Routine antiretroviral pharmacy refill information can predict failure postpartum in previously suppressed South African women living with HIV

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Abstract

Background
Detection of antiretrovirals (ARV) in biological specimens is a reliable objective way to measure adherence. However, routine ARV testing is not feasible in many high-burden settings. This study explored if pharmacy data could accurately predict HIV viremia postpartum in previously virally-suppressed women.

Methods
South African women living with HIV who initiated antiretroviral therapy (ART) during pregnancy and achieved viral suppression (VS; viral load [VL]≤50 copies/mL) were followed postpartum where plasma VL was measured and ARV adherence self-reported. A portion of samples were tested for the presence of ARV using mass-spectrometry. Patient-level routine pharmacy data were used to classify if women should have drug in hand in the past seven days prior to the visit date. Logistic regressions were used to calculate associations between adherence and viral non-suppression (VNS; VL>50) or failure (VF; VL>1000) at the first study visit of women who had ARV measured. Data for all women were examined for associations of self-reported adherence and drug in hand with VS and VF at two, six, and 12 months postpartum.

Results
Women with no ARV detected were significantly more likely to have VNS (odds ratio [OR]=26.4). Having no drug in hand for seven days was also predictive of VNS in these same women (OR=7.0), and the full cohort (n=572) at three (OR=2.9), six (OR=8.7) and 12 months (OR=14.5). Similar results were seen for VF.

Conclusion
These data show that routine pharmacy data can act as a highly predictive mechanism for identifying patients at risk of VNS and VF due to non-adherence.
Introduction

Detection of antiretrovirals (ARV) in biological specimens is a highly accurate objective measurement of adherence during ARV therapy (ART) [1]. Multiple strategies are currently being explored to test for the presence of ARV in several types of biological specimens [2,3]. These strategies vary in their accuracy, ease of sample collection, time of sample processing, and cost. Additionally, often these tests can only detect a single ARV, which would have limited usefulness in areas with multiple ART regiments that can also change as new and better drugs become available[3]. In part because of these challenges, routine ARV testing may have somewhat limited feasibility in high-burden settings, many of which are found in lower- and middle-income countries (LMIC) with limited resources.

While this may be the case, it is also true that current strategies of measuring ART adherence by self-report can be highly inaccurate in both clinical trials and during standard clinical care [3,4]. Therefore, other approaches are needed to accurately and objectively assess a patient’s ARV adherence in an objective way that ideally would limit unnecessary clinic visits.

One healthcare information system that may be helpful in this endeavour is the pharmacy. ARV are only accessible through a pharmacy, and pharmacy data has been shown in several settings to be a useful resource for drug usage data for an area, as well as individual patients [3,5–7]. In addition, pharmacies are ubiquitously located throughout the world, and are generally well-organized and staffed by highly trained individuals. While it is true that in many LMIC, as well as rural areas of high-income countries, pharmacy reporting systems can be limited, these systems could be upgraded to allow for real-time pharmacy data reporting. These data could be used to inform clinicians for rapid assessments of patients that are experiencing ARV adherence issues by identifying individuals who have not picked up their ARV, and therefore should be out of medication for certain amount of time (ie no drug in hand for seven days) assuming they took their previous refills as prescribed. Additionally, the
benefits of strengthening pharmacy reporting systems would extend beyond HIV, but could also be used to monitor other drug-related issues such as over prescribing of antibiotics, opioid abuse, and counterfeit drug sales [8–11]. This study aimed to examine if using ARV refill data obtained from pharmacy records could predict HIV viral load failure in a group of postpartum South African women.

**Materials and Methods:**

**Study Population**

Women living with HIV who participated in the previous MCH-ART clinical study were included in this study, which has been described in detail previously [1,12,13]. Briefly, South African women living with HIV who initiated ART with a once-daily, fixed dose combination of tenofovir 300 mg, emtricitabine 200 mg or lamivudine 300 mg, and efavirenz 600 mg during routine antenatal care in Cape Town, South Africa and achieved viral suppression (VS; viral load [VL] <50) at some point in the study period were examined. A portion of these women who experienced viral non-suppression (VNS; VL>50 copies/mL) or failure (VF; VL>1000 copies/mL) episode post suppression, as well as a nested control group of women who remained fully suppressed, were previously examined for presence of all currently approved ARV at several time points using mass-spectrometry [1]. Women who never achieved VS in the study period were excluded since the purpose of this study was to explore the predictive value of pharmacy refill data on ART-induced viral suppression maintenance, and not initial suppression.

