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Uptake Success and Cost Savings from Switching to a Two-Drug Antiretroviral Regimen

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Abstract

The emergence of dual therapy for antiretroviral (ARV)-experienced persons living with HIV (PWH) offers the opportunity to reduce lifetime exposure to unnecessary ARV drugs while maintaining viral suppression and reducing the cost of care. Our objective, using retrospective analysis of a quality care initiative, was to examine in routine clinical practice the clinical impact of switching PWH stable on a three-drug to a two-drug single-tablet formulation (STF) ARV regimen. We also examined the cost implications of this STF adjustment. Between January 1, 2020 and January 1, 2021 eligible patients (i.e., virally suppressed, no active hepatitis B infection, no documented nucleoside reverse transcriptase inhibitors/integrase strand transfer inhibitor resistance) were offered, on a convenience basis and as part of routine care, the opportunity to adjust their current three-drug STF to a two-drug STF (dolutegarvair/lamivudine). The acceptance, clinical efficacy, safety, tolerability, and cost of treatment were measured for patients who switched in 2020. Of 989 eligible PWH, 408 were approached and 391 (39.5%) switched to two-drug regimen; 99% remained on the two-drug STF at year's end (median 240 days follow-up). Only 2/391 patients who switched lost viral control. The total ARV drug cost for all 989 patients decreased by 10.3% generating an actual savings of $1,596,666 among patients approached and switched in 2020. Patient interest and uptake in switching to two-drug STF was substantial and resulted in few discontinuations for any reason. It provided significant and immediate cost savings within the first year. Our results bring clarity to discussions on whether using two-drug regimens would be practical and acceptable in nonclinical trial settings.

Keywords: HIV/AIDS, antiretroviral therapy, dual therapy, cost of care, Canada

Introduction

In the mid 1990s, it was reported that long-term successful suppression of HIV replication could be achieved by the concurrent use of a combination of three antiretroviral (ARV) drugs.[1,2] Such regimens were called combination ARV therapy or highly active ARV therapy.[3–6] However, these early regimens entailed taking a high pill burden, inconvenient dosing frequency and food requirements, significant intolerances and toxicities, as well as generating substantial costs to health care. To address these challenges, studies were soon undertaken to see if equivalent suppression of HIV replication could be achieved by taking only two of the newer drugs.[2,7,8] When such approaches were found to be unsuccessful in controlling HIV replication, three-drug regimens became, for the next two decades, the guideline-recommended standard for almost all ARV regimens.[9]

Recent shifts in many guidelines toward initiating lifelong ARV therapy soon after HIV diagnosis have exacerbated lingering concerns about the safety and toxicity resulting from the predictable huge lifetime cumulative exposure to ARVs.[10,11] These concerns have led to a reevaluation of the established dogma that an ARV regimen, even with the latest agents needs to contain three drugs.[12–14] The possible removal of a third agent, usually a reverse transcriptase inhibitor, could reduce potential and unnecessary toxicities

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from third agents such as tenofovir disoproxil fumarate and abacavir.[15–18] Several dual therapy regimens, usually based on new second generation integrase strand transfer inhibitors (INSTIs), have recently been licensed as being safe and effective for HIV treatment and are included as preferred regimens in most guidelines for both initial therapy and in some switch situations.[19,20] Dolutegravir (an INSTI) has been proposed as a good candidate for use in a two-drug regimen as it has a high genetic barrier to resistance, requires no pharmacological boosting, and is given once daily.[21] While some dual therapies using two drugs still under patent protection generate little cost saving, others containing only one patented agent may generate significant cost savings.[22] As such, these dual therapies may offer less drug exposure and potential toxicity, equivalent antiviral potency and should be, over a lifetime, far less expensive to payer. With increasing number of persons living with HIV (PWH; persons with HIV) on ART, such cost considerations may become important to HIV care programs to support their financial sustainability.[23–25]

