

Use of Compassionate Supply of Antiretroviral Drugs to Avoid Treatment Interruptions or Delayed Treatment Initiation among HIV-Positive Patients Living in Ontario: A Retrospective Review

Recours à la distribution compassionnelle de médicaments antirétroviraux afin d'éviter les interruptions de traitement ou les délais dans le début de traitement chez les patients séropositifs qui vivent en Ontario : revue rétrospective



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Abstract

Background: Without a national pharmacare plan in Canada, HIV-infected patients across the nation differ in their ability to obtain essential HIV therapy. Despite the fact there are public insurance programs in Ontario, patients are unable to access medication. The authors described how frequently patients in their urban clinic could not access medications and why they required a compassionate supply of HIV drugs, with the goals of minimizing treatment delays and avoiding interruptions.

Methods: The authors conducted a retrospective review and collected information about demographic characteristics, current drug insurance and the challenges encountered.

Results: Over one year, the authors provided 2,886 days of free HIV drugs to 42 patients who were predominantly citizens or permanent residents of Canada (88%). The most common obstacles were associated with the Trillium Drug Program and the total value of all drugs supplied was \$134,860.

Interpretation: This study suggests that Ontario's catastrophic drug insurance plan leaves some patients with significant gaps in drug coverage.

Résumé

Contexte : En l'absence d'une assurance médicaments nationale au Canada, il existe des différences, chez les patients séropositifs, dans la possibilité d'obtenir un traitement contre le VIH. Les auteurs décrivent à quelle fréquence et pour quelles raisons les patients de leur clinique urbaine n'ont pu accéder au médicament et, par conséquent, ont dû bénéficier d'une distribution compassionnelle de médicaments contre le VIH afin de minimiser les délais ou d'éviter l'interruption du traitement, et ce, malgré la présence de programmes d'assurance publiques en Ontario.

Méthode : Les auteurs ont effectué une revue rétrospective et ont recueilli des renseignements démographiques en plus d'informations sur l'assurance médicaments en place et sur les défis rencontrés.

Résultats : Pendant une année, les auteurs ont fourni gratuitement l'équivalent de 2 886 jours de médicaments contre le VIH à 42 patients qui étaient très majoritairement citoyens canadiens ou résidents permanents au pays (88 %). L'obstacle le plus fréquent était associé au Programme de médicaments Trillium. La valeur totale de l'ensemble des médicaments fournis était de 134 860 \$.

Interprétation : Cette étude laisse entendre que le régime d'assurance des médicaments onéreux ontarien donne lieu à d'importantes lacunes pour ce qui est de la couverture de médicaments chez certains patients.

Introduction

Current antiretroviral therapy regimens for people living with HIV have undeniable benefits but are also very costly. Antiretroviral therapy prolongs survival, reduces morbidity and decreases the risk of vertical and sexual HIV transmission to uninfected individuals (Connor et al. 1994; Cohen et al. 2011; Cooper et al. 2002; Hogg et al. 1999; Palella et al. 1998). The success of antiretroviral therapy, however, is highly dependent on adherence, where non-adherence is associated with increased or rebound viremia, the development of drug resistance and consequent HIV-associated morbidity and mortality (Bangsberg et al. 2001, 2007; Hogg et al. 2006; Fielden et al. 2008; Lima et al. 2009). As transmission of HIV is strongly correlated with HIV plasma concentration, treatment interruption also increases the risk of transmission from HIV-infected persons to uninfected sexual partners and from HIV-infected pregnant women to their children (Garcia et al. 1999; Quinn et al. 2000). The major determinants of non-adherence include regimen complexity, drug toxicity and financial burden to access the medications (Kranzer and Ford 2011; Nachega et al. 2014; Osterberg and Blaschke 2005; Vermeire et al. 2001). Research published in 2012 found that about 1 in 10 Canadians reported cost-related non-adherence, with proportions ranging from 3.6 to 35.6% depending on having drug insurance and total household income (Law et al. 2012). In an Australian study, HIV-infected patients who had suboptimal adherence owing to financial stress reported that they had delayed purchasing their medication or discontinued them altogether (McAllister et al. 2013). Thus, prescribing effective yet simple and tolerable regimens for which patients incur little or no out-of-pocket expense is likely to improve outcomes.

