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Improved antiretroviral refill adherence in HIV-focused community pharmacies

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Abstract

Objective—To determine differences in patient characteristics, antiretroviral therapy (ART) regimen characteristics, and regimen refill adherence for HIV-focused pharmacy (HIV-P) versus traditional pharmacy (TP) users.

Design—Retrospective cohort study

Setting—California Walgreens pharmacies, May 2007 – August 2009

Participants—HIV-positive (HIV+) patients with greater than 30 days of antiretroviral prescription claims.

Main outcome measures—Modified medication possession ratio (mMPR) to calculate regimen refill adherence, and dichotomous measure of optimal adherence ≥ 95%.

Results—4254 HIV-P and 11679 TP users were included. Compared to TP users, HIV-P users traveled farther to pharmacies (5.03 vs. 1.26 miles), filled more chronic disease medications (35% vs. 30%), and received more fixed-dose combination tablets (92% vs. 83%); all $p < 0.01$. Median mMPR was higher for HIV-P users (90% vs. 77%, $p < 0.0001$). After adjustment for age, gender, insurance, medication use, and distance from pharmacy, use of HIV-P (OR= 2.18, 95% CI 1.88–2.52) and use of fixed-dose combination antiretroviral tablets (OR=2.43, 95% CI 1.83–3.22) were factors most strongly associated with having ≥ 95% regimen refill adherence.

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Conclusion—For HIV+ patients struggling with antiretroviral adherence, clinicians could consider minimizing pill burden with combination tablets and referral to an HIV-focused pharmacy.

Keywords

antiretroviral; adherence; community pharmacy; HIV; medication therapy management

Introduction

For patients requiring long-term drug therapy for a chronic disease, medication adherence is a significant contributor to optimal health. A patient may schedule only two or three appointments per year to see their physician; however, that same patient may visit the pharmacy four to twelve times per year because medications are typically dispensed as monthly or quarterly supplies. The pharmacist may be the health care professional a patient has the most frequent contact with. Consequently, community pharmacies are at a unique and potentially influential juncture in the landscape of contemporary health care.

For patients infected with Human Immunodeficiency Virus (HIV), adherence to antiretroviral therapy (ART) is critical to maintain viral suppression, reduce HIV-related morbidity, and avoid acquisition of drug resistance.[1, 2] Achievement of optimal HIV treatment outcomes is complicated by an array of medication-related challenges such as regimen complexity and side effects that undermine adherence. Furthermore, lack of patient, provider, and pharmacist familiarity with ART nomenclature, numerous drug-drug interactions, and difficulties with state-funded payment assistance systems can all impact adherence. HIV+ patients are at higher risk for medication errors, duplicate therapy, and non-adherence due to HIV medications not being stocked and the inconvenience of making multiple trips to the pharmacy to procure a complete regimen.[3–6] To ameliorate these issues, some community pharmacies now provide longitudinal HIV medication therapy management (MTM) services at designated locations.[7–9]

While HIV-focused pharmacies are perceived to be beneficial, few studies have determined their impact on patients. Considering the availability of enhanced patient counseling, continuous availability of medication, and patient assistance in obtaining refills in a timely manner, one expected benefit of using a pharmacy focused on HIV might be increased medication adherence. The primary objective of this study is to determine whether use of these types of disease state-focused community pharmacies influences treatment adherence, using HIV as a model chronic disease primarily managed by drug therapy.

Methods

Study Population

De-identified prescription records for patients filling any ART prescription at any California Walgreens Pharmacy during the study period of 5/16/07 – 8/21/09 were retrieved. Patients were excluded if they were <18 years of age, if the prescription record did not have a recorded date of sale or if they had inadequate information to calculate a medication

possession ratio, if the patient had filled less than 30 total days of HIV medications total over the study period, or if the patient filled ART prescriptions at both a Walgreens HIV-focused pharmacy (HIV-P) and a Walgreens traditional pharmacy (TP) during the study period. Provisions within Walgreens Corporation's standards of practice ensured that the medication profiles were able to be used for the purposes of research. The study was approved by the University of California San Francisco Committee on Human Research.