The listing in most guidelines of a single pill coformulation of two ARV drugs dolutegravir/lamivudine (DTG/3TC) as a preferred regimen, offers the opportunity to reduce lifetime exposure to unnecessary ARV drugs. To date, most reports on two-drug regimens use have been from clinical trials or pilot studies[8,18,26–36] although more recent studies are beginning to document that in some situation in resource-rich nations a two-drug ARV regimen is becoming a regimen of choice with DTG/3TC a popular option.[37]

Beginning January 1, 2020 following its listing on the Province Wide high-cost drug plan, Dovato® became available for physicians to prescribe at the Southern Alberta HIV Clinic (SAC), Calgary, Canada. PWH stable on ART followed at SAC with no listed contraindications, who were on a modern three-drug single-tablet formulation (STF) regimen, were given the opportunity to move to a two-drug STF regimen to reduce unnecessary ARV drug exposure while still receiving the convenience of a brand name STF.

We wished to examine and report on in a routine clinical care setting, the interest, acceptability, tolerance, safety, and efficacy in maintaining viral control of PWH who were on one of four three-drug STF regimens and were offered a switch to a two-drug regimen (i.e., dolutegravir/lamivudine). We also wished to explore the cost implications of this ARV adjustment.

Methods

Beginning on January 1, 2020, patients followed at the SAC who were virally suppressed (VL <50 copies/mL), with no evidence of active hepatitis B infection (HBSAg negative or HBV DNA negative), and with no documented nucleoside reverse transcriptase inhibitors (NRTI) and INSTI resistance, were offered, as part of routine care, the opportunity to switch from their current modern three-drug STF to a two-drug STF (dolutegravir/lamivudine). Recruitment occurred during routine care using a convenience cohort model. Due to limitations of clinic contacts during the COVID-19 pandemic, not every eligible patient was approached. Phone calls rather than face-to-face visits were usually used by physicians and pharmacists during this time for PWH routinely followed at the clinic. Eligible patients were approached if the physician or pharmacist felt that the health status of PWH (e.g., virally suppressed, adherent to ART) was stable and that they could benefit from the switch. Offering switching ART was a clinical decision and not part of a research protocol. The removal of an unnecessary drug, the preferred first line status of the dual therapy STF as well as for some a possible reduction in pill size or reduced risk of inadvertent drug/drug interactions were discussed by the patient's physician or SAC pharmacists with the PWH during routine appointments and as time allowed. Patients were able to accept, defer their decision until further information had been gathered, or decline the switch for any reason; patients could return to their original STF regimen at any time for any reason. As SAC provides, under universal health care, exclusive and free HIV care, including the cost all ARV drugs to all PWH in our area, there was neither a financial or monetary incentive for the patient to switch, nor did any clinicians or pharmacists benefit financially from offering the switch.

Although a minority of patients on other regimens (STF or not) were switched to DTG/3TC in 2020, only PWH who met the inclusion criteria and who were on one of four modern STF ART regimens (i.e., Triumeq®, Odefsey®, Genvoya®, or Biktarvy®) were included in this study. Genvoya was considered as a three-drug regimen as cobicistat has no antiviral properties itself. These four STFs were chosen as they did not require a change in pill burden and, as of January 1, 2020, they accounted for $\sim$2/3 of the clinic's total ARV budget. We did not include, in this study, those who had previously desimplified from a STF or patients taking the older STF formulation of efavirenz/tenofovir/emtricitabine.[25] Although not a formal research study, eligible patients who switched to a two-drug STF regimen during 2020 were compared to patients who remained on their three-drug STF regimen for general comparative purposes.

Clinical data, including most recent CD4 count, viral load (<50 copies/mL was defined as viral suppression), and current ART regimen of eligible active patients on January 1, 2020 and January 1, 2021, were collected. Patients were followed until they moved, died, or until the study's end date (January 1, 2021).The date of any switch to a two-drug STF regimen was noted. For all patients in the study, both the continuity of and adjustments to ART (i.e., discontinued or switched regimens) were determined. Any comments made by PWH who switched to a two-drug STF regarding satisfaction or dissatisfaction were noted. Maintenance of viral suppression and ongoing use on a two-drug regimen were compared to patients who remained on their original STF.