**Patient Consent Statement**

All women provided informed written consent for the study, and all appropriate IRB approvals were obtained.

**ARV testing**
As previously described [1], plasma samples obtained from women were previously analyzed for the presence of ARV using a high resolution mass-spectrometry based assay at Johns Hopkins Hospital. The assay used provides qualitative detection of commonly used ARV drugs including all drugs used in South African first- and second-line ARV regimens (ARV drugs screened for by the assay include: Abacavir, Amprenavir, Atazanavir, Darunavir, Efavirenz, Emtricitabine, Indinavir, Lamuvidine, Lopinavir, Maraviroc, Nelfinavir, Nevirapine, Raltegravir, Rilpivirine, Ritonavir, Saquinavir, Stavudine, Tenofovir, Tipranavir, Zidovudine) [14]. Quality control, limits of detection, and other technical details were similar to earlier studies [14].

**Pharmacy ARV reporting and self-reported adherence**

Pharmacy dispensing data was obtained through the Western Cape Provincial Health Data Centre which combines multiple electronic medical records from public sector clinics in the province [15]. Data are linked across clinics using the unique patient folder numbers, allowing ascertainment of ARV dispensed at any public sector clinic in the province. A binary indicator for whether a woman had no drug in hand for ≥7 days from the date of their study visit was calculated for each VL measurement time point in the study based on last quantity of ARV dispensed. Several cut-offs were analyzed and seven days performed better than shorter time frames (ie 3-days) and equally well to longer time frames.

Self-reported adherence was measured as previously described [16]. Briefly, the Wilson three-item scale was administered by a trained interviewer. The scale includes the following three questions: 1) In the last 30 days, on how many days did you miss at least one dose of any of your HIV medicines? (0-30), 2) In the last 30 days, how good a job did you do at taking your HIV medicines in the way that you were supposed to? (1= very poor to 6 = excellent), 3) In the last 30 days how often did you take your HIV medicines in the way that you were supposed to? (1= never to 6 = always). Each item response is converted to a score
out of 100 and the average taken for a combined scale score where 100 indicates perfect self-reported adherence. Binary thresholds of <100 and <90 were used in analyses.

Statistical analysis

All analyses were conducted in R (version 4.12). The baseline demographics and clinical characteristics were described using frequencies and proportions or medians with interquartile range (IQR) as appropriate. Crude odds ratios (OR) and the area under the receiver operating curve (AUC) with 95% confidence intervals (CI) were calculated using Logistic regression to examine how well non-adherence using ARV assay, drug in hand based on routine pharmacy refill, and self-reported adherence predicted VNS (>50 copies/mL) or VF (>1000 copies/mL). Cross-sectional analyses were conducted for a) the first ARV assay time point for the existing nested case-control group, b) the first viral load time point after 12 weeks on ART (after which we would expect women to have reached suppression if adherent), c) the next viral load time point nearest 6 months postpartum, and d) the viral load time point nearest 12 months postpartum.

Results:

Pregnant women living with HIV but not on treatment who initiated ART and achieved VS during pregnancy and immediately postpartum were included in this analysis (n=572; Table 1). Women who later experienced VF, as well as a group of nested controls, were previously examined for presence of ARV (n=233; Table 1)[1]. These groups were largely similar with only small differences in relationship status and employment (Table 1).

In the previously examined nested case-control group with ARV testing, 87% (n=202) and 92% (n=214) of women had VL ≤50 and ≤1000, respectively (Supplemental Table 1 and 2). Lack of ARV detection at the earliest time point tested was highly predictive of non-suppression (OR=26.4; CI=10.8-69.4; Table 2), as well as for VF (OR=61.8, CI=18.5-285.7; Table 3). In this same group, having no drug in hand for seven days prior to the study visit
date, while less predictive, was also predictive of non-suppression (OR=7.0; CI=3.1-17.7; Table 2) and VF (OR=4.39; CI=1.6-13.1; Table 3). In contrast, self-reported non-adherence using a threshold of <100 total adherence score was not significantly associated with non-suppression (OR=2.2; CI=0.6-14.4; Table 2) or VF (OR=2.7; CI=0.5-49.56; Table 3).