Outcome of interest

The primary outcome of interest for this study was antiretroviral regimen adherence, as documented by prescription refill history. Pharmacy refill regularity has been found to correlate with immunologic and virologic outcomes in HIV-positive patients.[10–15] Adherence was based on whether the patient possessed an "adequate" antiretroviral regimen on a given study day. The definition of "adequate" was based on the U.S. Department of Health and Human Services HIV treatment guidelines and definitions created by observational cohort studies in the United States and Europe.[16–18] The regimen was considered "adequate" if it contained three or more antiretroviral drugs, one of which had to fall within the following categories: protease inhibitor, non-nucleoside reverse transcriptase inhibitor, abacavir, tenofovir, raltegravir, maraviroc, or enfuvirtide. If the patient's ART satisfied the "adequate" regimen criteria, he or she was considered "regimen adherent" for that study day. Regimen adherence was calculated using a modified medication possession ratio (mMPR) that summed the total number of regimen adherent study days, divided by the number of patient study days. To calculate the contributed number of study days the patient's first prescription date was subtracted from the last prescription date; the days supply for the last refill was then added to this value. Median ART regimen refill adherence and proportion of patients achieving optimal regimen adherence over the duration of the study (e.g. ≥ 95%) was compared between study groups. Although most modern ART regimens may maintain HIV viral suppression and avoid development of resistance mutations at lower levels of adherence, we selected 95% as our optimal cutoff because pharmacy refills serve as an adherence proxy and may overestimate actual pill-taking.[2, 19–22]

Exposure of interest and potential predictors

Participants were divided into two exposure groups: patients who used any one of seven Walgreens HIV-focused pharmacies versus patients who used traditional Walgreens pharmacy locations to fill their antiretroviral prescriptions. Walgreens HIV-focused pharmacies are located in various cities throughout California including San Francisco, Palm Springs, Los Angeles, San Diego, and in Orange County. Other relevant covariates such as age, gender, and third party payer, were included in the analysis. Other sociodemographic predictors which potentially affect the primary outcome of adherence are described in Table 1. As data were extracted from a prescription medication database, race and clinical outcomes such as CD4+ cell counts and viral loads were not available.

Statistical analyses

In order to detect a 10% difference in adherence between groups (standard deviation estimated at 0.30, with a two sided α of 0.05, and 80% power) the required sample size was

calculated to be 176 patients per group. However, because this was a retrospective cohort study, all eligible patients were included.

ART regimen refill adherence in the two groups was measured using the mMPR described previously and compared using the Mann-Whitney U Test for non-normally distributed data. Differences in patient and regimen characteristics were analyzed using Wilcoxon rank sum, Student's t-tests, and Chi Square tests for proportions. A multivariable logistic regression model was constructed to determine independent factors which contributed to having ≥ 95% regimen refill adherence. Covariates included in the logistic regression model included age, gender, insurance, use of AIDS Drug Assistance Programs (ADAP), patient's distance from home to the pharmacy, prescriptions filled per month, presence of medications for chronic conditions, presence of medications for psychiatric conditions, and use of opportunistic infection prophylaxis.

Results

21169 patients filled ART prescriptions during the study period. There were 140 patients under 18 years of age, 991 patients who did not have adequate information to calculate mMPR (such as missing prescription fill dates), 509 patients who did not have store information or who were HIV-P and TP dual users, and 3596 patients who had filled a 30 day supply of medicine or less who were excluded from the analysis, leaving 4254 HIV-P and 11679 TP users in the study. During the study period, 59 (0.6%) patients who used TP and 51 patients (1%) who used HIV-P died ($p < 0.001$). Patient characteristics for HIV-P and TP users are presented in Table 2. Compared to TP users, HIV-P users traveled farther to their pharmacies (5.03 vs. 1.26 miles, $p < 0.01$), filled more chronic disease medications (35% vs. 30%, $p < 0.01$) and psychotropic medications (42% vs. 39%, $p < 0.01$), and received same-class fixed dose combination (FDC) antiretroviral tablets or mixed-class FDC (also referred to as single-tablet regimens) more often than their counterparts (92% vs. 83%, $p < 0.01$). HIV-P users had significantly better regimen refill adherence as measured by median mMPR (90% vs. 77%, $p < 0.0001$).

Factors associated with achieving high regimen refill adherence are presented in Table 3. The multivariable model was adjusted for age, gender, insurance type, use of ADAP, distance from the pharmacy, median number of prescriptions filled per month, presence of a chronic disease other than HIV infection, pain, or psychiatric medications, and use of fixed dose combination antiretrovirals. Factors that were associated with ≥95% regimen refill adherence included use of HIV-P, use of fixed dose combination antiretroviral tablets, male gender, and private or other insurance versus public insurance. Factors associated with decreased adherence included younger age categories (30–65 years) and use of ADAP. Concurrent receipt of medications for psychiatric or pain conditions was also associated with a lower likelihood of achieving optimal regimen refill adherence.