The list price of the four ARV STF regimens was utilized for cost comparisons. The cost of ARV for the 12 months before January 1, 2020 (i.e., January 1, 2019 to December 31, 2019) was collected for all eligible patients and compared to costs for 2020. Costs are obtained directly from SAC's database and represent costs from the payers (Alberta Health) perspective in 2020 Cdn$.

This study was undertaken as quality care initiative. All PWH are automatically enrolled in the Southern Alberta Cohort, an ongoing longitudinal cohort study, and sign an informed consent allowing for the use of their data in research approved by the University of Calgary Conjoint Health Research Ethics Board (REB15-0929_REN7).

Standard descriptive statistics [e.g., frequencies (n) and percentages (%), sum, medians, IQR (interquartile ranges, means)] are used to summarize characteristics of our

outcomes of interest, both for the cohort overall and stratified by our specific population subgroups (i.e., patients remaining on their three-drug regimen or switching to a two-drug regimen during 2020).

Results

On January 1, 2020, 989 PWH who were being followed at SAC met the above study criteria. Of these, 63% were on Triumeq, 16% on Genvoya, 13% on Odefsey, and 8% on Biktarvy. By January 1, 2021, as the convenience study design allowed, 391 of the 408 patients approached had accepted, during an appointment, the switch to Dovato (349 from Triumeq, 36 from Genvoya, 5 from Odefsey, and 1 from Biktarvy). Most of the patients' concerns focused on whether two drugs were good enough to keep viral loads suppressed. Such concerns were discussed by the pharmacist or physician referring to clinical trial data and guidelines before the patient was asked to finally accept, decline, or defer the switch.

We acknowledge this was a convenience sample study, (recognizing not all eligible patients could be approached during the year and offered the ART adjustment). When compared to those not approached or declining switching, those who switched to a two-drug regimen were most likely male (79% vs. 68%), older (50 vs. 46 years), Caucasian (55% vs. 44%), and men having sex with men with HIV risk factor (52% vs. 40%; all $p < 0.05$; Table 1). There was no difference in CD4 count on January 1, 2020 between patients who switched versus patients who did not switch (median = 559/mm^3 vs. 548/mm^3), while time since HIV diagnosis in those electing to switch was on average 12 months longer (144 vs. 136, respectively; $p < 0.05$). By January 1, 2021, 99% of patients who switched to a two-drug STF remained in care compared to 93% of patients not switching ($p < 0.01$, Table 2). Only one of the patients who switched to two-drug regimen had left care and one had died compared to 37 (6.2%) and five (0.8%) of patients in the nonswitch group. All the six patients who died were due to non-HIV-related causes.

During 2020, 98.8% of the 391 eligible patients switching to the two-drug regimen (dolutegravir/lamivudine) from one of the four STF remained on their switch regimen at year end [median—240 days (IQR 161–302; range, 9–361 days)], while 3 (0.7%) switched to another ARV regimen and 1 discontinued ART (Table 2). Few patients switching to a two-drug regimen reported any side effects. Eighty-seven percent of patients switching to DTG/3TC came from DTG/3TC/Abacavir. As both combination pills were made by the same manufacturer, as expected, we did not see in these patients that removing one of the drugs led to any new side effects. Anecdotally, a handful felt that they felt better on the two-drug STF. In the remaining 13% of patients few side effects were reported reflecting a well-tolerated regimen. One patient switched off the two-drug regimen due to

Table 1. Sociodemographic and Clinical Characteristics of Eligible Patients Followed at the Southern Alberta Clinic, Calgary, Canada, as of January 1, 2020

