Use of Pharmacy Refill Data as a Measure of Antiretroviral Adherence

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Pharmacy refill adherence has become an increasingly important measure of adherence to antiretroviral medications. It offers a simple, inexpensive, and valid method for measuring adherence. Over the past year, there have been several published developments in the use of pharmacy refill data to measure adherence. Given the utility of this adherence measurement, it is likely that pharmacy refill will be the method of choice for measuring antiretroviral adherence in an increasing number of clinical and research settings.

Introduction

Adherence to antiretroviral therapy is critical to the successful treatment of HIV. Central to clinical practice and clinical research regarding adherence is accurate measurement. Although many different adherence measurement techniques exist, all have limitations. Self-reports tend to be specific but not sensitive. Microelectronic monitors tend to be expensive for clinical practice and can be cumbersome to work with in clinical research. Drug concentrations assess a combination of adherence and drug absorption and metabolism with the latter two factors adding undesirable variability to the measurement. Pharmacy refill measures have been used to assess adherence to a variety of pharmacotherapies. A major advantage of pharmacy refill data over self-reports is the objective nature of the data—that is, it does not rely on patient recall, which is fraught with both intentional and unintentional measurement error. Furthermore, for retrospective studies in which adherence measurement has not been formally included, pharmacy refill data are typically the only choices for assessing this critical variable.

Pharmacy data are likely to be accurate measures of actual refills because of the implications of data errors. If pharmacies could not capture actual prescriptions filled, they are unable to bill for the medication, thereby losing money. If they erroneously included data on medications not truly filled, they would be committing fraud and be subject to disciplinary action. Therefore, even though this technique does not measure medication taking behavior directly, it does assess medication refill behavior. Because obtaining refills takes effort and/or costs money, it is assumed to be relatively uncommon for individuals to obtain refills without actually having used up their prior supply. Moreover, the validity of refill data has been established in HIV because these measures have been associated with virologic response, a phenomenon virtually entirely dependent on exposure to antiretroviral drugs.

The seminal paper describing and validating the use of pharmacy refill data as a measure of medication adherence in general was published by Steiner et al. [1]. Subsequently, they went on to codify different approaches to using refill data as an adherence measure [2]. Because the adherence patterns that result in better or worse outcomes differ based on pharmacokinetics and pharmacodynamics, this paper provides approaches that may be more or less relevant for any one particular drug-disease relationship. The number of papers using these approaches outside of the HIV setting is too large to enumerate here.

Validation and Refinement of Pharmacy Refill Data as an HIV Adherence Measure

The pharmacy refill approach was first validated in HIV by the University of British Columbia Centre of Excellence in HIV/AIDS [3]. In that study, 886 patients on therapy for 1 year were included and followed thereafter for the outcome of virologic failure (viral load > 500 copies/mL). Adherence was defined as the number of refills obtained over time/number of months of follow-up and classified as less than 70%, 70% to less than 80%, 80% to less than 90%, 90% to less than 95%, and 95% or greater based on work assessing the relation between protease inhibitor (PI) adherence and suppression using microelectronic monitors. They found a dose-response relationship with a highly significant test for trend ($P = 0.001$). The limitation

to this approach was that it required 1 year of follow-up. If used over a shorter time period, the amount of variability in adherence that can be captured rapidly decreases. For example, using this measure over a 3-month period in which four refills are meant to be obtained, adherence can only be 100% (4/4), 75% (3/4), 50% (2/4), 25% (1/4), or 0% (0/4). Given the importance of the range of adherence between 75% and 100%, other approaches need to be taken for relatively precise adherence measurement over shorter time intervals.

To address the need for a more precise adherence measure over shorter time periods, Grossberg et al. [4•] used a time-to-refill approach. Here, rather than counting the number of refills over a fixed period of time, the authors calculated adherence for a fixed number of doses. They used the following formula: (number of doses/time between refills to calculate adherence) x 100%. Here, the number of doses was fixed (eg, 90 for a once-daily drug over 3 months), and only time varied based on an individual's refill pattern. This approach solved the problem of precision for a shorter time interval. Furthermore, it addressed some of the misclassification inherent in the Low-Beer approach. If an individual obtained one refill 1 day later than expected and all the rest on time over 3 months, the Low-Beer approach would not capture the final refill, and adherence would artificially drop to 75%. In the time-to-refill approach, the 1 day would only contribute a small amount to the overall adherence measure (eg, 90/91 = 99% adherence).

