 years prescribed ART for HIV-1 infection in our local HIV treatment service in the United Kingdom between 01 June 2022 and 31 May 2023. The exclusion criteria were HIV-2 infection or co-infection, current severe unstable HIV-

associated end-organ disease (defined by HARS data as above), persistent viraemia on antiretroviral therapy, AIDS-defining illness, patient no longer under ongoing care at the HIV outpatient clinic, current haemodialysis, and current use of injectable ART.

ART regimen recommendations were derived by an algorithm based on the BHIVA 2022 antiretroviral therapy guidelines for adults, which created individual recommendations based on HARS data as described above and renal function (see Figure S1 for detailed algorithm description). Recommendations were divided into first-line regimens suitable for most patients, first-line regimens in certain circumstances, and regimens suitable for suppressed switch or maintenance, as defined in the BHIVA guidelines. Regimens containing medication not in the Trust formulary (in this case, doravirine) were excluded. Regimens were compared based on cost, constituent medication, and tablet burden.

Where analysis revealed that an individual ART switch to a BHIVA-recommended regimen was cost-effective, arbitrarily defined as potential medication cost savings greater than or equal to £50 per month, a structured report was generated including patient information, current ART regimen, and cost-effective switch options, with potential cost savings and tablet burden for each option. This structured report was designed for efficient review by the responsible consultant clinician, and to form the basis for discussion and shared decision-making during an outpatient HIV consultation, and automatically included information relevant to each option including tablet burden and appropriate warnings such as those relating to borderline renal function (Figure S2; for full example workflow including clinical implementation, see Figure S3).

RESULTS

To explore the opinions of people living with HIV on switching antiretroviral therapy, a nine-question survey was sent by automated text message to the 582 out of 591 (98.5%) people living with HIV under the care of the South Tees HIV service who had previously consented to text message contact; 56 of 582 (9.6%) of messages failed to deliver, with responses received to 174 of 526 (33.1%) of the remaining messages. In all, 167 completed questionnaires were received and analyzed further. Respondents were most commonly male (73.8%), aged over 50 years (61.1%), and had used ART for over 10 years (55.7%) (Table 1).

Just under half of respondents recall being given the option to select their current HIV treatment regimen (77/166 [46.4%]); however, the majority stated they would

prefer to follow their doctor's advice regarding their choice of treatment (131/166 [78.9%]). Most respondents would like to know, or may want to know, what treatment options are available to them (150/167 [89.8%]), as well as the cost of these treatments (127/167 [76.0%]) to the NHS. The side effect profile and number of tablets

TABLE 1 Demographics of the respondents to the patient survey.

	Patients (<i>n</i> = 167)
Male sex	123 (74.3%)
Age	
18–30 years	4 (2.4%)
31–40 years	23 (13.8%)
41–50 years	38 (22.8%)
51–60 years	59 (35.3%)
>60 years	43 (25.7%)
Time on ART	
<2 years	14 (8.4%)
2–5 years	21 (12.6%)
5–10 years	39 (23.4%)
>10 years	93 (55.7%)

required were considered by respondents to be the most important factors when choosing a medication. Notably, 144 of 166 (86.7%) appeared to be open to changing to a lower-cost treatment regimen (Figure 1a), and most considered the cost of the medication to the NHS to be more important than factors such as tablet size (Figure 1b).

We next explored the attitudes of clinicians with a clinician-specific survey, sent out via email and messaging groups, to which 34% (16/47) of ART-prescribing clinicians in the region responded (Table 2). When asked about their prescribing considerations, 94% (15/16) of respondents stated that they choose lower-cost treatments over higher-cost ones where possible (Figure 2).

TABLE 2 Demographics of the respondents to the clinician survey.

