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Outpatient pharmacy care and HIV viral load response among patients on HAART

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Outpatient pharmacy care and HIV viral load response among patients on HAART

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Abstract *Adherence to highly active antiretroviral therapy (HAART) is necessary to achieve long-term effectiveness. The impact of HIV/AIDS-specific pharmacy services on patient adherence and HIV viral suppression is currently not well described. This study aimed to compare the impact of differing levels of HIV-pharmacy care on adherence and time to HIV viral suppression among participants on HAART enrolled in a population-based HIV/AIDS drug treatment programme in British Columbia. We performed a retrospective observational study of 788 treatment-naïve patients who started HAART between August 1997 and July 2000 and were followed until 31 March 2002. The degree of outpatient pharmacy care was defined according to pharmacy dispensing site for the participants' first prescription of HAART: highest at the AIDS-tertiary care hospital outpatient pharmacies, intermediate at HIV/AIDS drug treatment programme funded off-site pharmacies and lowest at family physician's offices. Cox-proportional hazard models examined the independent effect of pharmacy dispensing site on time to two consecutive HIV viral suppressions controlling for other prognostic factors including physicians' experience, age, gender, injection drug use, use of therapy containing NNRTI versus PI, adherence > 90%, AIDS diagnosis at baseline, baseline CD4 cell count and HIV viral load. The median time on antiretrovirals was 28 months (IQR = 14–38). There were 489 (62.1%) participants who obtained their medications from the AIDS-tertiary care outpatient pharmacies; 98 (12.4%) from off-site pharmacies and 201 (25.5%) from their physicians' offices. The proportion of patients exhibiting > 90% adherence to treatment was observed to be higher among patients receiving their HAART at the AIDS-tertiary care pharmacies compared to off-site pharmacies and to physicians' offices (70.4, 59.2 and 55.7%, respectively;* $p = 0.0001$*). After adjusting for other prognostic factors, subjects who were first dispensed medications from the AIDS-tertiary care pharmacy were 1.42 times (CI: 1.10–1.84) more likely to achieve HIV viral suppression than those getting their medications from off-site pharmacies and physicians' offices. Providing regular outpatient pharmacy care is independently associated with improved HIV viral load response through enhanced adherence to HAART. Standardization of pharmacy practices for dispensing HAART may improve outcomes for patients who receive their HIV medications from other non-tertiary care pharmacy sites.*

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Introduction

Highly active antiretroviral therapy (HAART) has been shown to prolong survival in persons with AIDS and those with intermediate-stage HIV-1 infection in both randomized clinical trials and observational, community-based studies (Hammer *et al*., 1997; Hogg *et al*., 1998; 1999; Palella *et al*., 1998). Plasma HIV viral load driven therapy has been adopted as a growing body of evidence has indicated that plasma HIV viral load can be a meaningful predictor of disease progression (Hogg *et al*., 1998; Mellors *et al*., 1995, 1996; O'Brien *et al*., 1997).

Adherence to complex regimens is necessary to achieve long-term effectiveness. Indeed, lack of adherence to antiretroviral therapy is considered an important cause of early virologic failure (Bangsberg *et al*., 2001; Ickovics & Meade, 2002; Ickovics *et al*., 2002). Ickovics and Meade (2002) reviewed the determinants of adherence and interventions to improve adherence to HAART. Patients' physical, psychological and sociodemographic characteristics, substance abuse, disease stage, physician experience, as well as health care administration and delivery have been shown to have an independent effect on adherence, but these associations are not well understood (Chesney *et al*., 2000; Ickovics & Meade, 2002; Mehta *et al*., 1997; Turner, 2002). Patient–provider relationship may play an important role in enhancing adherence to HAART (Malcolm *et al*., 2003; Stone, 2001; Stone *et al*., 1998). Numerous strategies have been studied that improve HAART adherence in clinical practice, including psychoeducative interventions to improve self-efficacy (Tuldra *et al*., 2000), cue dose training with medication feedback from MEMS caps and cash reinforcement (Rigsby *et al*., 2000), one-on-one medication adherence counselling and weekly pill organizers (McPherson-Baker *et al*., 2000), behavioural intervention (Molassiotis *et al*., 2003) and an educational and counselling intervention (Pradier *et al.*, 2003). Furthermore, the success of HAART has moved the management of HIV to a chronic disease model with multidisciplinary care and self-management (Gifford & Groessl, 2002).