Grossberg et al. [4•] demonstrated the validity of this approach in a study using data from the Philadelphia Veterans Affairs Medical Center. In that study, adherence was included as a continuous measure and dichotomized as good versus poor at 85%. Adherence correlated with change in viral load with each 10% increase in adherence resulting in a 0.12 log copies/mL reduction in HIV viral load (95% CI, 0.01–0.23 log copies/mL). This association, although statistically significant, was of a lesser magnitude than often found in studies measuring adherence using microelectronic monitors. Factors that may have prevented a stronger correlation between adherence and viral load were the inclusion of patients on various regimens for various periods of time and lack of data on the potential for preexisting resistance. When the data were limited to individuals with high viral loads at baseline (allowing for a broader range of values in the correlation analysis) and individuals who were on their first regimen (unlikely to have resistance), the association between adherence and viral suppression was stronger. This finding strengthened the validity of this methodologic advance.

Comparison of Pharmacy Refill and Self-reported Measure of Adherence

Self-report is the most commonly used measure of antiretroviral adherence. However, concerns regarding the sensitivity for nonadherence persist. Grossberg et al. [4•] compared pharmacy refill adherence using the time to event approach with a 4-day recall self-report measure. Both measures demonstrated the relation between adherence and virologic response, but the pharmacy refill measure was more strongly associated with the outcome. Furthermore, when limiting the analysis to individuals who self-reported 100% adherence, the refill measure was still able to demonstrate significant differences between patients who the refill measure classified as actually having less than 85% adherence versus 85% adherence or greater. Therefore, the refill measure was sensitive to nonadherence when the self-report measure was not. The strength of this comparison rests with the fact that the person asking the self-reported adherence questions was not associated with the clinical service, and therefore, less bias due to socially desirable answers would be expected. The major limitation of this study was not comparing the pharmacy refill measure to other self-reported measures including visual analog scale over 30 days or audio computer-assisted self-interview strategies. These other measures may compare more favorably with pharmacy refill data, but comparisons have not been performed to date.

Use of Pharmacy Refill Measures to Demonstrate Adherence/Outcome Relationships

Many studies have implemented pharmacy refill data to demonstrate the importance of adherence on clinical and virologic outcomes. Wood et al. [5,6] repeatedly demonstrated the relation between adherence and CD4 count gains in several populations. Harrigan et al. [7] demonstrated that individuals with high but suboptimal adherence (80%–90%) were at the highest risk for developing antiretroviral drug resistance. Wood et al. [8] demonstrated that starting antiretroviral therapy at CD4 counts of 350 cells/mm^3 (the current standard in much of the developed world) did not result in better survival than starting at 200 cells/mm^3 except in the individuals with poor adherence. Because predicting an individual's adherence is extremely inaccurate, this paper justified the rationale for starting therapy at 350 cells/mm^3 in settings where that is financially and logistically feasible.

Use of Pharmacy Measures to Determine Factors Associated with Adherence

Many variables have been associated with antiretroviral therapy adherence. Wood et al. [9] found those who had used injection drugs, in general, had lower rates of adherence than non-users. However, after controlling for adherence, injection drug users had similar rates of viral suppression. Palepu et al. [10] used pharmacy refill data in a study which found that methadone maintenance was protective against antiretroviral nonadherence among hepatitis C virus coinfected injection drug users. Turner et al. [11] found that

among drug users, females had worse adherence than males. Additionally, they found that mental health services were protective against nonadherence for women and addiction services were protective for men [11]. This finding supported earlier work in which postpartum women with HIV infection had overall poor adherence to antiretrovirals [12,13].

Gross et al. [14] used pharmacy refill records to assess pharmacy-based barriers to antiretroviral adherence. They found individuals who obtain their medications via mail order had better adherence than those who picked up their medication at the pharmacy itself. Braitstein et al. [15] found that hepatitis C virus infection was independently associated with worse adherence after controlling for other potential confounding factors. Braithwaite et al. [16] compared adherence across initial regimens and found that non-nucleoside analog reverse transcriptase inhibitor use was associated with better adherence than PI use ($P < 0.001$), although adherence with all regimens was relatively suboptimal.