The full cohort of women who suppressed during the trial were next examined for the predictive potential of having no drug in hand for seven days prior to their study visit, as well as self-reported adherence. At the first viral load after 12 weeks on ART, and the viral loads nearest 6 month postpartum (IQR=181-184 days), and 12 months postpartum (IQR=364-367) having no drug in hand remained predictive of non-suppression, with stronger associations at later timepoints (OR= 2.9 [1.8-4.7], 8.7 [5.2-15.0], 14.5 [8.4-26.0], respectively; Table 2) and VF (OR=5.3 [2.8-10.0], 10.6 [5.8-20.7], 18.0 [9.3-38.4], respectively; Table 3). In this larger data set, self-reported adherence measurements were statistically significantly predictive at some later time points but with smaller effect sizes (OR= 1.5 [0.8-2.8], 1.7 [0.9-3.6], 3.0 [1.3-8.0], respectively; Table 2) and VF (OR= 2.8 [1.0-11.6], 2.6 [1.1-7.7], 1.9 [0.8-5.3], respectively; Table 3).

**Discussion**

As would be expected from earlier studies, direct measurement of ARV was the most reliable method to predict VNS and VF in this population of postpartum women [17]. However, measurement of ARV requires at a minimum an active effort from a patient by either self-collection of samples for testing, or a clinical visit. In addition, and also as expected, self-reported adherence did not accurately predict non-suppression or viral failure. In contrast, using routinely collected pharmacy data to determine if a patient had no ARV in hand for seven days or more was found to be predictive of both VNS and VF. While pharmacy refill data were not as predictive as directly testing for ARV, these data are passive from a patients’ point of view as no additional samples or clinical visit are required. It should
be noted, that the data used for this study were collected retrospectively from electronic health information systems in the Western Cape, but these systems could be changed or upgraded to alert care providers, as well as the patients themselves, when they have gone seven days without drug in hand. To this point, electronic action lists are being piloted in the Western Cape. Facility missed appointment lists have been routinely used in HIV services as a proxy for adherence, but the use of routine linked electronic medical records provides the added benefit of observing if a patient has been dispensed ARV from another site, reducing the list of patients requiring follow up. These findings highlight that, even in the absence of scheduled next visits to determine missed appointments, flagging patients who appear to have had no drug in hand for seven days or more for action by health services would be valuable to identify patients at risk of VNS, and to get them back on therapy as soon as possible.

Pharmacy refill data is often examined as a continuous variable or a percentage of refills missed over a period of time to retrospectively determine ART adherence. A seven-day cut-off of drug in hand may be a more practical way to incorporate this information into clinical care. In addition, while costs were not examined here it is likely that a monitoring plan that utilizes the existing pharmacy reporting system like what was used here would be less expensive than adding an additional technology solely for ART monitoring.

There were several limitations of this study. As stated earlier, this is a retrospective analysis of data from the Western Cape South Africa, which maintains a relatively robust pharmacy monitoring system and so these results may not be as applicable to other settings with less developed reporting systems. In addition, this study only examined women who were previously virally suppressed during pregnancy and postpartum, and therefore would need to be repeated in a larger general population. It was not possible to test all the sample time points in the parent study for presence of ARV. However, the nested study was representative of the larger cohort, therefore these results should still be valid. Lastly, this
study did not compare these measurements against some newer adherence technologies such as electronic pill caps that attempt to measure adherence more directly.