Antiretroviral therapy is life-long, and a preferred first-line regimen currently costs about \$1,400 each month (MOHLTC 2014). Canadian jurisdictions vary considerably in the formulary listings and degree of public coverage for prescription medications used outside of a hospital setting (Demers et al. 2008). Antiretroviral drugs are no exception. They are provided free of all charges to all registered residents in British Columbia and Alberta through their specialized programs, while in most other jurisdictions, patients pay a co-payment or deductible (see Table 1 at www.longwoods.com/content/24148). In Ontario, all individuals who are 65 years old or older with a limited income or who are receiving social assistance can access many medications, including antiretrovirals drugs, through the Ontario Drug Benefit program for a nominal co-payment. Aboriginal Canadians can obtain HIV medications free of charge through Health Canada's Non-Insured Health Benefits program, while patients who are refugee claimants have free medication insurance through the Interim Federal Health Program. Patients who have legal status in Canada and have been living in Ontario for at least three months but do not qualify for any of these programs can enroll into the Trillium Drug Program (TDP), the catastrophic drug insurance plan that aims to protect Ontarians with high drug expenses (relative to their earnings) from financial hardship. The TDP requires payment of an annual deductible that varies relative to household income, followed by a co-payment once the deductible is reached. For example, the deductible for a single-person

household with a net income of \$25,000 is \$714 per year, while the deductible for a household of four persons with a net income of \$60,000 is \$2,139 per year. As the deductible is paid in instalments, once the quarterly deductible is met, patients then have a \$2.00 co-payment for every prescription until the next quarter.

Despite the availability of these programs, some patients in Ontario still encounter obstacles that typically fall into three categories. First, some patients are unable to manage the financial requirements and arrangements of the plan. This includes individuals who are eligible for the TDP but cannot consistently afford the program's deductibles as well as patients who have both private insurance and Trillium coverage but are unable to regularly pay the out-of-pocket co-insurance portion (such as 20% of an 80% coverage insurance plan) with each prescription and await reimbursement from the public plan. Second, some patients are in a coverage "gap" between insurance plans. For example, a patient whose refugee claim has been approved may find herself without coverage because she no longer qualifies for federal insurance and her application for a provincial plan is pending. Third, some patients are in Canada without legal status and thus do not qualify for public insurance. The potential consequence of these challenges are treatment delays or interruptions, which in HIV management results in uncontrolled viral replication, increased risks of HIV transmission, the development of drug resistance and disease progression (SMART study group 2006). Anecdotally, to avoid delays or HIV treatment interruptions, many physicians and pharmacists attempt to provide essential antiretroviral therapy to such patients who require treatment but face challenges in accessing the medications. These medications are typically donated on a compassionate basis by pharmaceutical manufacturers. Our objectives were to evaluate the gaps in drug coverage at our clinic by describing the frequency with which clinicians provided free supplies of antiretroviral medications, characterizing individuals who received these supplies and the reasons they needed compassionate supply and estimating the dollar value of the medications dispensed.

Methods

We retrospectively reviewed medications given to patients free of charge between June 2011 and May 2012 at the Positive Care Clinic of St. Michael's Hospital in Toronto, Ontario, which at the time provided tertiary outpatient care to approximately 1,200 HIV-positive patients. We collected data pertaining to individuals' demographic characteristics, the duration of their HIV diagnosis, their most recent CD4 count and viral load, their current prescription drug coverage plan, the obstacle encountered that led them to require assistance and the intended plan to re-establish drug access. When available, we recorded whether patients experienced a cost-related interruption in therapy and the duration of the gap.

We classified the type and quantity of antiretroviral medications provided according to the regimen and formulation in the compassionate supply. We defined a "regimen of choice" as continuation of the same drugs for patients who were currently receiving antiretroviral therapy.