	Total	*Switched to DTG/3TC*[a]	*Remained on STF*[b]	
N (%)	989	391 (39.5)	598 (60.5)	*p*
Gender				
Male (*N*; %)	721 (72.9)	312 (79.8)	409 (68.4)	0.008
Female	268 (27.1)	79 (20.2)	189 (31.6)	
Age (years) as of January 1, 2020				
Median	48	50	46	0.021
IQR	[40–57]	[41–58]	[39–55]	
Self-reported ethnicity				
Caucasian	478 (48.3)	216 (55.2)	262 (43.8)	0.0002
Non-Caucasian	473 (47.8)	158 (40.4)	315 (52.7)	
Not reported	38 (3.8)	17 (4.3)	21 (3.5)	
Most likely HIV exposure				
MSM	442 (44.7)	203 (51.9)	239 (40.0)	0.0008
Heterosexual	446 (45.1)	163 (41.7)	283 (47.3)	
PWID	66 (6.7)	17 (4.3)	49 (8.2)	
Other	20 (2.0)	3 (0.8)	17 (2.8)	
Not reported	15 (1.5)	5 (1.3)	10 (1.7)	
CD4 count (/mm^3) as of January 1, 2020				
Median	551	559	548	0.946
IQR	[392–760]	[417–787]	[380–749]	
Time (in months) since HIV diagnosis as of January 1, 2020				
Median	143	144	136	0.001
IQR	[72–204]	[70–200]	[72–204]	

Eligible patients include stable patients who were virally suppressed (VL <200c/mL), with no evidence of active hepatitis B infection (HBSAg negative or HBV DNA negative), and with no documented NRTI and INSTI resistance.

Heterosexual: women having sex with men.

[a]DTG/3TC—Dovato®.

[b]Triumeq®, Genvoya®, Odefsey®, or Biktarvy®.

IQR, interquartile range; INSTI, integrase strand transfer inhibitor; MSM, men having sex with men; NRTI, nucleoside reverse transcriptase inhibitors; PWID, persons who inject drugs; STF, single-tablet formulation.

Table 2. Status and Clinical Outcomes of All Eligible Patients Followed at the Southern Alberta Clinic, Calgary, Canada, on January 1, 2021 by Antiretroviral Use

	Total	*Switched to DTG/3TC*[a]	*Remained on original STF*	p
N (%)	989	391 (39.5)	598 (60.5)	
Status[b] at January 1, 2021				
Remained active	944 (95.4)	388 (99.3)	556 (93.0)	0.0001
Inactive	38 (3.9)	1 (0.2)	37 (6.2)	
Died	7 (0.7)	2 (0.5)	5 (0.8)	
ART status for patients active on January 1, 2021				
N	944	388	556	
Remained on ART	874 (92.6)	384 (98.9)	490 (88.1)	0.0001
Switched to new ART	111 (11.8)	3 (0.7)	108 (19.4)	
Discontinued ART	5 (0.5)	1 (0.2)	4 (0.7)	
Viral suppression for patients active on January 1, 2021 (<400c/mL)				
Yes	930 (98.5)	386 (99.5)	544 (97.8)	0.039
No	14 (1.5)	2 (0.5)	12 (2.2)	
CD4 count as of January 1, 2021				
Median (mm^3)	572	581	564	0.823
IQR	[412–750]	[426–751]	[397–759]	

Eligible patients as of January 1, 2020 include stable patients who were virally suppressed (VL <200c/mL), with no evidence of active hepatitis B infection (HBSAg negative or HBV DNA negative), and with no documented NRTI and INSTI resistance.

[a]DTG/3TC—-Dovato.

[b]Active defined as ≥1 clinic visit in the prior 4 months; Moved defined as relocating out of the region; LTFU (lost to follow-up) defined as no clinical contact for 12 consecutive months; Died from any cause.

gastrointestinal upsets and another due to weight gain. One patient was concerned about the long-term metabolic side effects of INSTIs and switched from Dovato to another newly listed three-drug STF Delstrigo®, which had become available during the year. Another patient had Dovato discontinued due to suspected low-level viral failure (genotypic resistance testing failed to document any mutations to either lamivudine or dolutegravir). By comparison, 108 (19%) of eligible patients who were not approached changed their STF to another ARV regimen (i.e., non-two-drug regimens) and 4 (0.7%) discontinued ART; 85 switched to another ART to simplify their regimen, 14 due to side effects, and 9 due to patient decision or new adherence concerns.

