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Self-report and dry blood spot measurement of antiretroviral medications as markers of adherence in pregnant women in rural South Africa

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Abstract

Antiretroviral (ARV) adherence is essential to prevent mother-to-child transmission of HIV. This study compared self-reported adherence versus ARV detection in dried blood spots (DBS) among N=392 HIV-infected pregnant women in South Africa (SA). Women completed two self-reported adherence measures [Visual Analog Scale (VAS), AIDS Clinical Trials Group Adherence (ACTG)]. Adherence was 89% (VAS), 80% (ACTG), and 74% (DBS). Self-report measures marginally agreed with DBS (VAS: Kappa=0.101, Area Under the ROC Curve (AUROC)=0.543; ACTG: Kappa=0.081, AUROC=0.538). Self-reported adherence was overestimated and agreement with DBS was poor. Validation of self-reported ARV adherence among pregnant HIV+ women in SA is needed.

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Compliance with Ethical Standards

Conflict of Interest

All authors declare that they have no conflicts of interest.

Ethical Approval

Ethical approval was granted by the Human Sciences Research Council (HSRC) Research Ethics Committee (REC), protocol approval number REC4/21/08/13. Study approval was also obtained from the Department of Health REC, Mpumalanga Provincial Government, South Africa and the University of Miami Miller School of Medicine Institutional Review Board. All procedures performed in studies involving human participants were also in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Voluntary informed consent was provided by all individual participants prior to enrollment and participation in any study procedures.

Keywords

Adherence; women; HIV; South Africa; antiretrovirals; measurement

Introduction

Adherence to antiretroviral (ARV) therapy is an essential component of Prevention of Mother to Child Transmission (PMTCT) programs, as viral suppression is necessary to decrease perinatal transmission, minimize the risk of antiretroviral (ARV) drug resistance, and achieve a generation born free of HIV. South African PMTCT treatment protocols provide ARVs to expectant mothers until after the cessation of breastfeeding (option B). Currently, first-line ARV regimens for PMTCT are tenofovir (TDF) plus lamivudine (3TC) or emtricitabine (FTC) plus efavirenz (EFV), and the use of a single combination pill is recommended when possible (such as TDF + FTC + EFV combination pill or TDF + FTC combination pill). (1)

In South Africa and worldwide, adherence to PMTCT among pregnant women is suboptimal. Previous research on PMTCT adherence has utilized self-report and pill count measures and found rates of ARV adherence around 61% in South Africa, and 75% worldwide. (2) Additionally, accurate measurement of adherence to ARV is challenging as most adherence tools utilize self-report. Validated measures of self-reported ART adherence include visual analog scales (VAS) and 4-day recall of missed medication (AIDS Clinical Trials Group Adherence scale, 4-days) but are subject to bias. (3) The use of computerized interview self-administration may reduce social desirability bias when measuring self-reported adherence using the VAS or the ACTG scale, compared to interpersonal interviews. (4) The use of pill counts, even more advanced pill-counting strategies, e.g., electronic pill-counters track the number of openings and closings, to measure adherence to ARV decrease recall bias, but may also be inaccurate, as pills may be stored in multiple containers when unannounced pill counts occur or may purposely be discarded prior to clinic visits, providing an imprecise measurement of adherence. (5)

Dried blood spots (DBS) are markers of adherence that measure the presence of ARV in the blood. DBS are obtained by placing a drop of blood on a filter paper and measuring the presence of ARV. DBS are a biological measure of the presence of ARVs, and the absence of ARVs in the blood may indicate increased risk of perinatal transmission in PMTCT programs. Though there is no gold standard adherence measurement, DBS is superior to self-reported measures, and is a simple and reproducible measure of ARV adherence. (6) Although DBS have been used as markers of adherence to ARV in prevention and treatment studies, they have not previously evaluated in PMTCT programs in rural areas of South Africa, which continue to have antenatal HIV rates as high as 46% despite significant reductions in urban areas. (7) This study compared the accuracy of two measures of self-reported adherence with DBS used to detect ARVs to estimate the accuracy of self-reported adherence among HIV-infected pregnant women in rural South Africa.

Methods

Participants and Procedures

Participants (n = 392) were HIV-infected women at week 32 of pregnancy, 18 years of age or older, having a sexual male partner, and living in rural South Africa. Women at different stages of gestation (M = 18.07, SD = 5.54) were recruited into the baseline phase of a large randomized control trial. Three hundred and ninety two participants completed the study visit scheduled at 32 weeks of pregnancy, which included assessment of adherence using DBS. This study was conducted in 12 community health centers in Gert Sibande and Nkangala districts, Mpumalanga province, South Africa. The larger study evaluated an intervention, Protect Your Family, to improve PMTCT among pregnant HIV-infected women. Participants were recruited at week 24 of pregnancy or less, and completed assesssments on adherence (self-reported adherence using the VAS and ACTG scales, and measurement of ARV by DBS) at 32 weeks of pregnancy. All participants were on ARV therapy per the South African PMTCT protocol (TDF + 3TC or FTC + EFV). Participants completed study measures in their preferred language (English, Zulu, Sotho) using an Audio Computer-Assisted Self-Interview (ACASI) to enhance disclosure and reduce bias. Prior to the onset of recruitment, all measures were translated into local languages and were adapted to the local setting as appropriate. Details of the Protect Your Family study intervention have been previously described. (8) Participants were compensated with R100 (South African Rand or ZAR ~US$10) for their time and transportation to the assessment.