	Doctors (<i>n</i> = 16)
Specialty	
Infectious diseases	14 (87.5%)
Sexual health	2 (12.5%)
Grade	
Consultant	10 (62.5%)
Registrar	6 (37.5%)

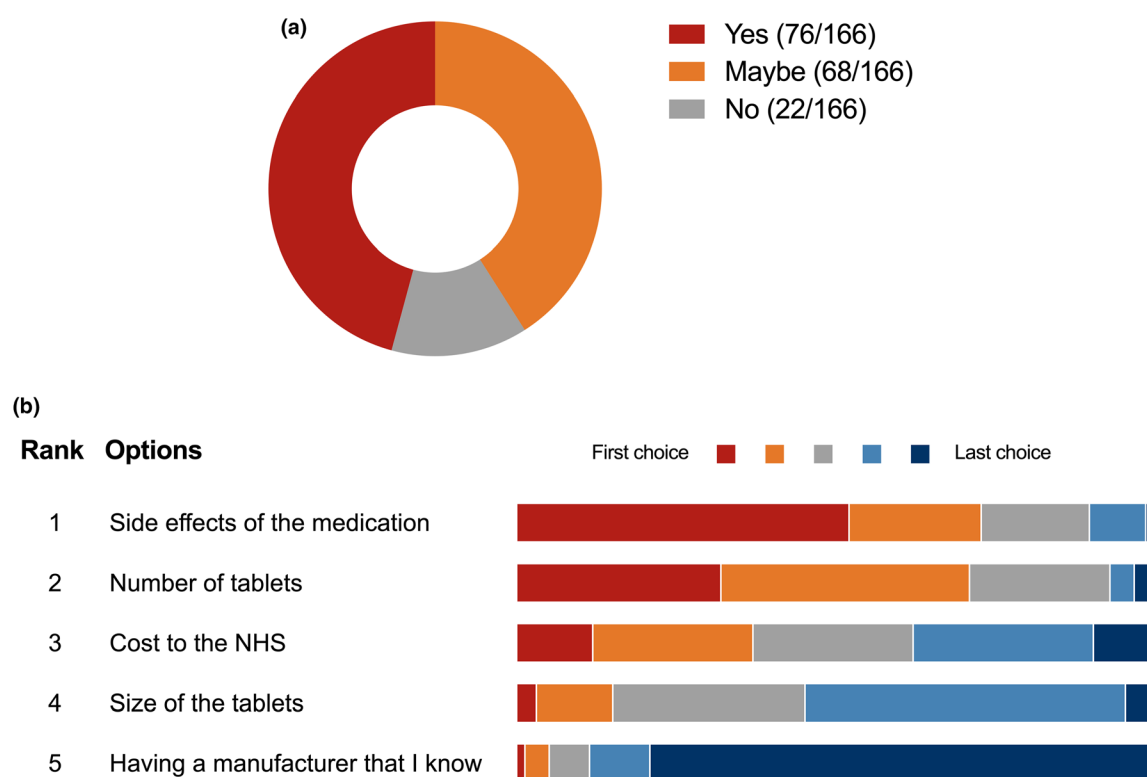


FIGURE 1 (a) The proportion of people living with HIV who would consider switching to a lower-cost antiretroviral therapy (ART) regimen. (b) The relative importance to people living with HIV of specified characteristics of an ART regimen. Rank 1 corresponds to the overall most important characteristic, and rank 5 to the overall least important characteristic.

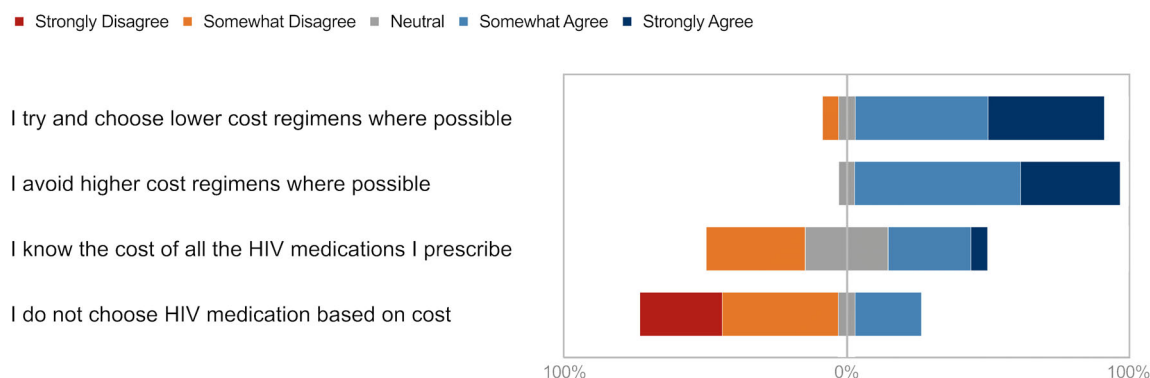


FIGURE 2 Cost-related prescribing considerations among surveyed antiretroviral therapy (ART)-prescribing clinicians.