Discussion

Clinicians counsel patients to take their medications, yet a patient's resolve may diminish without timely assessment or detection of poor-adherence behaviors. Community

pharmacies remain an underutilized resource to detect and intervene in response to poor adherence. Pharmacists make ideal treatment advocates because they can build trusted relationships with patients and are trained to discuss medication-related problems and adherence when conducting MTM evaluations.[23, 24]

Pharmacist MTM models for diabetes, hypertension, asthma and other chronic diseases have been evaluated, yet few studies have addressed HIV-focused community pharmacies.[25–28] HIV is an excellent model for studying adherence in a chronic disease. It requires the patient to take multiple medications in combination over a prolonged time period, the medications have challenging side effects and interactions, and the consequences of poor adherence include development of resistance, opportunistic infections, and increased mortality. In 2005, the California Department of Health Services developed a pilot program which provided funding to ten pharmacies that met the following criteria: they possessed a high proportion (>90%) of HIV/AIDS patients, provided specialized, individualized, face-to-face services, and had appropriate personnel to identify patients for MTM services. Similar to the findings in our study, patients using these 10 community HIV specialty pharmacies were more likely to be classified as adherent (69.4% vs 47.3%, $p < 0.001$) compared to those who used non-pilot pharmacies.[7, 8] Face-to-face services and MTM were not predefined or standardized by the pilot program. A follow-up study determined that most of the pharmacies engaged in patient counseling only when overuse or poor adherence was detected, and that most pharmacies offered telephone refill reminders to their patients.[9] However, the California pilot pharmacy program only included patients with Medicaid insurance, included patients who did not fill all their ART prescriptions at HIV-focused pharmacies, categorized optimal adherence as greater than 80%, and assessed adherence using a single benchmark drug within a regimen. Lastly, ART regimens have changed dramatically since the completion of the aforementioned study, and more streamlined options (such as complete regimen fixed-dose regimen tablets) which facilitate adherence are now available.[29, 30]

Most adherence interventions are multi-modal. Within HIV-focused pharmacies there may be specific interventions or combinations of interventions which impact adherence. HIV community pharmacists can provide knowledgeable adherence counseling, facilitate insurance coverage of antiretrovirals, enroll patients in state-funded ADAPs, oversee novel adherence programs, offer special medication reminder packaging, and other patient-specific services. For the HIV-focused pharmacies included in this study, one unique element may have been intensive staff education. Pharmacists undergo more than 25 hours of training in an HIV certificate program designed for community pharmacists offered through the University of Buffalo and are also provided with internally prepared supplemental training materials. HIV pharmacotherapy, medication management, and social and cultural issues around HIV are topics covered in the coursework. The program’s overarching goal is to equip the pharmacy staff with the knowledge and skills needed to appropriately assess, counsel and manage patients living with HIV and related comorbidities. Further studies are needed to identify the components of specialized pharmacy models which have the greatest impact on adherence, to allow these practices to be adopted across the spectrum of all pharmacies.

Although the adherence intervention is not easily characterized, our study still found higher ART refill adherence in HIV-focused pharmacies. For patients who are new to ART, who are having difficulty adhering to therapy, or who are having difficulties understanding and obtaining their medicines, clinicians might consider a referral to an HIV-focused community pharmacy to help the patient overcome these challenges. For other patients who are stable and who do not have difficulties with their ART, retaining their relationship with a traditional community pharmacy may be optimal. It is important for clinicians to ask their patients whether they are having difficulties with their medications, so that the patient can be offered the best pharmacy care possible.