We defined a “formulation of choice” as a continuation of the same formulation. For example, a patient who was receiving a combination tablet containing efavirenz, tenofovir and emtricitabine and was subsequently given each medication as separate tablets would be classified as having received the regimen of choice but not the formulation of choice. For patients who did not receive the regimen of choice, we classified the new regimen as “preferred,” “alternative” or “acceptable,” using the most current U.S. Department of Health and Human Services guidelines (January 2011; October 2011; March 2012). A patient who was antiretroviral-naïve and given a regimen from the preferred category was also defined as having received a “regimen of choice.” The number of days without antiretroviral medications that were averted was calculated based on the number of days of drug supply dispensed. Finally, we calculated the cost of the supplied antiretroviral medications using Ontario Drug Benefit formulary prices, excluding mark-ups and professionals’ fees (MOHLTC 2014). The study was approved by the Research Ethics Board of St. Michael’s Hospital and was not externally funded.

Results

Over one year, we gave antiretroviral medications free of charge to 42 HIV-positive patients at 95 visits, representing about 4% of the total patients followed and 4% (95/2,279) of the clinic volume seen during that period. The median number of visits per person was two (interquartile range: 1–3). The median age of patients receiving medications was 40 years, most were men and 23 (55%) were immigrants from an endemic country (Table 2). Of the patients who received a compassionate supply of antiretroviral therapy, only five (12%) were not a Canadian citizen or landed immigrant. This group included people who were refugee claimants appealing a negative decision, individuals in Canada under a student visa and people in Canada without documented status. Among the 35 patients who were currently receiving antiretroviral therapy, 26 (74%) had an undetectable viral load at their first visit. Of the seven patients who were antiretroviral-naïve at the first visit, five (71%) had a CD4 count less than 200 cells/mm³ and two were HIV-positive pregnant women.

Among the 35 patients who had taken antiretroviral medications before receiving a compassionate supply, the most common prior coverage was through the Ontario public drug program; 13 (37%) were insured by the TDP and five (14%) were insured through public assistance. The clinic gave medications to seven patients (21%) who had received medication benefits through the Interim Federal Health Program, six (17%) who had private insurance and four (11%) who had started antiretroviral therapy during a hospitalization and had no medication insurance at discharge. While we did not systematically evaluate cost-related non-adherence, three patients recalled missing approximately one week, six months and one year of antiretroviral medications for this reason, with two patients specifically stating they were unable to afford the deductible of the public plan.

Use of Compassionate Supply of Antiretroviral Drugs to Avoid Treatment Interruptions or Delayed Treatment Initiation among HIV-Positive Patients Living in Ontario: A Retrospective Review

TABLE 2. Demographic characteristics of 42 patients who received a compassionate supply of antiretroviral drugs*

Characteristic	N (%)
Age—years, median (IQR) [†]	40 (32–47)
Male	29 (69)
Ethnicity	
White	9 (21)
Black	25 (60)
Other [‡]	8 (19)
Canadian citizen or landed immigrant	37 (88)
HIV risk factor	
Men who have sex with men	18 (62)
Immigrant from endemic country	23 (55)
Injection drug use	0 (0)
Duration of HIV infection diagnosis – years, median (IQR)	3.4 (0.8–6.4)
Taking antiretroviral medication at the first visit	35 (83)
Duration of antiretroviral therapy – years, median (IQR)	1.4 (0.7–3.5)
CD4 count – cells/mm ³ , median (IQR)	
Most recent	430 (234–594)
Nadir	235 (82–322)
Viral load – copies/mL, median (IQR)	
Most recent	Undetectable (undetectable to 46)
Highest viral load documented	38,786 (2,026–129,094)
Not taking antiretroviral medication at the first visit	7 (17)
Most recent CD4 count – cells/mm ³ , median (IQR)	132 (31–377)
Most recent viral load – copies/mL, median (IQR)	53,266 (1,353–107,196)

*Numbers in table are N (%) unless otherwise indicated.

[†]IQR denotes interquartile range.

[‡]Other ethnicity includes South and South East Asian, Latin and Arab or West Asian.

We analyzed the reasons for problems in drug coverage by visit (Table 3). Over 95 visits, the most common problem with drug insurance coverage (at 29 visits [31%]) was that patients were waiting for their application to the TDP to be approved or had been asked for additional paperwork. Among all obstacles, 63 (66%) were associated with the TDP and were primarily

due to pending activation, status change requiring enrolment into Trillium, inability to make a payment towards the annual deductible or incomplete renewal paperwork to maintain enrolment. Other obstacles that patients encountered with TDP included an incorrect activation date and in five occurrences (5%), the inability to afford the co-insurance upfront and await reimbursement.