At year's end, the median CD4 had increased in both groups to 581/mm^3 and 564/mm^3, respectively, but the difference remained not significant. Only 2 patients (0.5%) who switched to the DTG/3TC had an unsuppressed viral load test after initiation compared to 12 patients (2.2%; $p < 0.05$) of patients remaining on their original STF (Table 2). There were no new AIDS events in either group.

The total cost in Cdn 2020$ (based on standard list price of ARV drugs in 2019) for the 989 eligible patients on one of

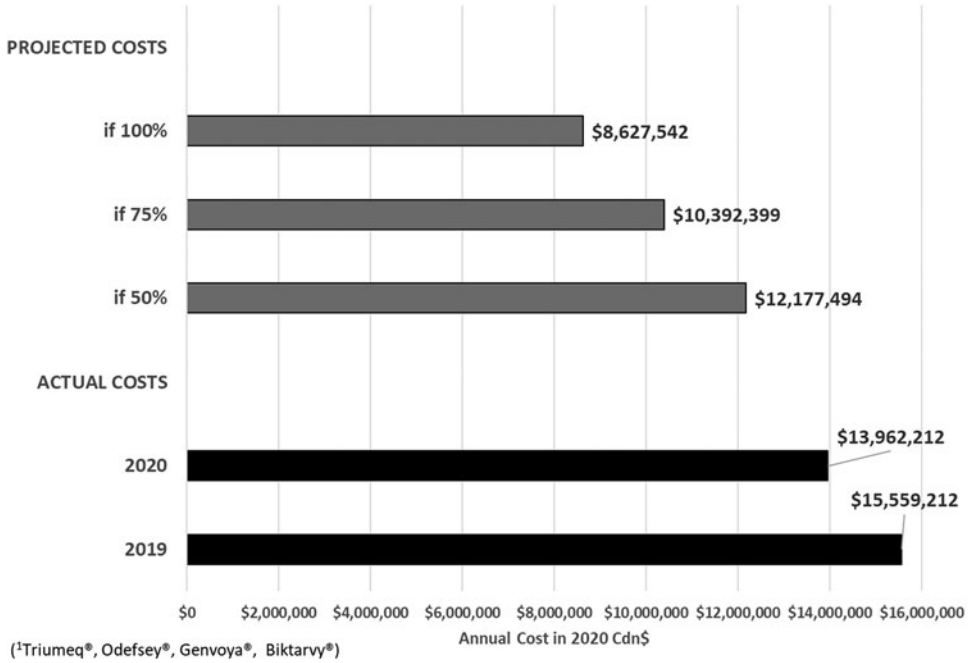

FIG. 1. Actual and Projected cost comparisons of eligible patients ($N = 989$) on three-drug regimen STF1 on December 31, 2019 who switched to a two-drug regimen STF in 2020 at the Southern Alberta Clinic, Calgary, Canada. Costs in 2020 Cdn$. STF, single-tablet formulation.

the four modern STFs was $15,559,212. During 2020, the total ARV cost for all of these eligible 989 patients had decreased 10.3% (with only 39% being eligible for the switch, approached and then successfully switching), generating a savings of $1,596,666 to the total 2020 budget. Cost differences were calculated for patients who had switched to the two-drug STF (DTG/3TC; Fig. 1). The total ART costs of 391 patients who were approached and switched therapy as per study generated an immediate 29% savings during 2020 from the difference between the cost of their past and new ARV regimen. The actual cost savings in 2020, reflecting the ongoing accrual of switch patients during year is shown in Fig. 1. As this was a convenience sample and not all eligible patients could be or were approached, we estimated cost savings if 50%, 75%, and 100% of eligible patients could be approached, agreed to switch, and then remained on therapy for the next 12 months. The projected savings (all else being equal) were estimated to be $3,525,916, $5,259,616, and $9,227,112, respectively (Fig. 1).

