Combination antiretroviral therapy among immigrant and indigenous HIV infected patients: quality of life and treatment adherence

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Abstract

Background: Refill data are increasingly used to assess adherence in HIV-infected patients on combination antiretroviral therapy. However, it is not clear how feasible this method is when multiple pharmacies are involved. Also, the effects of inclusion of leftover medication from previous refills and prescribed treatment time on adherence calculations are unknown. We addressed these questions in the present study.

Methods: Adult HIV-1-infected patients were recruited at the outpatient clinic of the Academic Medical Centre in Amsterdam and asked for their pharmacies’ names. Refill data were obtained from pharmacies. Percentages of patients misclassified as nonadherent when disregarding leftover medication and prescribed treatment interruptions were calculated. Finally, we investigated whether an average adherence calculation of all drugs or a calculation based on one drug in the regimen best predicted virological failure (plasma HIV-1 RNA >40 copies/mL).

Results: Two hundred one patients were included. Collecting data from multiple pharmacies (132) was found to be feasible. Forty-three percent of patients were misclassified as nonadherent when disregarding leftover medication and 2 percent when disregarding prescribed treatment time. There was no difference in predicting virological failure by different calculations of adherence.

Conclusions: These findings suggest that studies using pharmacy refill data should include leftover medication.

Key-words: Adherence; cART; Pharmacy refills; Operationalizing; Misclassification; Virological failure

Introduction

HIV-infected patients have to take lifelong combination antiretroviral treatment (cART). To prevent treatment failure, high levels of adherence to cART are necessary. Treatment adherence can be measured in numerous ways, although the main strategies used to date include self-reports of taken medication, electronic monitoring device systems and pharmacy refill counts. Pharmacy refill counts are increasingly used because data are generally available, it does not require large efforts from patients, its use is inexpensive, and data are objective. Additionally, pharmacy data are assumed to be reliable because pharmacies have to register medication refills to claim expenses with insurance companies. The validity of pharmacy refill adherence among HIV-infected patients has been supported by studies showing a relation between pharmacy refill adherence and virological response. Although pharmacy refill adherence is a promising method, a number of pertinent questions remain unanswered about the optimal way to operationalize this method. First, previous studies were carried out in “closed pharmacy systems” in which all data were retrieved from 1 registry. However, in many populations, medication is claimed at different pharmacies. The question arises how feasible collection of data is in a population with multiple pharmacies.

The second question relates to leftover medication from previous refills and how far back one needs to go to calculate leftover medication. An individual is classified as nonadherent when the pills collected are insufficient, while in reality he/she could have been adherent because he/she might have leftover medication in possession.

The third question relates to the added value of comparing pharmacy refills with prescribed treatment time. A physician might have advised the patient to stop taking medication because of, for example, adverse effects. Calculating adherence based on refills only would classify such a patient as nonadherent, while he or she actually adheres to an instructed treatment interruption.

Fourth, several calculations for adherence are possible, because cART regimens consist of more than 1 drug. Some studies defined nonadherence based on only a single drug in the regimen, typically the protease inhibitor (PI), non-nucleoside transcriptase inhibitor (NNRTI) or abacavir, that is, the index drug, whereas others used the lowest adherence percentage of any of the drugs used. The alternative is to calculate the average adherence to all drugs in the regimen. All methods illustrated that higher adherence resulted in a higher chance of HIV–RNA suppression. To date, no direct comparison among these methods in their ability to predict virological outcome has been published.

The first aim of the present study was to examine the feasibility of collecting pharmacy refill data in a population of HIV-infected patients with multiple pharmacies. The second aim was to investigate the added value of including leftover medication and prescribed treatment time in the calculation of pharmacy refill adherence when predicting virological failure. The final aim was to examine whether an average adherence measure or an adherence measure based on only 1 drug is the best predictor of virological failure.
Methods

Patients

Adult non-pregnant HIV-1-infected patients were recruited at the outpatient clinic of the Academic Medical Centre in Amsterdam between January 2008 and June 2009. Patients were eligible if they initiated cART after 1997, were using cART for at least six months, and had sufficient fluency in Dutch or English. Following a scheduled regular consultation, physicians or HIV counselors asked eligible patients whether they were willing to participate. Patients signed an informed consent, allowing the investigators to consult their pharmacies about medication refills and to check the patients’ medical files for information about socio-demographic variables, prescribed treatment time, and viral load results. The first viral load measure following inclusion in the study was retrieved. A detectable plasma viral load was defined as a load >40 copies HIV-RNA per milliliter of blood. During the entire study period, the Abbott m2000rt HIV-1 assay was used. The study was approved by the Institutional Review Board of the Academic Medical Centre, Amsterdam.