Pharmacy refill to measure the dynamics of adherence

Refill adherence typically measures adherence over a single, fixed time period. For example, refill adherence can be calculated as a percentage of the number of days of medication prescribed over the number of days between refills for a set number of refills. However, at least two recent articles looked at adherence as a time-varying phenomenon. Gross et al. [17••] reported the use of refill data to examine the dynamic nature of adherence over time. Based on an analysis of data from the British Columbia Centre for Excellence in HIV/AIDS and its HIV/AIDS Drug Treatment Program, the investigators studied the time to virologic failure (viral load > 1000 copies/mL on two successive measurements) in a cohort of patients who had achieved viral suppression. Refill adherence was measured across multiple prescription intervals in each patient, with a prescription interval spanning three refills. Adherence was thus measured as a time-varying variable. They found that a time-updated measure of adherence was associated with virologic outcome, with a higher proportion of virologic failures occurring in patients with declining adherence. The validation of a measure that accounts for changes in an individual's adherence over time has important clinical implications as it may be a useful tool for predicting an individual's risk for virologic failure.

In another study examining the dynamic nature of adherence, Gardner et al. [18] reported results from a retrospective study based in an integrated public health and pharmacy system in Denver, Colorado. They used a refill adherence measure of the number of doses obtained/the number of doses prescribed x 100 and examined sequential 120-day periods of data for each patient. They analyzed adherence over time with respect to changes in adherence over the course of an initial regimen and changes in adherence across subsequent regimens. Adherence to an initial regimen declined over time at a rate of 2.6% per year. This effect remained significant when patients were grouped by duration of the regimen, because this may have been an effect modifier. Even in patients on initial regimens for longer than 28 months, there was a 5% per year decline in adherence. Additionally, regimen adherence defined as refill adherence over the course of an entire regimen declined with each subsequent regimen (first regimen 90.4% adherence, second regimen 86.3%, third regimen 79.5%). Both of these findings suggest that adherence declines over time and may support the hypothesis of pill taking fatigue as a factor affecting adherence over time. The authors suggest that unique interventions are called for to address adherence over the course of a regimen, even long lasting ones.

Pharmacy refill adherence in the developing world

Most studies that have used pharmacy refill data as a measure of adherence have been located in the developed world. Adherence measurement in the developing world poses unique challenges including those related to cost and health infrastructure. Most studies in the developing world, therefore, have used self-report to measure adherence to highly active antiretroviral therapy (HAART). Pharmacy refill, because of its low cost and applicability to large populations, has made inroads in studies in resource-limited settings.

Nachega et al. [19•] reported results from an observational cohort study in southern Africa using pharmacy claims data from a private HIV/AIDS disease management program. This program is linked to private medical insurance and covers the cost of antiretroviral medications without copayment. In their cohort, they measured adherence as a percentage of the number of months of claims submitted for HAART divided by the number of months between the date HAART commenced and death, termination from the program, or the end of the study. They found that adherence, as measured by pharmacy claims data, was strongly associated with survival [19•]. Supporting this finding was a dose-response relationship of adherence and survival with each 20% decrease in adherence below 80% associated with decreased survival. Overall, the risk of death in those with adherence less than 80% was threefold that of those with adherence greater than 80% (relative hazard 3.01, $P < 0.001$). In a subsequent report, the same investigators reported an association of adherence to non-nucleoside reverse transcriptase (NNRTI)-based HAART with virologic outcome [20]. As with their prior findings, they noted a dose-response relationship of adherence with viral suppression. Additionally, the authors reported that there were high rates of virologic suppression even at relatively modest levels of adherence to NNRTI-based regimens, supporting the use of these agents over unboosted PIs.

Bisson et al. [21] used a pill count–adjusted pharmacy refill measure in examining causes of virologic failure in patients initiating NNRTI-based HAART in Botswana.

The authors conducted a case-control study of patients initiating NNRTI-based HAART and either maintaining virologic suppression (controls) or experiencing virologic failure (cases, viral load > 1000 copies/mL). Patients received medication from Botswana's National Antiretroviral Therapy Program where HAART was dispensed from the clinic by a pharmacist, who recorded the quantity and date of dispensing and the number of pills remaining since the last refill. Adherence was measured over an interval 90 days prior to the viral load value used to define cases and controls and was calculated as: (number of days for which HAART was dispensed – number of days of therapy remaining)/(number of days from HAART commencement to the end date) x 100%. This measure combined pharmacy refill data and the pill count performed by the pharmacy. The findings in this study included that virologic failure may occur despite high levels of adherence. Importantly, the authors note that the simplicity and low cost of using pharmacy refill to measure adherence may prove essential to monitoring HIV care in resource-limited settings.