However, only 38% (6/16) agreed that they know the cost of the HIV medications that they prescribe. A support tool that identifies BHIVA recommendations and calculates the cost of treatment regimens would be considered ‘extremely’ or ‘somewhat’ useful by up to 88.2% of respondents.

Clinicians were provided with four common hypothetical clinical scenarios of people living with HIV of different ages, comorbidities, and antiviral resistance profiles (Table S2b) and asked to recommend ART (using free text) for each scenario. A median of six different regimens was suggested per scenario. For example, in a young, otherwise healthy male with newly diagnosed HIV, a CD4 count of 400 and an HIV viral load of 50 000, where HLA-B*5701 was negative, six different ART regimens were proposed including four different ART classes, with tablet burdens ranging from one to three tablets daily (Table S2b).

Having established that the people living with HIV in our cohort were open to considering lower-cost ART regimens, and that clinicians in the region both considered cost important and displayed heterogeneity in prescribing suggestions, we sought to establish whether current ART prescribed to people living with HIV in our cohort could be theoretically switched to or within BHIVA-recommended ART while representing cost savings.

Between 01 June 2022 and 31 May 2023, 2459 prescriptions to 585 individuals in the local HIV outpatient department were analyzed; 522 individuals were able to be matched to available HARS data and were included in further analyses; 19 individuals were further excluded: six who were currently not engaged in care at the Trust, five with AIDS-defining illnesses or severe unstable HIV-associated end-organ disease, four with complex medical backgrounds necessitating non-standard ART regimens (including intermittent haemodialysis), two patients receiving injectable rather than oral ART, one patient

TABLE 3 Demographics of individuals included in switch analysis, $n = 503$.

	Median [IQR] (range)
Age, years	48 [38–57] (20–85)
<i>n</i> (%)	
Gender	
Female	172 (34.2)
Male	331 (65.8)
Ethnicity	
White British/White Other	239 (47.5)
Black/Black British/Black Other	114 (22.7)
Other ethnicities	27 (5.4)
Not documented	123 (24.5)
Comorbidities	
Current hepatitis B virus infection	5 (1.0)
Current treatment for tuberculosis	0 (0)
Currently under care of psychiatry	1 (0.2)
Clinical parameters	
HIV-1 RNA < 50 copies/mL	474 (94.2)
HIV-1 RNA 50–199 copies/mL	16 (3.2)
HIV-1 RNA ≥ 200 copies/mL	13 (2.6)
CD4+ T-cell count ≥ 350 cells/mm ³	455 (90.5)
CD4+ T-cell count < 350 cells/mm ³	48 (9.5)
eGFR ≥ 90	276 (54.9)
eGFR 60–89	191 (38.0)
eGFR 45–59	29 (5.8)
eGFR 30–44	6 (1.2)
eGFR 15–29	1 (0.2)
eGFR < 15	0 (0.0)

Abbreviations: eGFR, estimated glomerular filtration rate; IQR, inter-quartile range.

TABLE 4 Cost savings attained by a simulated switch to antiretroviral therapy (ART) regimens meeting a cost-effectiveness threshold of £50 per month savings.

ART regimen	Current prescription (n)	Primary switch recommendation (n)	All cost-effective options (n)	Final distribution after switch (n)	Net change (n)
TDF-emtricitabine-efavirenz	91	0	0	91	0
Abacavir-lamivudine-dolutegravir	78	0	2	1	-77
Dolutegravir-lamivudine	60	26	121	35	-25
Abacavir-lamivudine + efavirenz	41	0	0	41	0
TDF-emtricitabine + raltegravir	34	144	152	178	144
TDF-emtricitabine + rilpivirine	22	0	144	22	0
TAF-emtricitabine-elvitegravir-cobicistat	15	0	0	0	-15
Abacavir-lamivudine + raltegravir	12	4	79	16	4
TDF-emtricitabine + dolutegravir	10	0	83	1	-9
TDF-emtricitabine + darunavir + ritonavir	9	8	8	17	8
TDF-emtricitabine-rilpivirine	6	0	136	0	-6
TAF-emtricitabine-rilpivirine	6	0	0	0	-6
TAF-emtricitabine-bictegravir	1	2	30	3	2
Others	118	0	254	98	-20
Monthly total cost	£ 93623.28	N/A	N/A	£ 69614.28	-£24009.00

Note: Primary switch recommendation represents the frequency with which each regimen was identified as the most cost-effective switch option compared with other regimens. All cost-effective options represent the frequency with which each regimen appeared among the top ten cost-effective alternatives. Abbreviations: N/A, not applicable; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

with HIV-2 co-infection, and one for whom no CD4 count was available.