TABLE 3. Obstacles encountered with drug insurance plans that prevented patients from accessing HIV medications, by visit

Obstacle	Problem related to the Trillium Drug Program	
	No (n = 32)	Yes (n = 63)
	N (%)	N (%)
Awaiting activation or additional paperwork required for Trillium	0 (0)	29 (31)
Status change requiring enrolment into new program	8 (8)	10 (11)
Renewal of Interim Federal Health Insurance denied	15 (16)	0 (0)
Unable to meet deductible set by Trillium	0 (0)	10 (11)
No insurance and unable to pay out of pocket	8 (8)	0 (0)
Program enrolment expired	0 (0)	5 (5)
Limits on private insurance requiring enrolment into new program	0 (0)	3 (3)
Other*	1 (1)	6 (6)

*"Other" obstacles included the inability to pay a co-insurance upfront and wait for reimbursement from the public plan, an incorrect request for a delayed start date to the Trillium Drug Program and the inability to pay for a private plan's premium.

We generally provided 30 days of medications to allow sufficient time for the coverage issue to be resolved, although 23 patients (55%) required at least one additional visit to establish or re-establish coverage. Based on availability, we gave medications that resulted in a regimen of choice at 78 visits (82%) and at 32 (41%) of these visits, we gave formulations of choice (Table 4). We did not provide any antiretroviral medications that produced "unacceptable" regimens, although at 58 visits (61%), we gave medications that resulted in regimens with an increased pill burden and at five visits (5%), the resultant combination led to an increased pill burden and frequency of administration compared with the regimen received before the gap in coverage or what would have been desired had there not been a financial obstacle in initiating therapy.

Overall, we gave out 202 antiretroviral drugs and the total number of medications dispensed averted 2,886 cost-related non-adherence days. The most common product dispensed was combination tenofovir/emtricitabine, which was given 64 times (32%) and was valued at \$54,126, followed by efavirenz, which was given 48 times (24%) and valued at \$25,329. The median value of medications given per individual was \$1,995 (inter-quartile range: \$1,341 to \$4,024), and the maximum amount for any single individual was \$16,958. The total value of all medications given was \$134,860.

Use of Compassionate Supply of Antiretroviral Drugs to Avoid Treatment Interruptions or Delayed Treatment Initiation among HIV-Positive Patients Living in Ontario: A Retrospective Review

TABLE 4. Characteristics of compassionate antiretroviral regimens supplied over 95 visits

Regimen characteristic	N (%)
Regimen of choice	78 (82)
Formulation of choice	32 (43)
Change in daily pill burden and frequency	
No change	32 (34)
Increased pill burden	58 (61)
Increased pill burden and frequency of administration	5 (5)
Not regimen of choice	17 (18)
"Preferred" regimen*	0 (0)
"Alternate" regimen*	13 (14)
"Acceptable" regimen*	4 (4)
May be acceptable but "use with caution" or "not acceptable"	0 (0)

*"Preferred," "Alternate" and "Acceptable" regimens are as those defined by the Department of Health and Human Service guidelines that were current at the time of the study (January 2011; October 2011; March 2012); those with "optimal and durable efficacy, favorable tolerability and toxicity profile, and ease of use," "effective and tolerable but have potential disadvantages compared with preferred regimens" and less satisfactory than preferred or alternative regimens, respectively.

Interpretation

Our results suggest that HIV-positive individuals residing in Ontario may be experiencing challenges in accessing and affording their antiretroviral medications. Over one year, to avoid treatment delays or treatment interruptions, we gave out close to eight years worth of antiretroviral medications valued at \$134,860 to 42 patients, an average of 69 non-adherence days averted per person. We believe this is likely an underestimate of the number of patients facing financial challenges, as we only included individuals who informed us that they were experiencing a financial problem accessing their medications. We did not systematically categorize other patients and did not include patients who might receive supply from the hospital pharmacy, visit the Toronto People With AIDS Foundation (which runs a large medication access program), share medications with others, buy medications informally from non-pharmacy or non-Canadian sources, not return for a clinic visit and be lost to follow-up, discontinue taking their therapy or defer initiating antiretroviral therapy. We think it is unlikely that patients who could otherwise afford the cost of drugs used compassionate antiretroviral drug supplies to avoid out-of-pocket payments, as each patient received a comprehensive assessment of the financial obstacle from the multidisciplinary team, including a social worker.