The impact of HIV/AIDS-specific pharmaceutical services on patient adherence and HIV-1 RNA suppression is currently not well described. A number of institutions providing HIV/AIDS care have reported on the integration or expansion of pharmacy services within HIV/AIDS-care teams (Colombo, 1997; Michelle *et al*., 1996; Warnock, 1994). This expansion has been influenced by the widespread use of HAART and ambulatory care where HIV-infection is managed as a chronic disease (Michelle *et al.*, 1996). It is recognized that these patients exhibit numerous drug-related needs given the nature of the disease (Greco *et al*., 1992), the complexity of HAART regimens and a poly-pharmacy phenomena due to the common use of complementary therapies, investigational drugs, over the counter medications and nutritional products (Bretzel *et al*., 2001; Risa *et al.*, 2002; Standish *et al.*, 2001). The spectrum of pharmaceutical care services reported has ranged from medication counselling, monitoring drug-related problems, to educating other HIV care team members (Colombo, 1997; Michelle *et al.*, 1996; Warnock, 1994). It is expected that these interventions lead to improved health outcomes through improved adherence.

The present study was undertaken to compare the adherence of patients on HAART by levels of pharmaceutical care and to assess the impact that these different levels of pharmacy care might have on the HIV viral load response to HAART among individuals participating in a population-based HIV/AIDS drug treatment programme in British Columbia, Canada. We hypothesized that patients receiving their HAART from the tertiary AIDS care pharmacy will have higher adherence and be more likely to achieve HIV viral suppression than patients receiving their antiretroviral therapy from off-site pharmacies and family physicians' offices.

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Methods

HIV/AIDS Drug Treatment Program

The BC Centre for Excellence HIV/AIDS Drug Treatment Program distributes antiretroviral agents at no cost to eligible HIV-infected individuals in British Columbia. Antiretroviral therapy is distributed according to the specific guidelines generated by the Therapeutic Guidelines Committee. In June 1996, the centre adopted plasma HIV viral load driven antiretroviral therapy guidelines, consistent with those put forward by the International AIDS Society-USA (Carpenter *et al.*, 1996). The guidelines used at the centre have been updated and consistent with those recommended by International AIDS Society-USA (Carpenter *et al.*, 1997, 2000; Yeni *et al.*, 2002).

Data collection

Physicians enrolling an HIV-positive individual in the Drug Treatment Program must complete a drug request enrollment form. This form acts as a legal prescription and compiles information on the patient's address, enrolling physician, past HIV-specific history, CD4 cell count, HIV viral load and current drug requests. A qualified practitioner reviews all requests to verify that they follow the centre's therapeutic guidelines. Approved prescriptions are renewed at least every one–three months. At the time of first refill, each patient is asked to complete an enrollment survey that elicits sociodemographic information, and also to sign a consent form for their data to be linked to other databases. The Providence Health Care Ethics Committee for Human Experimentation has also approved the use of the data generated from the programme for research purposes.

According to patients' preferences and place of residence, medications are dispensed from different sites. These sites can be grouped into three categories: AIDS-tertiary care hospital outpatient pharmacies ($n = 2$), off-site pharmacies ($n = 4$) and family physicians' offices ($n = 123$). The degree of pharmacy care provided varies among the three groups. In the first category, experienced pharmacists and nurses have been specifically trained to meet HIV-positive patients' medication needs. They regularly provide medication counselling, individualize regimens and monitor for adverse drug effects. The patients are typically seen for medication counselling every two months for 15–30 minutes for refill medications and at least 30 minutes for new medications. They also constitute a liaison between patients and HIV/AIDS specialists. Off-site pharmacies receive various levels of funding to provide HIV-specific pharmacy care. Patients receiving their medications from their family physicians do not have contact with pharmacists at the time of HAART dispensing.