Collecting data about refills

Patients provided the investigators with names of the pharmacies from which they collected medication. Each pharmacy in the Netherlands has its own registration system. Patients typically collect their drugs every 90 days; however, this refill period may range from one week to 3 months. For each collected drug, the pharmacies register date of refill, collected number of medication, dosing instructions, prescription duration and prescriber. We sent a fax to each patient’s pharmacy to ask for medication refill data. We contacted more than one pharmacy per patient if applicable. For some patients who were receiving cART since at least two years, it was not possible to obtain medication refill data for the entire period of being on the current regimen because those patients could not provide us all former pharmacies. For those patients, we collected data on pharmacy refills for a period of at least two years preceding study inclusion. For our analyses, we assumed that medication was taken as prescribed until the supply was finished.

Calculation of adherence

We used an episode of ninety days prior to the viral load measurement as monitoring episode for refill adherence (figure 1). Within this episode, we considered all refills, including the last refill prior to the start of the 90-day episode, to calculate adherence. The number of refills within the episode could be 2 or more, resulting in 1 or more periods between refills in the 90-day episode. The first refill period runs from the last refill prior to the 90-day episode until the first refill within the 90-day episode. In this first refill period, only the number of days since the start of the 90-day episode is considered. The last refill period runs from the last refill in the 90-day episode till the date of viral load measurement.

For each period between 2 refills since starting the regimen used at study inclusion, we calculated adherence using the formula: collected medication at refill / prescribed medication per day / number of days between refills. If the supply of pills for a refill period exceeded beyond the 90-day episode or the date of a switch, we truncated adherence at 100%. Within the 90-day episode, we averaged the adherence percentages over all periods between refills for each drug separately.

Adding information about leftover medication and prescribed treatment time

We calculated adherence with and without taking into account leftover medication and/or prescribed treatment time information. This resulted in 4 adherence metrics: prescription-refill adherence including leftover medication (PRL), refill-only adherence including leftover medication (RL), prescription-refill adherence without leftover medication (PR), and refill-only adherence without leftover medication (R). Leftover medication of each refill period was rolled over to the next period between refills since starting the current regimen. In addition, we calculated leftover medication accounting for refills in periods of 6 months, 1 year and 2 years preceding the 90-day episode to investigate how far one needs to go back. We assumed that patients had leftover medication if they refilled medication while the number of pills dispensed at a former refill divided by the prescribed daily doses and multiplied by the days since the previous refill was higher than zero. The residual number of pills was rolled over to the next refill period leading to the following formula for nonadherence: (leftover medication of previous refills + collected medication at refill) / prescribed medication per day / number of days between refills.
Based on information in the medical files, we were able to adjust for treatment interruptions instructed by the physician (PR and PRL). The period of treatment interruption was considered as a period in which no medication had to be taken. This might result in leftover medication, which was in the patient’s possession at the restart of the treatment. This leftover medication was therefore added to the collected medication during the treatment interruption and taken to the next refill period.

Handling of multiple drug regimens in calculation
For each drug in the regimen, adherence was calculated. The first method to handle the multiple drug regimens was to calculate the average adherence of all drugs (usually 3). Adherence percentages could be higher than 100% because of the leftover medication and refill before the final date of the prescribed treatment time. Before averaging, we truncated the adherence percentage of each drug to 100%. Second, we calculated index adherence, for which we only captured the adherence percentage of a predefined index drug (PI, NNRTI or abacavir/tenofovir). Third, we assessed the lowest adherence percentage of any drug in the regimen.

Statistical analyses
We calculated what percentage of patients would be misclassified as nonadherent due to disregarding leftover medication and prescribed treatment time. Logistic regression was conducted to investigate the prediction of each adherence calculation on detectable viral load. In addition, for each adherence calculation we calculated the sensitivity (ie, percentage of patients with detectable viral load which is identified as nonadherent), specificity (ie, percentage of patients with undetectable viral load which is identified as adherent), positive predictive value (PPV) (ie, percentage of nonadherent patients who has a detectable viral load), and negative predictive value (NPV) (ie, percentage of adherent patients that has an undetectable viral load).