Of the 503 patients who met the inclusion criteria for switch analysis, the median age was 48 years, and 172 of 503 (34.2%) were female. In all, 474 of 503 (94.2%) met the BHIVA criteria for virological suppression with an HIV-1 viral load under 50 copies/mL, and 455 of 503 (90.5%) had a CD4+ T-cell count greater than or equal to 350 cells/mm³ (Table 3).

Forty-seven unique ART regimens were identified, with the most common being TDF (tenofovir disoproxil)-emtricitabine-efavirenz (91 individuals), abacavir-lamivudine-dolutegravir (78 individuals) and dolutegravir-lamivudine (60 individuals [Table 4]). The current overall medication cost was £93623.28 per month, a mean of £186.13 per person per month.

We devised an algorithm based on the 2022 BHIVA guidelines (Figure S1), which identified suitable cost-effective switch options to BHIVA-recommended therapy in 274 of 503 (54.5%) patients. Overall potential cost savings of £26630.25 (28.4%) per month were calculated if all 274 possible switches to the most cost-effective option identified by this algorithm were made. On closer examination however, £24009.00/£266630.25 (90.2%) of this saving came from 184 of 274 (67.2%) individuals when a minimum saving threshold of £50 per switch was implemented, and these individuals were included in further analyses.

Up to 10 suitable switch options were generated per individual, with a median (IQR) of 4.5 (3–8) ART switch options per individual found to be cost-effective relative to current ART. Analyzing the most cost-effective option for each individual, the most frequent option was TDF-