Study subjects

Study participants were 18 years of age or older and naïve to antiretroviral therapy when they started HAART consisting of two nucleoside reverse transcriptase inhibitors, with one protease inhibitor or one non-nucleoside reverse transcriptase inhibitor, between August 1997 and July 2000.

Outcome measures and independent variables

The primary outcome for this study was time from initiating HAART to achieving HIV-1 RNA suppression, defined as having at least two consecutive HIV-1 RNA determinations below 500 copies/mL during the follow-up period. The following independent variables were

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included in our study: HAART dispensing site category (AIDS care pharmacy, outpatient pharmacy, family physician office), age, gender, baseline CD4 cell count, baseline HIV viral load, AIDS diagnosis, injection drug use, physician experience and type of HAART (two nucleosides and a non-nucleoside reverse transcriptase inhibitor [NNRTI] versus two nucleosides and a protease inhibitor). Injection drug use was defined as ever-injected drugs (yes or no), which was physician or self-reported. Physician experience was estimated for the first follow-up physician of each patient. It was defined as the cumulative number of HIV-positive patients receiving antiretroviral therapy within their practice, by the date of subject's first known eligibility (Strathdee *et al.*, 1998). Adherence to treatment was estimated using pharmacy refill compliance. In brief, we divided the number of months of HAART dispensed by the number of months of follow-up in the first year of therapy; this measure of adherence has been found to be independently associated with HIV viral suppression and survival among HIV-infected persons enrolled in the HIV/AIDS Drug Treatment Program (Hogg *et al.*, 2002; Palepu *et al.*, 2001).

Statistical analyses

Statistical analyses were performed using distribution-free methods. For the univariate analyses, categorical variables were compared using Pearson's chi-square test, while continuous variables were compared using the Wilcoxon rank-sum test. Fisher's exact test was used for 2×2 contingency tables in which any of the expected cell frequencies was less than five.

Time to HIV viral suppression was compared among the three dispensing categories using Kaplan Meier methods and the log-rank test. Time zero was the first dispense date of HAART for each patient. The HIV viral suppression end point was the first HIV viral load test date in a series of at least two consecutive HIV viral load determinations < 500 copies/mL. Patients who did not reach the endpoint were censored at the last available HIV viral load test date, and all patients were followed until March 2002. The Cox-proportional hazard assumptions were first tested and models were constructed to identify independent factors associated with time to HIV viral suppression below 500 copies/mL on at least two consecutive visits. An interaction term was used to test for possible interactions between physician experience and pharmacy dispensing site, as well as injection drug use and pharmacy dispensing site. We did not include our measure of adherence in the multivariate models because we hypothesized that enhanced adherence to HAART was the mechanism by which the level of pharmacy care would affect HIV-1 RNA suppression.

Results

A total of 788 antiretroviral-naïve subjects (645 [81.9%] men and 1143 [18.1%] women) started HAART between August 1997 and July 2000. Of these, 489 (62.1%) patients obtained their first prescription from the AIDS care pharmacy, 98 (12.4%) from off-site pharmacies and 201 (25.5%) from their physicians' offices. The median time on HAART was 28 months (IQR = 14–38).

The AIDS–tertiary care pharmacies had the highest proportion of patients exhibiting $> 90\%$ adherence compared to the off-site pharmacies and the physicians' offices (70.4, 59.2 and 55.7%, respectively, $p = 0.0001$). The proportion achieving 90% adherence was not significantly different when comparing the off-site pharmacies to the physicians' offices group ($p = 0.52$).