DSB collection and analysis

At 32 weeks of pregnancy, participants were requested to provide five drops of blood obtained using a sterile lancet and a Guthrie card; participants had the option to refuse the DBS collection with no reprisals. No participants refused collection of DBS. The DBS was collected by trained nursing staff at each of the 12 study community health center and couriered to an independent University of Cape Town Division of Pharmacology laboratory blinded to study outcomes. DBS were identified using only participant ID and a laboratory barcode to maintain anonomity. DBS were tested for ARVs distributed by the South African government as first line regimens for PMTCT, all of which include some combination with TDF, EFV or 3TC. Antiretroviral drug detection was used by using liquid chromatography/ tamdem mass spectrometry.

Measures

Demographic and Medical History Questionnaire—Demographics assessed included age, educational attainment, employment status, monthly income, number of children, whether their pregnancy was planned, and whether they had two on drinks on one occasion in the past 4 weeks. Medical history questions included whether women had been diagnosed during the current pregnancy, whether they had disclosed to anyone, months since ART initiation, and the number of HIV-infected children.

Partner Related Questions—Partner related questions included whether women had disclosed to their parner, the partner was HIV infected, and whether condom was used at last sex.

Male Involvement—Male involvement was assessed using the male involvement index. In this sample, reliability for this scale was acceptable ($\alpha = 0.83$). Scores for this scale ranged from 0 to 11, where scores indicate greater partner involvement. (9)

Dried Blood Spot Adherence—Levels of TDF, EFV, and 3TC levels were assessed among all participants. Cut-off values for all ARVs were undetectable if below 0.02 μg/ml and detectable if above 0.02 μg/ml. Adherence was defined as either 2 or 3 drugs detected (TDF, EFV, or 3TC). As FTC was not measured and the combination of TDF + FTC in a single pill is recommended, the combination of TDF + EFV detected was also considered adherent. Nonadherence was defined as no detectable ARV, one ARV detectable, or a combination of two ARVs detectable that did not include TDF + EFV (e.g., TDF + 3TC or 3TC + EFV). Efavirenz has the longest half life and levels can be detected up to a median of 48 hours after discontinuation of the mediciation, and although some reports indicate individual variability in the metabolism of the drug, we assume that participants who did not take a drug in the prior 3 days would have undetectable levels. (10)

Visual Analog Scale Adherence—The Visual Analog Scale (VAS) has participants rate their level of adherence on a scale of 0 (*took none of my medication*) to 1 (*took half of my medication*) to 2 (*took all of my medication*) for each day in the past week. (3) For the purposes of this study, only the past 3 days were scored as totals, to match the maximum number of days covered by the DBS detection window. Participant responses consistent with having missed a dose in the past 3 days were considered nonadherent, whereas participants who reported having missed zero doses were considered adherent.

AIDS Clinical Trials Group Adherence—The AIDS Clinical Trials Group (ACTG) adherence scale has participants report how many ARV doses they had to take each day in the past 4 days. Then, for each day in the past 4 days, participants report the number of missed ARV doses of their expected number of doses. (11) To match the maximum number of days covered by the DBS detection window, if the participant reported any missed ARV doses in the past 3 Days, their response was considered nonadherent; those reporting zero missed doses in the past 3 days were considered adherent.

Statistical Analyses—Descriptive analyses were conducted to examine overall adherence and demographic characteristics of participants. Bivariate and multivariable logistic regression models were used to estimate associations with DBS ARV adherence. Only variables reaching the $p < 0.05$ level of significance in bivariate logistic regression models were included in multivariable models.

An ROC (receiver operating characteristic) curve analysis was estimated to examine the performance of the VAS and the ACTG scales in identifying participants as adherent, using DBS as the gold standard. ROC curves and area under the ROC curve (AUROC) values were also calculated. AUROC values estimated the probability of identifying an adherent participant when two participants from each group (adherent and nonadherent) were selected at random. An AUROC of 0.50 suggests that the scale is no better than chance at predicting adherence, whereas an AUROC of ≥ 0.90 is indicative of excellent performance at predicting adherence. Kappa statistics, accuracy, sensitivity, specificity, negative predictive values, and

positive predictive values were calculated. Kappa statistics measured precision, intermeasure agreement between the DBS and the scales, in which a Kappa value of 0 indicated less than chance agreement, and a value of 0.99 indicated perfect agreement.

Accuracy was calculated as the number of participants truly adherent or nonadherent in the total sample. Sensitivity values were calculated as the proportion of participants categorized as adherent by ACTG/VAS and DBS (true positives) out of the total number of participants classified as adherent by DBS (true positives plus false negatives). Specificity values were calculated as the proportion of women identified as nonadherent by ACTG/VAS and DBS (true negatives) out of the total number of participants classified as nonadherent by DBS (true negatives plus false positives). The positive predictive values were calculated as the proportion of adherent women by VAS/ACTG and the DBS (true positives) out of those classified as adherent by the VAS or ACTG (true positives plus false positives). The negative predictive values were the proportion of nonadherent participants by VAS/ACTG and the DBS (true negatives) out of the the total number of participants classified as nonadherent by VAS/ACTG (true negatives plus false negatives).