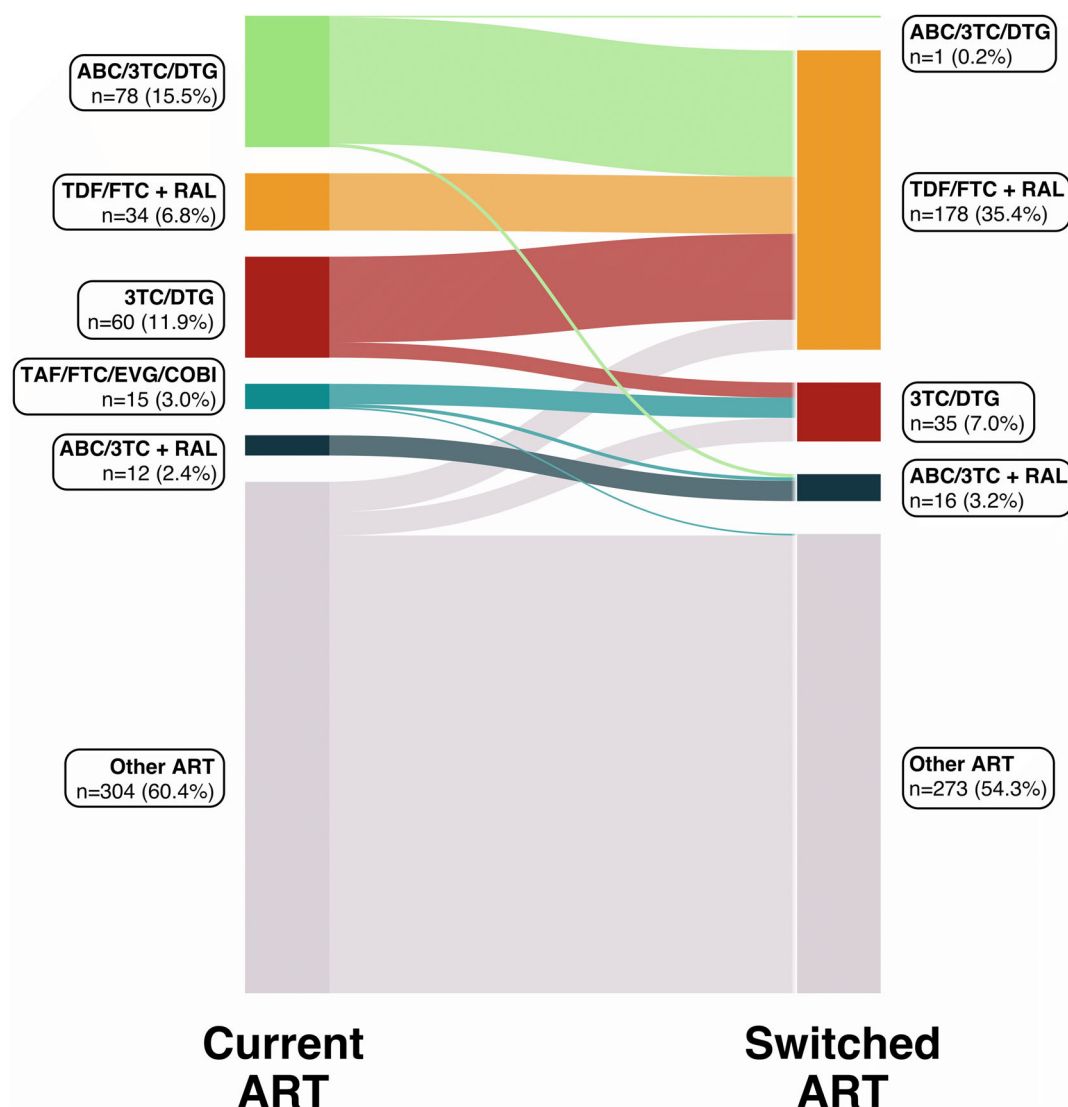


FIGURE 3 Changes in antiretroviral therapy (ART) regimens after simulated switching. The width of flows is proportionate to the number of switches between regimens. Selected ART is shown for clarity. 3TC, lamivudine; ABC, abacavir; COBI, cobicistat; DTG, dolutegravir; EVG, elvitegravir; FTC, emtricitabine; RAL, raltegravir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

emtricitabine + raltegravir (Figure 3). The algorithm could not find cost-effective alternatives for some regimens, including those containing efavirenz. Although ART containing rilpivirine was not the most cost-effective switch option for any individual in our analysis, it was frequently cost-effective relative to current ART and therefore featured within the top 10 switch options for 173 of the 184 individuals (Table 4).

Given that ART tablet burden was considered one of the most important factors for people living with HIV surveyed in our cohort, we examined the tablet burden of currently prescribed ART and of the proposed switched regimens. Within current prescriptions, we found that 157 of 184 participants (85.3%) were currently on a single-tablet regimen, while our cost-effective simulated switch regimens contained options with the same or

fewer tablets than current ART for 174 of the 184 (94.6%) individuals, with single-tablet options for 171 (92.9%) individuals in our cohort.

DISCUSSION AND CONCLUSIONS

Our findings suggest that a DST such as ART_switch1 could be an acceptable and valuable aid to prescribing antiretroviral therapy to people living with HIV, with the potential for increased shared decision-making, cost-optimization, and guideline-based prescribing.

A key finding of this study is the openness of the majority (86.7%) of people living with HIV respondents to consider switching to a more cost-effective ART regimen in this survey, indicating a strong potential for

shared decision-making taking cost into account alongside other factors such as tablet burden and potential side effects. The survey also demonstrated that while most people living with HIV prefer to be informed of their treatment options, many were happy to defer treatment decisions to their clinician. Without further information, it is not possible to further analyze the rationale behind this preference, but it may reflect the lack of decision tools available that represent the patient-inclusive perspective when selecting ART regimens. Other individual factors not collected by the survey such as depression [8, 9], health literacy [8, 10], and self-efficacy [8], may also impact on a person's ability to engage in shared decision-making processes when selecting ART regimens. Supporting people living with HIV to be included in treatment decisions is crucial, as this is associated with improved adherence to ART compared with people living with HIV where prescribing decisions were made independently [8, 11], and thus is associated with better outcomes. Access to the potential options from the ART_switch1 application ahead of a consultation would help empower this decision-making.

The perspectives of people living with HIV regarding changes to treatment regimen for reasons other than adherence and viral suppression have not been widely documented in the UK [12]. Other countries with universal healthcare have also illustrated that most people living with HIV are open to the idea of changing ART regimen for the purpose of cost saving to the service [12–15], but similarly highlighted the concern of experiencing side effects [13, 14]. As such, it is important to people living with HIV that when discussing treatment options, the cost of medication should also be discussed as well as the potential side effects of alternative regimens, in order for people living with HIV to be supported to participate in shared decision-making in an informed manner.