Results
Patients
Two hundred one patients were included in the study. Fifty-five percent (n = 110) were male, their median age was 43 years [interquartile ratio (IQR): 37-49]. Median number of years since first positive HIV-test was 6.4 (IQR: 3.5-9.3) and median number of years on cART was 5.3 (IQR: 2.3-7.8) with a minimum of 6 months. Twenty-seven patients (13%) used a combination tablet at study inclusion in which all drugs in the regimen were combined. Twenty-two patients (11%) had a detectable viral load (range: 42-490,111 HIV-1 RNA copies/mL blood) at the first viral load measurement after study inclusion. Fifty-four percent of patients were on NNRTI regimens, 3% on triple nucleoside reverse transcriptase inhibitor regimens, 38% percent on boosted PI-regimens, 2% on single PI-regimens, and 3% on regimens containing an NNRTI and a PI. More than 50% of patients reported more than 1 pharmacy since starting their current regimen, and we asked 132 pharmacies for refill data.

Adherence calculation including leftover medication and prescribed treatment time information
For 8 patients, we could not distinguish between nonadherence in the 90-day episode and difficulty in remembering the pharmacy. The pharmacies of 7 patients informed us that those patients did not claim medication for a while, and 1 patient was completely unknown to the reported pharmacy, which might indicate nonadherence for those 8 patients. Exclusion of those patients did not change our results, and therefore, we considered them nonadherent. We will only describe the results of the entire sample. There were no differences in using the average adherence calculation or a measure based on one antiretroviral drug (either an index drug or any drug with lowest adherence) in the prediction of detectable viral load. For example, the prediction on viral load of average adherence with a cutoff of 100% [odds ratio (OR) = 5.0; 95% confidence interval (CI): 2.0 to 12.6] was not significantly different from the adherence value based on the index drug (OR = 4.8; 95% CI: 1.9-12.0). Consequently, we decided to show only the results of the average adherence calculation.

One hundred fifty-six patients (78%) had leftover medication in possession at the last refill date before the start of the 90-day episode based on rollover medication since starting the current regimen. The median refill-only adherence of all patients was 89% for the adherence calculation excluding leftover medication (R) and 100% for calculations including leftover medication (RL). For prescription refill adherence, the medians were 90% (PR) and 100% (PRL) respectively.

Table 1 shows the number of patients who were classified as adherent with adherence cutoff values of <70%, <85%, <95% and <100%, for calculations including leftover medication and prescription information (PR). Additionally, Table 1 shows the percentage of patients that were misclassified as nonadherent when not including leftover medication or prescription information. Not taking into account leftover medication resulted in 43% of adherent patients being misclassified as nonadherent when using a cutoff of <100% and 24% when using a cutoff of <95%. When accounting for refills of 6 months prior to the 90-day episode, misclassification was 15%, for 12 months, it was 9% and for 2 years, it was 4% when using a cutoff value of 100% (Table 2). Lowering the cutoff value reduced the percentage of patients misclassified. If the prescription information was taken into account, the percentage of patients misclassified as nonadherent was around 2%.
Table 1: Percentage of patients misclassified as nonadherent due to not taking into account leftover medication and prescribed treatment time

<table>
<thead>
<tr>
<th>Cutoff Value, %</th>
<th>N</th>
<th>PR</th>
<th>RL</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 100</td>
<td>148</td>
<td>43%</td>
<td>2%</td>
<td>43%</td>
</tr>
<tr>
<td>&lt; 95</td>
<td>166</td>
<td>24%</td>
<td>2%</td>
<td>25%</td>
</tr>
<tr>
<td>&lt; 85</td>
<td>176</td>
<td>14%</td>
<td>1%</td>
<td>15%</td>
</tr>
<tr>
<td>&lt; 70</td>
<td>185</td>
<td>3%</td>
<td>2%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Table 2: Percentage of patients misclassified as nonadherent when taking into account different lengths of time for roll-over medication

<table>
<thead>
<tr>
<th>Cutoff Value, %</th>
<th>N</th>
<th>Rollover since start cART</th>
<th>No rollover (6 mo)</th>
<th>Rollover (1 yr)</th>
<th>Rollover (2 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 100</td>
<td>148</td>
<td>15%</td>
<td>9%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>&lt; 95</td>
<td>166</td>
<td>7%</td>
<td>2%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>&lt; 85</td>
<td>176</td>
<td>4%</td>
<td>1%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>&lt; 70</td>
<td>185</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>

Prediction of detectable viral load

Figure 2 shows the ORs for having a detectable viral load by different cutoff values of average adherence. All calculations of adherence predicted having a detectable viral load significantly (P < 0.05); the 95% confidence intervals overlapped. The ORs for prediction of having a detectable viral load were lower with a cutoff value of < 100% compared with other cutoff values; however, the CIs were much smaller.