One limitation to our study is the challenge of measuring antiretroviral adherence accurately. Dispensing pharmacies are a valuable and underutilized resource for measuring adherence; refill records are a readily obtainable, practical marker to identify patients with poor adherence with a specialized pharmacy “intervention”. These records estimate the time a patient is able to adhere to a medication because they have an available drug supply.[31] Until a significantly more accurate method of adherence quantification is developed, availability and practicality remain equally important characteristics for widespread adoption in clinical practice. Our study assumed a closed system in which patients only filled their medications at the pharmacy chain studied, and not at other pharmacies. Many methods have been used to calculate adherence from pharmacy refill records.[32] We chose a modified medication possession ratio because it is one of the most commonly used measures and has been determined to be more robust compared to others.[33] ART offers additional methodological challenges in that adherence to a whole regimen, not just one drug, must be calculated. Unlike other studies which use a benchmark antiretroviral to calculate regimen adherence (this assumes similar adherence to all components of the regimen) we incorporated a more robust definition of regimen adherence.[17, 18] This definition, though more strict than single drug calculations, allows for some odd combinations to be credited as “complete” ART regimens (e.g. boosting doses of ritonavir plus another protease inhibitor plus one nucleoside reverse transcriptase inhibitor). Our definition does not consider patients who were highly adherent to non-standard regimens containing less than three ART drugs prescribed for tolerability or resistance reasons. The definition cannot account for early refills. These two limitations may underestimate adherence in both groups. Studies which assess pharmacy refill adherence for less than 6 months may not accurately reflect ART adherence; however, in our study patients were followed for approximately 2 years.[34] This was a cross sectional study which did not have information about patients’ duration on ART and how that may affect pharmacy use. Patients who are new to ART or who are more motivated may seek out specialized pharmacies; alternatively, patients who are on salvage therapy due to poor adherence may have been referred by providers to an HIV focused pharmacy. Lastly, while laboratory data such as CD4+ cell count or HIV viral load were unavailable, pharmacy refill measures correlate well with virologic and immunologic outcomes.[10–12, 15]

Conclusion

Our study found that use of an HIV-focused community pharmacy was associated with improved adherence compared to use of traditional pharmacies. Specific interventions

associated with this improved adherence are unclear. Pharmacist training, consistent stocking of key ART regimens, assistance with third party payer reimbursement, and other factors are all possible explanations for this finding. For HIV+ patients having difficulty with adherence to ART, clinicians might consider minimizing pill burden and referring them to an HIV-focused pharmacy.

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Table 1

Study Definitions

Regimen adherent	Possession of three or more antiretrovirals on any given study day. In order to be categorized as regimen adherent, one of the three drugs must fall into the following categories: protease inhibitor, non-nucleoside reverse transcriptase inhibitor, abacavir, tenofovir, raltegravir, maraviroc, or enfuvirtide.
Fixed Dose Combination Tablet	Ever use of any of the following combination tablets: • zidovudine/lamivudine/abacavir • zidovudine/lamivudine • lamivudine/abacavir • tenofovir/emtricitabine • tenofovir/emtricitabine/efavirenz • lopinavir/ritonavir
Received prophylaxis for opportunistic infections	Inferred by the presence of any of the following prescriptions filled to prevent *Pneumocystis jirovecii* pneumonia or *Mycobacterium avium* complex during the study period: • Sulfamethoxazole/trimethoprim 800/160 mg, 1 tablet orally daily for > 14 days • Dapsone 100mg orally daily for > 14 days • Atovaquone 750 mg orally twice daily or 1500 mg orally daily for > 14 days • Azithromycin 600 mg two tablets orally once weekly, 500 mg orally daily for > 14 days, or 250 mg orally daily for > 14 days • Clarithromycin 500 mg orally twice daily for > 14 days
Co-morbid conditions	Inferred by the presence or absence of a prescription claim for any medications within the following classifications: diabetes, hypertension, hypercholesterolemia, psychiatry (classified by mood, anxiety, depression), or pain (classified by pain and inflammation).
Average medications per month	Average number of medications per patient per month. Medications were identified by a generic product indicator and normalized for any fills greater than 30 days.
Distance to pharmacy	Geocoded from patient's address using either rooftop (most sensitive) or zipcode centroid, to the pharmacy which the patient utilized most often during the study period.

Table 2

Baseline Characteristics of HIV-positive patients using Walgreens Pharmacies, 5/16/2007 – 8/21/2009