Ad Hoc Refill Data Collection

Most studies using pharmacy refill data in HIV research have relied upon automated databases. However, clinicians and researchers outside of settings such as the Veterans Affairs Medical Centers or the British Columbia Centre of Excellence in HIV do not have access to such records. A concern with contacting pharmacies in the United States is potential confusion over the Health Insurance Portability and Accountability Act. Anecdotes of health professionals refusing to share medical information regarding patients have become commonplace. Although this refusal typically stems from misinterpretation of the law and unfounded fear of liability for sharing medical information for appropriate ends (ie, assessment of adherence to assist with treatment), the potential barrier remains.

Graham et al. [22•] conducted a study in which the pharmacies of research patients at two academic HIV practices in Philadelphia were contacted directly to obtain antiretroviral refill data. They recruited 87 patients who had been on HAART for at least 3 months to prevent inclusion of patients who may have been on their regimen for too short a period of time to achieve viral suppression. The PI or NNRTI was the index drug except for boosted PI regimens and triple nucleoside regimens where ritonavir and abacavir were the index drugs, respectively. Adherence over the previous 3 months was defined as: (days' supply dispensed/days between refills) x 100% and could range from 0% to greater than 100%. Thirty-three of 45 (73%) individuals with greater than 95% adherence per pharmacy refill data had viral loads less than 50 copies/mL whereas only 19 of 42 (45%) with less than 95% adherence had undetectable viral loads ($P < 0.01$)

Interestingly, the authors did not encounter resistance on the part of pharmacists to share the refill information with the study team. Although it is possible that the barrier was lowered by the team having obtained informed consent for collecting the data, few pharmacies actually requested this information. They concluded that ad hoc contact of pharmacies was feasible for adherence measurement, at least on the relatively small scale of this study.

Other Methodologic Developments

Most studies that have used pharmacy refill as a measure of adherence have used at least 90 days, or three monthly refills, as the duration over which adherence is measured. It would be advantageous for both research and clinical practice to be able to rely on pharmacy refill measures over shorter periods of time. Acri et al. [23] analyzed data collected from a cohort at the Philadelphia Veterans Affairs Medical Center to determine if pharmacy refill measurement over 60 days and 30 days correlated with change in viral load. Using the number of days' supply dispensed divided by the number of days between refills for 60-day and 30-day time intervals, the authors concluded that pharmacy refill adherence over 60-day periods were significantly associated with viral load change, but the 30-day time intervals were not. Therefore, shorter interval measurements that detect nonadherence may allow for interventions that forestall the virologic failure that would have been inevitable over long periods of time.

Future Needs

Although pharmacy refill methods provide a valuable adherence measurement resource, more development is needed. These measures need to be expanded to the developing world where pharmacy records are typically kept electronically but have been underused to date. Given the strong relation between adherence and response and the limited resources for obtaining viral load measurements, pharmacy refill data should be explored as a tool for determining whether an individual is likely to fail therapy in the absence of viral load measurement. Furthermore, unlike measuring viral load, measuring adherence prior to virologic failure would allow for interventions to be implemented to forestall treatment failure due to nonadherence. Methodologically, advances are needed in assigning an adherence value to individuals who stop taking their medications and stop returning to the pharmacy. As currently constructed, refill measures require a final refill date to calculate the adherence over the prior interval. Without that final date, a percent adherence cannot be calculated. Therefore, research is needed in determining the length of the refill interval that could be used to construct this adherence percent.

Conclusions

Although recent advances in antiretroviral drug development have been remarkable, including once daily therapy and lower pill burdens, adherence is likely to remain a critical factor in treatment success. Issues such as substance abuse and depression are unlikely to be eliminated as adherence barriers in the developed world. Logistic problems and unrecognized behavioral barriers are likely to continue or emerge in the developing world despite current adherence rates that outstrip the developed world. A variety of adherence interventions are being studied. However, without the measurement of adherence, it would be impossible to uncover unrecognized barriers and evaluate novel interventions. Advances in pharmacy refill measurement methods make it an even better choice for monitoring adherence over the next generation of HIV treatment evolution.

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