Nearly all clinician respondents to our survey stated that they would choose to prescribe lower-cost ART regimens where possible. Amongst other healthcare professionals in high-income countries, between 73% and 100% of those surveyed would agree in all or some cases to offer either generic antiretrovirals or a de-simplified regimen in order to save costs to a publicly funded healthcare system [12, 16–18]. There is particular motivation to prescribe cheaper alternatives if the money saved would be reinvested in HIV care [17, 18]. Willingness to prescribe these cost-saving regimens was reduced if this would lead to increased tablet burden or dosing frequency, the main concern being the risk of non-adherence [12, 16–18]. Our survey also identified a lack of clarity about the cost of HIV medications amongst clinicians, and the majority agreed that a tool to calculate the cost of various treatment regimens would be useful. There are few studies on

physician awareness of ART costs; however, one study found that more information on the effectiveness and safety (57.4%) and pricing of generic ART (72.8%) would be considered useful [17]. Overall, data suggest that there is motivation amongst medical professionals to prescribe cost-effective treatments, provided that this would not lead to reduced treatment adherence because of increased tablet burden or fear of adverse effects.

Our switch analysis demonstrated that data that are already routinely collected for the care of people living with HIV could be used to suggest suitable switch options, with the potential for savings of 28.4% of medication costs if the most cost-effective ART options identified were implemented in our cohort. Given the current climate of rising healthcare costs, balancing high-quality care with financial responsibility is increasingly necessary, while maintaining clinical outcomes and satisfaction for people living with HIV. The ART switch options proposed by our DST were guided by BHIVA's evidence-based recommendations for safety, efficacy, and tolerability. In this study, the vast majority of people living with HIV eligible for a switch (94.6%) could be offered a regimen with the same or fewer tablets while remaining cost-effective, addressing one of the main patient concerns about tablet burden.

While other antiretroviral decision support tools such as HIV-ASSIST can offer detailed clinical guidelines for individual prescribing situations, ART_switch1 was developed to address the specific requirements of NHS prescribing workflows. ART_switch1 deliberately focuses on readily available and robust electronic health record data to support clinical decision-making, while recognizing that final prescribing decisions are nuanced, personal, and require clinician expertise and knowledge of individual circumstances, comorbidities, viral resistance data, ART history, and any previous therapeutic interruptions. The implementation of ART_switch1 within Microsoft Excel, a widely available platform within healthcare systems, enables secure local processing of patient data and cohort-scale analysis without the need for external data transmission. Although initially designed for NHS workflows, relatively minor adaptations to the data processing and algorithm steps could enable its adaptation for use in other healthcare settings.

The high proportion of raltegravir-containing regimens recommended as the most cost-effective option by the algorithm highlights both the strengths and limitations of an automated approach. While these regimens represent cost-effective switch options aligned with current BHIVA guidelines, their lower genetic barrier to resistance and tablet burden may make them less suitable for individuals with medication concordance challenges or complex lifestyles, further emphasizing the intended

role of ART_switch1 as a prescribing support tool rather than a replacement for clinical expertise.

We acknowledge further limitations of this feasibility study. The survey of people living with HIV achieved a response rate of only 33.1%, and respondents were required to engage with digital tools, introducing potential selection bias. Language barriers may also have led to the underrepresentation of those with English as a second language. While this DST was developed non-commercially, and deployed only within a secure environment on NHS computers, concerns about data privacy and the integration of such tools into clinical workflows would need to be explored and addressed prior to wider implementation. Additionally, only a limited proportion of patients identified by a DST would likely consider switching, particularly if the tablet burden were to increase or there were concerns about side effects.

In conclusion, our study demonstrates that a DST based on BHIVA recommendations would be considered useful by our cohort of infection specialists and may be acceptable to patients. In our cohort, a significant proportion of people living with HIV appear to be open to a discussion about switching their ART due to cost savings. This tool has the potential to improve the cost-effectiveness of prescribing while maintaining guideline-informed practice. Further work to implement a pilot study to assess the real-world impact of such a DST is being planned.

AUTHOR CONTRIBUTIONS

A. T. I. and C. L. conceived the study. A. T. I., J. W. and H. D. collected data. A. T. I. performed the main analysis. All authors drafted, revised and approved the manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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