That being said, these data suggest that it might be beneficial to directly examine strengthening pharmacy reporting systems to provide a real-time assessment of drug in hand information for standard clinical care management. While that may be a larger endeavour than just providing clinicians with a point of care ARV test, the benefits of the former would go well beyond simply assisting HIV patient care and could be utilized for several other prominent issues in LMIC. These benefits could include better monitoring of antibiotic usage in a population to help limit the spread of multi-drug resistant bacterial diseases, which is a growing issue in LMIC and wealthy nations alike [8,11]. In addition, these data can be used to better monitor prescription opioid use and even counterfeit drugs by cross-referencing with regional or national drug purchases [9,10]. It is possible that real-time pharmacy data could also be used as an early warning system for the emergence of possible emerging pathogens by monitoring sudden increases in medicines such as cough suppressants or anti-diarrhoeal medicines.

This study’s findings that postpartum women who did not have ARV drugs in hand for seven days was highly predictive of viral failure suggests that utilizing this type of pharmacy data could be a valuable tool for monitoring ARV adherence and should be explored further.

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Potential Conflicts of Interest: No conflicts of interest are reported.

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References:


Table 1. Characteristics of women who achieved viral suppression and were included in the analysis, and the subset of women who had at least one ARV assay available. Presented as n (%) unless specified.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All women (n=572)</th>
<th>Women with an ARV assay (n=233)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median log_{10} viral load prior to ART initiation (IQR)</td>
<td>4.0 (3.4-4.6)</td>
<td>3.9 (3.4-4.5)</td>
</tr>
<tr>
<td>Median CD4 cell count at presentation for antenatal care (IQR) n=559</td>
<td>346 (236.3-515.0)</td>
<td>353 (251.5-495.0)</td>
</tr>
<tr>
<td>Median weeks gestation at presentation for antenatal care (IQR) n=556</td>
<td>20.4 (15.8-25.4)</td>
<td>21.1 (15.9-25.6)</td>
</tr>
<tr>
<td>Median maternal age (IQR)</td>
<td>28.1 (24.6-32.2)</td>
<td>27.8 (24.4-31.7)</td>
</tr>
</tbody>
</table>

Education

- Less than secondary: 426 (74) vs 177 (76)
- Completed secondary/any tertiary: 146 (26) vs 56 (24)

Employment

- Unemployed: 352 (62) vs 156 (67)
- Employed: 220 (38) vs 77 (33)

Relationship

- Unmarried/not cohabiting: 334 (58) vs 150 (64)
- Married or cohabiting: 238 (42) vs 83 (36)

Timing of HIV diagnosis

- Before this pregnancy: 262 (46) vs 98 (42)
- During this pregnancy: 310 (54) vs 135 (58)

Poverty tertile

- Most disadvantaged: 202 (35) vs 81 (35)
- Moderate disadvantage: 191 (34) vs 77 (33)
- Least disadvantaged: 179 (31) vs 75 (32)

Pregnancy intention

- Unintended: 399 (70) vs 171 (73)
- Intended: 173 (30) vs 62 (27)

Gravidity

- Not first pregnancy: 468 (82) vs 194 (83)
- First pregnancy: 104 (18) vs 39 (17)

Previously received ARVs for PMTCT (Among women with prior pregnancies)

- No: 316 (67) vs 133 (69)
- Yes: 153 (33) vs 60 (31)
Table 2. Crude logistic regression models showing odds ratios (OR) and area under curve (AUC) with 95% confidence intervals (CI) for the associations between non-adherence (based on ARV assay, pharmacy refill and self-report) and viral load non-suppression (>50 copies/mL) at the first ARV assay time point, first viral load time point after 12 weeks, 6 and 12 months on treatment for all women.