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Table 1 presents baseline demographic and clinical characteristics groups according to the dispensing site. No difference was observed among the three sites with respect to median age, CD4 cell count or HIV-1 RNA. However, the highest percentage of injection drug users was in the physicians' offices group, followed by off-site pharmacies and the AIDS-tertiary care pharmacies (33.3, 27.6 and 16.2%, respectively, $p = 0.001$). More male patients attended the AIDS-tertiary care pharmacies compared to the off-site pharmacy group and the physicians' offices (86.3, 84.7 and 69.6%, respectively; $p = 0.001$). The AIDS-tertiary care pharmacy group had the highest median physician experience compared to the off-site pharmacies and the physicians' offices (99, 54 and 5, respectively, $p = 0.001$).

As depicted in Fig. 1, the probability of HIV-1 RNA suppression by 12 months of follow-up by dispensing site was 74.6% for the AIDS-tertiary care pharmacy, 59.4% for the off-site pharmacies and 60.0% for the physicians' offices (log rank $p = 0.001$). The unadjusted relative hazard revealed that those who were in the AIDS-tertiary care pharmacy group were more likely to be suppressed when compared to those attending off-site pharmacies (RH: 1.42; 95% CI: 1.09–1.84), and also when compared to physicians' offices (RH: 1.58; 95% CI: 1.30–1.92). There was no significant difference in HIV-1 RNA suppression between the off-site pharmacy group and the physicians' offices (RH: 1.10; 95% CI: 0.82–1.48, log rank $p = 0.46$).

Due to the similarity shown above between the off-site pharmacies and the physicians' office groups, they were collapsed to one category in further univariate and multivariate models. Table 2 presents the univariate associations with time to achieving HIV-1 RNA suppression. Relative to this new comparison group of off-site pharmacies/physicians' offices, the AIDS care pharmacies were positively associated with achieving HIV-1 RNA suppression (RH: 1.58; 95% CI: 1.30–1.82). In addition, male gender, physician experience, age and NNRTI-based therapies were factors positively associated with HIV-1 RNA suppression. Injection drug use and higher baseline higher HIV-1 RNA were the factors negatively associated with HIV-1 RNA suppression.

In the univariate analysis, the interaction terms of injection drug use and pharmacy dispensing site and physician experience and pharmacy dispensing site were significant ($p = 0.04$ and 0.01, respectively) and we therefore included them in the multivariate model. After adjusting for age, gender, physician experience, CD4 cell count, HIV-1 RNA and injection drug use, the Cox proportional hazard model showed that patients receiving their medications from the AIDS care pharmacy were 1.42 times (CI: 1.10–1.84) more likely to achieve HIV-1 RNA suppression when compared with patients receiving their HAART from the off-site pharmacies/physicians' offices group (Table 3).

Discussion

We found that among 788 antiretroviral naïve patients who started HAART, the proportion of patients achieving HIV-1 RNA suppression was significantly higher among patients receiving their HAART at an AIDS-tertiary care outpatient pharmacy compared to the patients receiving their HAART from off-site pharmacies or physicians' offices. They were 1.49 times more likely to achieve an HIV viral load < 500 copies/mL at least twice consecutively, after adjusting for age, gender, physicians' HIV-related experience, baseline HIV viral load, baseline CD4 counts and injection drug use. In addition, adherence, as measured by pharmacy refill compliance, was observed to be significantly higher among patients for whom the drug was dispensed at the AIDS-tertiary care outpatient pharmacy, relative to patients in the other two pharmacy-dispensing groups. The use of pharmacy records is more reliable than

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Table 1. *Baseline characteristics for 846 HIV-infected patients receiving HAART by pharmacy-dispensing site*

Variable		Physicians' offices $n = 201$	Off-site pharmacy sites $n = 98$	AIDS care pharmacy $n = 489$	p
Gender	(M vs. F)	140 (69.7%)	83 (84.7%)	422 (86.3%)	0.001
Median age	(years)	37 (IQR: 30–43)	39 (IQR: 33–45)	37 (IQR: 32–44)	0.06
Median CD4	(cells/mm^3)	280 (IQR: 140–420)	240 (IQR: 110–400)	260 (IQR: 130–400)	0.57
Median HIV-1 RNA	(copies/mL)	78K (IQR: 26–210K)	116K (IQR: 32–334K)	91K (IQR: 28–280K)	0.52
AIDS diagnoses	(Yes vs. No)	21 (10.4%)	18 (18.4%)	57 (11.7%)	0.12
Ever injected drugs	(Yes vs. No)	67 (33.3%)	27 (27.6%)	79 (16.2%)	0.001
Median physician experience	NNRT-based vs. PI-based	5 (IQR: 0–42)	54 (IQR: 7–81)	99 (IQR: 76–163)	< 0.001
HAART	(number of patients)	62 (30.9%)	38 (38.8%)	181 (37.0%)	0.24