Discussion

We found that in our clinic population, a switch from one of four widely used STFs (containing three agents) to a new two-drug STF (DTG/3TC) regimen was acceptable to most eligible patients approached. Despite slight differences (e.g., Triumeq: 22 mm/Dovato: 19 mm/Genvoya: 19 mm/Biktarvy 15 mm/Odefsey: 15 mm tablet length), pill size was not noted by any patient to be a factor before or after in the decision process or tolerance of any switch. Reduced exposure to unnecessary drugs resonated with almost all patients approached. The switch was self-reported to be well tolerated by patients and achieved ongoing excellent viral suppression and stable immunity (CD4 counts) in routine clinical practice supporting the clinical trial evidence that led to the switch option being included in guidelines. We found very few subsequent discontinuations of two-drug regimen for any reason.

Within our region and under universal health care, there were no financial or monetary considerations motivating any patient to switch regimen for lower prices. There was also no financial or other motivation, beyond optimizing care delivery, to the physicians or pharmacists to offer switching. The payer (Alberta Health) plays no role beyond ARV listing in ARV selection. Over the course of the year, the incremental cost savings to the provincial ARV budget were significant. Projections of further savings based on a higher proportion of eligible and stable patients switching from modern three-drug STF to lower costing two-drug regimen are substantial.[38] Other studies have discussed similar savings on switching to regimens with fewer ARV drugs.[18,24,39] In a US modeling study, Girouard and colleagues[22] projected savings of >3 billion US dollars over 5 years if only 25% of currently suppressed patients (who have never experienced virologic failure) were switched to DTG/3TC. These real and potential savings will likely attract increasing and serious consideration from payers especially if clinical efficacy and enhanced safety can be maintained at reduced costs.

This study has several limitations. First, there is a potential selection bias of approaching patients with stable health, stable on ART, and attending clinic visits on a routine basis. These patients were already highly adherent in most cases and, hence, comparisons of clinical outcomes would most likely reflect more favorable in this group. The slightly higher ''fail rate'' for those remaining on their three-drug STF when compared to those approaches to switch to a two-drug STF suggests that there may have been a small but measurable subconscious selection bias in our convenience sample study design (despite all being successfully suppressed at January 1, 2020). Second, as we examined efficacy, safety, and costs for less than 12 months of our follow-up is relatively short, we cannot predict with certainty beyond that time frame. This study is ongoing as more patients are switched to two-drug regimens in clinic practice. We did not address some immediate short-term potential benefits (or risks) from some switches of each regimen such as removal of QT issues, food requirement, and avoidance of drug/drug interaction risk by removal of booster or weight gain from first time use of an INSTI. Third, for this study, we did not evaluate patients on an old STF containing TDF/FTC/EFV (as the vast majority of PWH on this regimen had previously declined switching to an alternate more modern STF regimens) or PWH on other two-drug STF pill regimens (e.g., Juluca®) as that regimen was usually driven by resistance. Fourth, while cost saving are likely to be universal across most health care systems, the exact size of savings may vary depending upon contract and costs. The convenience study design makes it difficult to establish the full potential number of all patients who might elect to switch to two-drug regimen, but the projections for 50% and 75% uptake show large potential savings.

Our study does show that patient uptake of a switch from some three-drug STF regimens to two-drug STF in routine clinical practice was popular with patients, was safe with few discontinuations for any reason, and provided significant cost savings within first year of treatment switch. Our results obtained from a real-world clinical cohort help bring clarity to the discussions[39,40] on whether using two-drug regimens would be practical and acceptable in nonclinical trial settings.

These results, if confirmed in other programs, suggest that significant costs savings can be safely achieved and may relieve pressure on drug budgets. This may allow programs to address challenges of increased number of patients and still have funds for new innovative, although more expensive, approaches to PWH prevention and care.

Authors' Contributions

All authors contributed to the design of the study; M.L./S.C./H.B.K. collected the data; S.C./H.B.K./M.J.G. analyzed the data; all authors contributed to construction and writing the article.

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Author Disclosure Statement

M.J.G. reports being an ad-hoc advisor on National HIV advisory Boards to Gilead, ViiV, and Merck. The other authors do not report any conflicts of interest.

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