ORs for the risk of having a detectable viral load were lower for adherence calculations without leftover medication (PR and R) than for adherence calculations including leftover medication (PRL and RL), and the ORs were higher for measures of refill-only (RL and R) compared with prescription refill (PRL and PR).

Table 3 shows the sensitivity, specificity, PPV, and NPV of predicting having a detectable viral load by different cutoff values for adherence, for each of the adherence calculations. Higher cutoff values have a higher sensitivity but a lower specificity and PPV. When including leftover medication, the PPV (percentage of nonadherent patients who actually has a detectable viral load) is higher; for example, a PPV of 25% for PRL versus a PPV of 14% for PR, for a cut-off value of < 100. There is no much difference in sensitivity, specificity, PPV, and NPV between prescription-refill adherence and refill-only adherence (eg, the sensitivity is 59% for both PRL and RL for a cutoff value of < 100%).
they all register the same information considering refills, and data are therefore comparable.

Although the pharmacies have different registry systems, entering, cleaning and coding the database. Nevertheless, in our study, this is traced by the Accessing multiple pharmacies is feasible; however this requires additional efforts in time for studies using pharmacy refill adherence.

These results implicate that it is important to include leftover medication in the adherence calculation. Additionally, not taking into account the physicians’ instructions predicted virological failure a little better. There was no difference in predicting virological failure by different calculations (average or any drug) of adherence. These results implicate that it is important to include leftover medication in studies using pharmacy refill adherence.

Leftover medication is particularly relevant when patients are already on cART. A large percentage of patients were misclassified nonadherent when not taking into account leftover medication. This percentage differed when accounting for refills of different periods, but even accounting for 1 year resulted in 9% misclassification. We expected that taking leftover medication into account would result in an improved prediction of virological failure. Indeed, it resulted in an improved PPV. However, in our study, only 11% of patients had a detectable viral load and all patients who would be misclassified as nonadherent had an undetectable viral load. Consequently, in this sample, the prediction of virological failure was not more accurate.

In our study, we did not find any influence of adding prescribed treatment time in the prediction of virological failure. This was due to the low percentage of patients having a prescribed treatment interruption in inclusion in the study. However, we assume taking into account prescribed treatment time information is highly relevant to distinguish between nonadherence and instructed treatment interruptions.

The prediction of virological failure by pharmacy refill adherence calculations was found and validated in former studies.[5-7, 15] Kitahata et al. point out the importance of accounting for adherence of each drug in the regimen,[7] However, we did not find a difference in prediction between the average measure and adherence based on a single drug (data not shown in results). A possible explanation might be the increased use of pills in which drugs are combined. Another possible explanation might be that patients collect all of their drugs together. However, looking into our detailed data, we found this is not the case. For example, patients collect 84 tablets of ritonavir while for other drugs this number is 90. However, often a new collection of drugs is done after 90 days and not after 84 days, leading to nonadherence regarding ritonavir.

One limitation is that patients need to remember their pharmacies. If we did not receive data of a large enough period, we asked the patient’s physician or counselor for more information. Still, there were 8 patients of whom we did not receive complete data for the past 2 years, even after prompting the patients about their pharmacies several times. We considered them as nonadherent. Restricting our analyses to patients with complete data did not change the results.

We assumed that treatment adherence would be distributed equally over the periods between refills. This assumption, however, cannot be verified in pharmacy refill data. Pharmacy refill adherence differs both in terms of intervals of assessment (day by day) and in terms of the target of the measures (access versus consumption) from other adherence assessment methods, such as electronic medication monitoring and self-report. Because we do not have data about day-to-day intake, a patient who refills medication might have been classified as adherent, although in the 90-day period, he/she was actually nonadherent. Conversely, when a patient does not refill medication, it is sure he/she cannot take medication.