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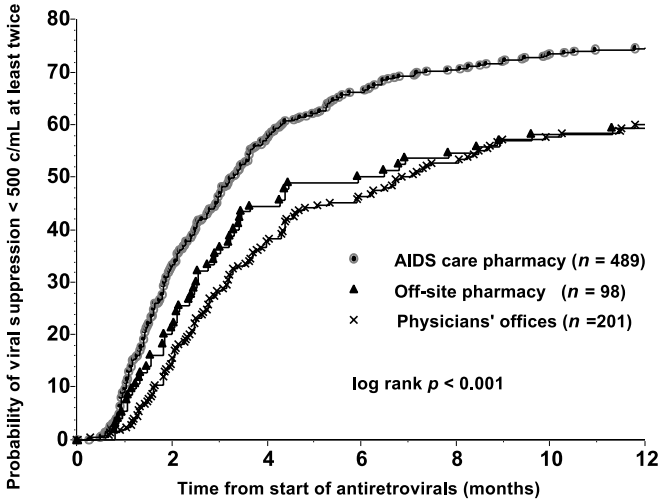

AIDS care pharmacy	*N*=489	197	131	109
Off-site pharmacy	*N*= 98	50	39	34
Physicians' office	*N*=201	119	86	72

FIG. 1. *Probability of suppression at 12 months by pharmacy dispensing category* (N = *788).*

Table 2. *Univariate Cox-proportional hazard analysis for factors associated with time to HIV-1 RNA < 500 copies/mL at least twice for 788 patients*

Variable		Relative hazard	95% CI
AIDS care pharmacy	(Yes vs. No)	1.53	1.30–1.82
Gender	(Male vs. female)	1.45	1.16–1.82
Physician experience	(by 100-patient increment)	1.13	1.04–1.24
Age	(by 10-year increment)	1.28	1.18–1.39
AIDS diagnosis	(Yes vs. No)	1.12	0.88–1.43
CD4 cell count	(by 100 cells/mm3 increment)	0.94	0.90–0.98
HIV-1 RNA	(by $\log_{10}$ increment)	0.85	0.76–0.94
Injection drug use	(Yes vs. No)	0.62	0.50–0.76
HAART	(NNRTI- vs. PI-based therapies)	1.32	1.11–1.56

medical records in terms of medication dispensing for HIV medications (de Maat *et al.*, 2002).

Our results demonstrate the importance of HIV-specific pharmacy services for HIV/AIDS patients in terms of their treatment outcomes (Turner, 2002). Our findings are supported by one recent study that characterized the pharmacy-related interventions in a pharmacist-directed HIV clinic that followed 70 patients over a four-year period. The authors found that each patient received an average of seven medications and two interventions. The most common interventions were medication counselling (39%), recommendations of monitoring parameters (17%) and prescription processing (9%). Most interventions were deemed to be clinically significant (89%) and enhanced treatment efficacy (62%). These authors concluded that the pharmacists' interventions and direct patient care at an HIV clinic

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Table 3. *Multivariate Cox-proportional hazard model for factors associated with time to HIV-1 RNA suppression < 500 copies/mL at least twice for 788 patients**