About two-thirds of the problems encountered were associated with the TDP, Ontario's catastrophic drug insurance plan. Each jurisdiction in Canada develops and administers its own independent medication insurance program, with varying eligibility criteria and

cost-sharing requirements. Following the 2004 federal-provincial health accord that had a goal of ensuring “no Canadian suffers undue financial hardship in accessing needed drug therapies” (Health Canada 2004), most provinces and territories have arranged to provide comprehensive drug coverage with minimal or no out-of-pocket spending for social assistance recipients and many have since adopted an income-based catastrophic coverage model for their general, non-senior population (Daw and Morgan 2012). Our results, however, suggest that the cost-sharing arrangement required of many HIV-positive patients in Ontario may have an impact on the affordability of antiretroviral medications for a significant number of people. We found that the TDP deductible, which is approximately 4% of the previous year’s household net income, often presents a challenge; this may be particularly true for patients who are intermittently employed and have a variable income throughout the year. This financial hardship may compel some people to make difficult decisions such as remaining unemployed and thus qualifying for social assistance. Other patients, like two in our study, might discontinue treatment until they can afford to restart.

In addition to financial barriers, administrative difficulties with the TDP seem to represent burdens for some individuals. Initial enrolment into the program involves navigating, completing and mailing of a paper application by the patient along with mandatory accompanying documentation, including proof of income. This process typically takes four to six weeks; however, delays include incomplete forms, the time it takes for the Ministry to receive the application, the volume of applications to be reviewed and the availability of completed tax returns or other acceptable documents confirming income and private insurance benefits. Without an efficient and automated system, we found some patients were left in a coverage gap, particularly when there was an unexpected change in qualifying for their current insurance program, causing them to apply to the TDP and wait for their paperwork to be approved. Other patients who were already enrolled in Trillium occasionally found their plan was suspended and not renewed due to the requirement for new additional documents or signatures. During this interim of pending activation or renewal, only the few patients who could afford to pay the full cost of HIV medications can access their medications. The majority must delay initiation or experience a treatment interruption.

Refugee claimants appealing a negative decision were another vulnerable group requiring compassionate medication supplies. While they are legally allowed to remain in Canada, at the time of our study, they no longer qualified for health insurance, including medication coverage. On January 1, 2014, however, the Ontario Temporary Health Program was launched to address coverage gaps from the downscaling of the Interim Federal Health Program and to provide essential health and medication coverage to people whose refugee claims were denied. This program would have provided drug coverage to only two of our patients.

Financial constraints contribute to medication non-adherence in HIV (Boyer et al. 2009; Johnston et al. 2012; McAllister et al. 2013) and non-HIV (Kennedy and Morgan 2006; Law et al. 2012; Tamblyn et al. 2014) populations, and non-adherence has been shown to

affect outcomes (Nachega et al. 2010; Piette et al. 2004). A systematic review found that cost-sharing, such as co-payments or deductibles, by vulnerable populations in high-income countries led to reductions in prescription drug use and associated increases in use of other health services, including hospitalizations (Lexchin and Grootendorst 2004). It has been shown that removing financial barriers for patients who survive a myocardial infarction can improve health outcomes without increasing overall health costs (Choudhry et al. 2011). Specific to HIV care, unlike many chronic diseases where drugs remain effective even after a period of disruption, treatment interruption in HIV management can lead to emergence of drug resistance, loss of treatment options and increased costs (Krentz et al. 2013). Provision of free antiretroviral medications has been shown to lead to more rapid treatment initiation (Solomon et al. 2013), and an economic evaluation from South Australia demonstrated that removing co-payment fees for antiretroviral medications can be cost-effective (Heymer et al. 2012). Disparities in drug coverage might explain, at least in part, why HIV-positive residents in British Columbia who have free access to antiretroviral drugs were more likely to be taking HIV therapy than in Ontario (Hogg et al. 2012).