Characteristic[a]	Traditional Pharmacy Users (N=11679)	HIV-focused Pharmacy Users (N=4254)	p[c]
Age, years, mean (SD)[b]	47.1 (10.2)	47.1 (10.2)	0.38
Male gender, n (%)	10119 (87)	3850 (91)	<0.001
Insurance, n (%)			<0.001
Public[d]	3536 (30)	1192 (28)	
Private	5476 (47)	959 (23)	
Other	2151 (18)	2025 (48)	
Unknown	516 (4)	78 (2)	
AIDS Drug Assistance Program during study, n (%)	3700 (32)	2764 (65)	<0.001
Distance from pharmacy, miles, median (IQR)[e]	1.26 (0.5–3.4)	5.03 (1.7 – 22.0)	<0.0001
Number of prescriptions filled per month, median (SD)	1.9 (0.9–3.6)	1.8 (0.9–3.6)	0.15
Filled medicines for common chronic diseases[f], n (%)	3560 (30)	1505 (35)	<0.001
Diabetes, n (%)	713 (6)	265 (6)	
Hypertension, n (%)	1382 (12)	415 (10)	
Hyperlipidemia, n (%)	2517 (22)	1269 (30)	
Filled prescription for psychiatric condition, n (%)	4537 (39)	1767 (42)	0.004
Filled prescription for pain medication, n (%)	3924 (34)	1403 (33)	0.03
Filled prescription for opportunistic infection prophylaxis[g], n (%)	2041 (17)	883 (21)	<0.001
Ever use of fixed dose combination tablets			
NRTI fixed dose combination tablets	7106 (61)	2840 (67)	
Multi-class fixed dose combination tablet	3010 (26)	1197 (28)	
Types of antiretroviral regimens represented[h,i]			
NRTI-based regimen	5888 (50)	927 (22)	<0.001
NNRTI-based regimen	5224 (45)	1873 (44)	0.431
PI-based regimen	5659 (48)	2309 (54)	<0.001
Other regimen	1504 (13)	699 (16)	<0.001
Ever in possession of ART inconsistent with treatment guidelines[h]	6281 (54)	1200 (28)	<0.001
Median proportion of days in possession of an “adequate” antiretroviral regimen (mMPR), (IQR)	0.77 (0.34–0.92)	0.90 (0.80–0.96)	<0.0001
Possessed “adequate” regimen 50–79% of study days, n(%)	2485 (21)	713 (17)	
Possessed “adequate” regimen 80–94% of study days, n(%)	3673 (31)	1994 (47)	
Possessed “adequate” regimen ≥ 95% of study days, n(%)	1833 (16)	1187 (28)	

[a] Percentages may not add up to 100% due to missing data

[b] SD=standard deviation

[c] Chi-Square used for categorical variables & Student’s T-Test or Wilcoxon Rank Sum used for continuous variables.

[d] Public health insurance includes Medicaid/Medi-CAL and Medicare

[e] IQR=Interquartile Range

[f] Common chronic diseases screened for include diabetes, hypertension, hyperlipidemia

[g] Opportunistic infection prophylaxis included pneumocystis jirovecii and mycobacterium avium complex

[h] Determined by medications a patient was in possession of, on any given study day

[i] NRTI=nucleoside reverse transcriptase inhibitor, NNRTI=non-nucleoside reverse transcriptase inhibitor, PI=protease inhibitor

Table 3

Factors associated with > 95% antiretroviral regimen refill adherence

	Univariate RR[a] (95% CI)	Adjusted RR[a] (95% CI)
Use of HIV-focused pharmacy	2.08 (1.91–2.26)	2.18 (1.88–2.52)
Age		
< 30 years	Ref	Ref
30–49	0.70 (0.59–0.83)	0.75 (0.56–0.99)
50–69	0.58 (0.49–0.70)	0.74 (0.55–0.99)
70+	0.30 (0.20–0.46)	0.50 (0.24–1.02)
Male gender	1.54 (1.34–1.76)	1.34 (1.07–1.68)
Insurance		
Public[b]	Ref	Ref
Private	1.30 (1.17–1.44)	1.32 (1.12–1.56)
Other	2.01 (1.81–2.24)	1.62 (1.29–2.05)
Unknown	1.16 (0.92–1.46)	1.40 (0.95–2.05)
AIDS Drug Assistance Program use during study	1.38 (1.27–1.49)	0.75 (0.61–0.93)
Distance from pharmacy		
< 10 miles	Ref	Ref
10–29 miles	1.33 (1.13–1.57)	1.08 (0.82–1.43)
30+ miles	1.19 (1.09–1.29)	0.98 (0.85–1.12)
Number of prescriptions filled per month, median	0.92 (0.91–0.94)	0.99 (0.96–1.02)
Use of any fixed dose combination tablets	3.74 (3.16–4.41)	2.43 (1.83–3.22)
Filled any medicines for common chronic diseases[c]	0.89 (0.82–0.97)	0.95 (0.81–1.11)
Filled prescription for psychiatric condition	0.81 (0.75–0.88)	0.74 (0.64–0.85)
Filled prescription for pain medication	0.70 (0.64–0.77)	0.82 (0.71–0.94)
Filled prescription for opportunistic infection prophylaxis	1.05 (0.93–1.19)	0.94 (0.83–1.08)

[a] Abbreviations: RR, relative risk; 95% CI, 95% confidence interval

[b] Public health insurance includes Medicaid/Medi-CAL and Medicare

[c] Chronic diseases include hypertension, diabetes, hyperlipidemia