Variable*		Relative hazard	95% CI
AIDS care pharmacy	(Yes vs. No)	1.42	1.10–1.84
Gender	(Male vs. female)	1.25	0.99–1.58
Physician experience	(by 100-patient increment)	0.74	0.54–1.04
Age	(by 10-year increment)	1.26	1.15–1.38
AIDS diagnosis	(Yes vs. No)	1.12	0.88–1.43
CD4 cell count	(by 100 cells/mm3 increment)	0.93	0.90–0.97
HIV-1 RNA	(by $\log_{10}$ increment)	0.79	0.71–0.88
Injection drug use	(Yes vs. No)	0.90	0.66–1.22
HAART	(NNRTI- vs. PI-based therapies)	1.23	1.04–1.47
Interaction term	(injection drug use * Pharmacy dispensing site)	0.66	0.43–1.01
Interaction term	Physician experience* Pharmacy dispensing site	1.34	0.95–1.90

translated to good patient adherence to treatment and provided clinical benefits for patients (Geletko & Poulakos, 2002).

According to our data, the pharmacy care delivered at the tertiary care institution had the greatest effect on HIV viral load response. Surveys among pharmacists in Wales and Canada have shown that community pharmacies have potential for an expanded role in HIV management and have acknowledged the need for service-specific training (Cockerill *et al.*, 1996; Sheridan & Strang, 1998; Tseng *et al.*, 2001).

The literature has been inconsistent with respect to other factors we found to be associated with HIV viral suppression, such as age and injection drug use. Younger age has been associated with lower adherence in some studies (Chesney *et al.*, 2000; Gifford *et al.*, 2000; Gordillo *et al.*, 1999) but not in others (Eldred *et al.*, 1998; Stone, 2001). Injection drug use has also been associated with lower adherence (Gordillo *et al.*, 1999). Studies examining the effect of injection drug use on HIV viral suppression have been inconsistent. Some have found no significant association (Mocroft *et al.*, 1999; Palepu *et al.*, 2001; Roca *et al.*, 1999), while other studies that specifically examined active illicit drug use have found a negative association with HIV viral suppression (Arnsten *et al.*, 2002; Lucas *et al.*, 2001; 2002; Palepu *et al.*, 2003). As previously noted, higher baseline CD4 cell counts (Hogg *et al.*, 2001) and lower baseline HIV viral load (Hogg *et al.*, 2001; Palepu *et al.*, 2001) were positively associated with achieving HIV-1 RNA suppression.

There are a number of features of our study that should be highlighted. Our study was carried out within a province-wide treatment programme in which all individuals had access to medical attention, HAART and laboratory monitoring free of charge. Our results are, therefore, not influenced by access to therapy-related issues, which have often compromised the interpretation of similar population-based or cohort-based studies. We studied treatment-naïve individuals and our results are not, therefore, confounded by previous therapy use. Referral bias may account for some of the differences observed by pharmacy-dispensing sites, as patients who are more likely to have favourable treatment outcomes may attend the AIDS tertiary pharmacies. We did control for the distribution of injection drug use in our model, as well as examine the interaction of injection drug use and pharmacy site, as active drug use has been associated with poor HIV-1 treatment outcomes (Arnsten *et al.*, 2002; Lucas *et al.*, 2001; 2002). However, we could not control for licit drug use such as alcohol that can affect

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adherence (Cook *et al.*, 2001). We also adjusted for physician HIV prescribing experience as well as the interaction of this and dispensing site, but there may have been other variations by site that we were unable to control for. Finally, our measure of adherence is based on pharmacy refill compliance data and does not address whether or not the participant ingested the medication. We did not include this measure of adherence in our multivariate models as it represented one of the mechanisms by which the level of pharmacy care would affect adherence (Hernan *et al.*, 2002).

In summary, we found that patients who had HAART dispensed from the tertiary AIDS care outpatient pharmacy were more likely to achieve HIV viral suppression than patients receiving their antiretroviral drugs from other sites, controlling for other prognostic factors. This effect is likely mediated through enhanced adherence that may be achieved by the medication counselling and support provided by the AIDS care pharmacy. Given that management of HIV/AIDS as a chronic disease requires multidisciplinary care, standardization of pharmacy practices for dispensing HAART may improve outcomes for patients who receive their HIV medications from other sites.

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