<table>
<thead>
<tr>
<th></th>
<th>a) First ARV assay time point (n=233)</th>
<th>b) First viral load after 12 weeks on ART (n=572)</th>
<th>c) Viral load nearest 6 months postpartum (n=428)</th>
<th>d) Viral load nearest 12 months postpartum (n=378)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARV assay</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug detected</td>
<td>Ref (0.790) (0.703-0.878)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>No drug detected</td>
<td>0.726 (10.8-69.4)</td>
<td>0.589 (0.545-0.634)</td>
<td>0.747 (0.697-0.797)</td>
<td>0.786 (0.744-0.829)</td>
</tr>
<tr>
<td><strong>Pharmacy refill</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Drug in hand</td>
<td>Ref (0.726) (0.640-0.812)</td>
<td>Ref 0.589 (0.545-0.634)</td>
<td>Ref 8.7 (0.697-0.797)</td>
<td>Ref 14.5 (0.744-0.829)</td>
</tr>
<tr>
<td>No drug in hand</td>
<td>7.0 (3.1-17.7)</td>
<td>2.9 (1.8-4.7)</td>
<td>8.7 (5.2-15.0)</td>
<td>14.5 (8.4-26.0)</td>
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<tr>
<td><strong>Three-item self-reported adherence</strong></td>
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<tr>
<td>≥100</td>
<td>Ref (0.538) (0.483-0.592)</td>
<td>Ref 0.521 (0.489-0.552)</td>
<td>Ref 0.529 (0.493-0.565)</td>
<td>Ref 0.545 (0.515-0.575)</td>
</tr>
<tr>
<td>&lt;100</td>
<td>2.2 (0.6-14.4)</td>
<td>1.4 (0.8-2.8)</td>
<td>1.7 (0.9-3.6)</td>
<td>3.0 (1.3-8.0)</td>
</tr>
<tr>
<td>≥90</td>
<td>Ref (0.512) (0.413-0.610)</td>
<td>Ref 0.515 (0.468-0.561)</td>
<td>Ref 0.567 (0.513-0.622)</td>
<td>Ref 0.573 (0.519-0.626)</td>
</tr>
<tr>
<td>&lt;90</td>
<td>1.1 (0.5-2.5)</td>
<td>1.1 (0.8-1.7)</td>
<td>1.7 (1.1-2.8)</td>
<td>1.8 (1.2-3.0)</td>
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Table 3. Crude logistic regression models showing odds ratios (OR) and area under curve (AUC) with 95% confidence intervals (CI) for the associations between non-adherence (based on ARV assay, pharmacy refill and self-report) and viral load failure (>1000 copies/mL) at the first ARV assay time point, first viral load time point after 12 weeks, 6 and 12 months on treatment for all women.

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<th>a) First ARV assay time point (n=233)</th>
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<tr>
<td></td>
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<td>AUC (95% CI)</td>
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</tr>
<tr>
<td>ARV assay</td>
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<td></td>
</tr>
<tr>
<td>Drug detected</td>
<td>Ref 0.881 (0.795-0.968)</td>
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<tr>
<td>No drug detected</td>
<td>61.8 (18.5-285.7)</td>
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<tr>
<td>Pharmacy refill</td>
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</tr>
<tr>
<td>Drug in hand</td>
<td>Ref 0.677 (0.561-0.793)</td>
<td>0.665 (0.588-0.741)</td>
<td>Ref 0.763 (0.711-0.816)</td>
<td>Ref 0.789 (0.747-0.831)</td>
</tr>
<tr>
<td>No drug in hand</td>
<td>4.4 (1.6-13.1)</td>
<td>5.3 (2.8-10.0)</td>
<td>10.6 (5.8-20.7)</td>
<td>18.0 (9.3-38.4)</td>
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<td>Three-item self-reported adherence</td>
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</tr>
<tr>
<td>≥100</td>
<td>Ref 0.543 (0.480-0.605)</td>
<td>0.544 (0.508-0.580)</td>
<td>Ref 0.547 (0.512-0.581)</td>
<td>Ref 0.529 (0.495-0.563)</td>
</tr>
<tr>
<td>&lt;100</td>
<td>2.7 (0.5-49.6)</td>
<td>2.8 (1.0-11.6)</td>
<td>2.6 (1.1-7.7)</td>
<td>1.9 (0.8-5.3)</td>
</tr>
<tr>
<td>≥90</td>
<td>Ref 0.533 (0.411-0.655)</td>
<td>0.507 (0.436-0.577)</td>
<td>Ref 0.575 (0.515-0.636)</td>
<td>Ref 0.540 (0.481-0.600)</td>
</tr>
<tr>
<td>&lt;90</td>
<td>1.3 (0.5-4.0)</td>
<td>0.9 (0.5-1.7)</td>
<td>1.9 (1.1-3.2)</td>
<td>1.4 (0.8-2.3)</td>
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