A national pharmacare plan would address gaps in coverage and disparities between provinces as well as other health policy objectives (Morgan et al. 2013; Stanbrook et al. 2011). In the absence of such a program, policy makers might consider prioritizing universal access to medications that have an impact on public health. Antiretroviral use is associated with a marked reduction in HIV transmission, and widespread use has been proposed to reduce regional HIV incidence (Fang et al. 2004; Hogg et al. 2012; Montaner et al. 2014). As with the national approach taken to the prevention and control of tuberculosis, policy arguments can be made for eliminating financial barriers to the treatment of HIV. Such universal antiretroviral coverage is likely feasible, as it is already available in some provinces (including British Columbia, which has one of the highest HIV prevalence rate in Canada).

Ontario policy makers might pay particular attention to the administrative and financial barriers faced by patients and consider restructuring the TDP. Specific reforms to address these barriers might include enabling immediate electronic or telephone enrolment to access antiretroviral drugs and making eligibility not dependent on submission of documents or obtaining signatures (which can be particularly challenging when spouses live overseas). As well, TDP could easily accommodate changes in information that may affect deductibles, such as change in status to a single-person household without requiring a signature from an ex-spouse. Finally, consideration should be given to eliminating or lowering deductibles. Deductibles or co-payments could be fixed or based on drug costs alone, eliminating the need to confirm income or other private insurance benefits.

Strengths and limitations

Our study has several strengths. We included all patients who consulted us for assistance with antiretroviral drugs, not a sample of the population. We also collected detailed information on the financial obstacles that patients faced. Our study also has several limitations. First, while

we conducted our study within a large tertiary care urban HIV clinic, the number of people in our study was still small and we are unable to make inferences about specific populations. Second, we did not systematically record socioeconomic characteristics of our patients and, therefore, cannot make conclusions about income level and the need for compassionate care, for example. The majority of our patients requiring free medications, however, did not qualify for social assistance due to income level. Third, our study was conducted at a single site and may not be generalizable to other sites or representative of the population of people living with HIV in Ontario. Fourth, we were unable to assess the impact of patients' financial burdens on clinical outcomes, given the short time horizon of our study, although outcomes may have been difficult to assess, as leaving our patients without coverage and not intervening, when alternatives were available, would have been unethical.

Conclusion

To achieve the UNAIDS 90-90-90 goals and Diagnostics Access Initiative where 90% of all people living with HIV know their HIV status, 90% of all people with diagnosed HIV infection receive antiretroviral therapy and 90% of all people receiving HIV treatment are virally suppressed, decision-makers need to examine barriers to HIV drug access. We have shown that there are HIV-positive patients living in Ontario who qualify for provincial drug insurance but experience challenges in obtaining their medications. Future research should address the scale of this problem and the impact on clinical and public health outcomes. Clinicians need to be alert to such possible challenges and should directly question patients about their individual situation about antiretroviral drug access to identify opportunities to intervene and minimize non-adherence. Medication adherence is important for achieving the significant clinical health benefits of antiretroviral medications, and studies have shown that financial burdens can influence adherence. Out-of-pocket medication spending is a barrier to adherence that is directly amenable to policy intervention. Restructuring Ontario's Trillium's enrolment process and financial requirements may at least ease some barriers to obtaining essential medicines. Our results suggest that reform of Ontario's catastrophic drug insurance system would minimize a substantial number of obstacles in accessing antiretroviral drugs, thereby likely influencing medication adherence, possibly improving the health of people living with HIV and potentially having an impact on reducing HIV incidence.

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Use of Compassionate Supply of Antiretroviral Drugs to Avoid Treatment Interruptions or Delayed Treatment Initiation among HIV-Positive Patients Living in Ontario: A Retrospective Review

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Use of Compassionate Supply of Antiretroviral Drugs to Avoid Treatment Interruptions or Delayed Treatment Initiation among HIV-Positive Patients Living in Ontario: A Retrospective Review

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