The last limitation is that we only included a single viral load measure as endpoint and that we were not able to distinguish between blips and virological failures because we did not have adequate data of subsequent viral load measures. We repeated the analyses with those patients who were undetectable (<40 copies/mL blood) in 2 previous measures and in the

| Table 3: Sensitivity, specificity, PPV, NPV and OR for the prediction of having a detectable viral load by different adherence calculations |
|----------------|-------|-------|-------|-------|---------|-----|
| Cutoff value   | Sensitivity | Specificity | PPV % | NPV % | OR (95%CI) P |
| PRL            | <100   | 59    | 78    | 25    | 94      | 5.0(2.0-12.6) | <0.01 |
|                | <95    | 59    | 88    | 37    | 95      | 10.3(3.9-26.9) | <0.01 |
|                | <85    | 45    | 92    | 40    | 93      | 9.1(3.4-24.6)  | <0.01 |
|                | <70    | 32    | 95    | 44    | 92      | 8.8(2.9-27.0)  | <0.01 |
| PR             | <100   | 73    | 45    | 14    | 93      | 2.2(0.8-5.9)   | 0.11  |
|                | <95    | 59    | 66    | 18    | 93      | 2.9(1.2-7.1)   | 0.02  |
|                | <85    | 50    | 79    | 22    | 93      | 3.7(1.5-9.2)   | <0.01 |
|                | <70    | 36    | 93    | 40    | 92      | 8.0(2.8-22.7)  | <0.01 |
| RL             | <100   | 59    | 80    | 27    | 94      | 5.7(2.3-14.5)  | <0.01 |
|                | <95    | 59    | 89    | 39    | 95      | 11.5(4.4-30.3) | <0.01 |
|                | <85    | 45    | 93    | 45    | 93      | 11.6(4.2-22.4) | <0.01 |
|                | <70    | 45    | 97    | 63    | 94      | 24.0(7.5-77.3) | <0.01 |
| R              | <100   | 77    | 47    | 15    | 94      | 3.0(1.1-8.5)   | 0.03  |
|                | <95    | 64    | 67    | 19    | 94      | 3.6(1.4-9.0)   | <0.01 |
|                | <85    | 55    | 79    | 24    | 93      | 4.6(1.8-11.5)  | <0.01 |
|                | <70    | 45    | 93    | 43    | 93      | 10.3(3.9-29.3) | <0.01 |

Sensitivity is the percentage of patients with detectable viral load who are correctly identified as nonadherence; specificity is the percentage of patients with undetectable viral load who are correctly identified as adherence; PPV is the percentage of nonadherent patients who have a detectable viral load; and NPV is the percentage of adherent patients who have an undetectable viral load.

Discussions

Our study shows that collecting data in a population of patients using multiple pharmacies is feasible. A large percentage of patients were misclassified as nonadherent when not including leftover medication from previous refills in the adherence calculation. Additionally, not taking into account the physicians’ instructions predicted virological failure a little better. There was no difference in predicting virological failure by different calculations (average or any drug) of adherence. These results implicate that it is important to include leftover medication in studies using pharmacy refill adherence.

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The last limitation is that we only included a single viral load measure as endpoint and that we were not able to distinguish between blips and virological failures because we did not have adequate data of subsequent viral load measures. We repeated the analyses with those patients who were undetectable (<40 copies/mL blood) in 2 previous measures and in the
whole sample with a cutoff value for undetectable viral load of <400 copies per milliliter of blood. These analyses showed ORs with similar magnitude. However, they were not statistically significant because the percentage of patients with a detectable viral load was small. Because of the low prevalence of a detectable viral load, replication of this study in larger samples and samples with larger proportion of patients with a detectable viral load would be useful.

Strength of our study is that we had access to both refill information from pharmacy registries and to prescription information and clinical data from medical files. This resulted in the possibility to investigate adherence to cART taking into account the leftover medication and prescribed treatment time in relation to virological failure.

In conclusion, our study shows that collecting data in a population with several pharmacies is feasible and that data on leftover medication is necessary to calculate adherence based on pharmacy refills. Future studies should consider leftover medication. Although we would advise to include refill information since starting the regimen, the question how far one needs to go back in including leftover medication depends on the population in regard to number of years on cART and the balance between the accuracy of adherence measurement needed and the extra efforts.

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Reference List

(1) Bangsberg DR. Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. Clin Infect Dis 2006 Oct 1;43(7):939-41.