Finally, exact binomial confidence limits were calculated for sensitivity, specificity, and positive and negative predictive values. R statistlical software [caret, Epi and epiR packages] was used for statistical analyses.

Results

Demographic Characteristics

Sample demographic characteristics were available for 379 of 392 (97%) women. Median participant age was 28 ± 6. Nearly three-fourths (72%) of women had completed at least 10 years of education, 82% were unemployed, and 40% had a monthly household income of less than 310 ZAR, ~USD$24. Most women (82%) had at least one child, nearly half (46%) planned their pregnancy, and 12% reported having more than 2 drinks in the past 4 weeks on one occasion. More women who were adherent by DBS criteria had disclosed their HIV serostatus to at least one person (76 vs 65%; $p = 0.028$), more had their disclosed their HIV serostatus to their partner compared with nonadherent women (62 vs 49%; $p = 0.023$), and more reported having an HIV infected partner (28 vs 18%; $p = 0.049$) compared to nonadherent women. No other differences emerged between DBS adherent and nonadherent women ($ps > 0.05$). A summary of participant demographic, HIV-related, partner-related characteristics is presented in Table I.

Prevalence of and Associations with DBS Antiretroviral Adherence

Using DBS, 74% of participants were classified as adherent. Among adherent women, 72% had TDF and EFV detected and 2% had all three ARVs detected. Among nonadherent women (26%), 11% of women had none of the 3 ARVs detected, 12% had only 1 ARV detected, and 4% had two ARVs that were not TDF and EFV detected. In bivariate analyses, baseline disclosure of HIV status to anyone, disclosure of HIV status to partner, and having an HIV positive partner were associated with nonadherence at 32-weeks of pregnancy. In

multivariate analyses, no associations were found. A summary of bivariate and multivariate logistic regression models is presented in Table I.

VAS, and ACTG Adherence

According to the VAS, 89% of women self-reported 100% adherence; 80% were adherent by ACTG.

VAS and ACTG scales performance relative to DBS

VAS relative to DBS—The AUROC for the VAS was 0.543, suggesting the VAS performed poorly in predicting adherence by DBS. The Kappa statistic was $\kappa = 0.101$, indicating slight intermeasure agreement between the VAS and the DBS. Accuracy was estimated to be 0.719 [95% CI 0.67, 0.76].

VAS sensitivity was 0.907 [95% CI 0.87, 0.94] and specificity 0.178 [95% CI 0.11, 0.27]. The positive predictive value (PPV) for the VAS was 0.761 [95% CI 0.71, 0.80], and negative predictive value (NPV) 0.400 [95% CI 0.26, 0.56].

ACTG relative to DBS—The AUROC for the ACTG was 0.538, suggesting the ACTG performed poorly in predicting adherence by DBS. The ACTG Kappa statistic was $\kappa = 0.081$, indicating poor intermeasure agreement between the ACTG and the DBS. Accuracy was estimated at 0.673 [95% CI 0.63, 0.72].

ACTG sensitivity and specificity values were 0.818 [95% CI 0.77, 0.86] and 0.257 [95% CI 0.18, 0.35], respectively. The PPV was 0.760 [95% CI 0.71, 0.81], and NPV 0.329 [95% CI 0.23, 0.44].

Discussion

This study evaluated adherence to ARV among HIV-infected pregnant women in rural South Africa using DBS, factors potentially associated with DBS and ARV nonadherence, and compared the accuracy of two measures of self-reported adherence with DBS ARV adherence. DBS ARV adherence was poor, and we did not identify sociodemographic, HIV or partner related factors associated with nonadherence. Self-reported adherence was poorly associated with DBS adherence, highlighting the importance of validation of self-report with alternative methods of assessment, such as biological markers, to optimize PMTCT goals.

Despite the use of ACASI to enhance accuracy and reduce bias, participants self-reported higher levels of adherence than identified by DBS. Previous studies utilizing ARVs for pre exposure prophylaxis (PrEP) found poor agreement between self-reported adherence measures and biological assessments among women; over 80% self-reported adherence vs. less than 25% detectable ARVs. (12) Both research and clinical settings necessitate the use of accurate adherence assessments, and results confirm that adherence by self-report methods should be validated. However, therapeutic drug monitoring in clinical practice is not the norm in sub Saharan Africa, and the use of DBS in routine management of pregnant HIV-infected women is unrealistic due to cost and delays associated with obtaining results. Facilitating a therapeutic alliance with patients that optimizes adherence and continuity of

care and better correlates self-report with biological assays may require clinical strategies that clarify the importance of adherence to patients, encourage patients to take an active role in their own treatment, and increase accurate self-reporting.

Low levels of adherence to ARVs among pregnant sub-Saharan African women have previously been described (2), and in this study, only three quarters of respondents in this sample were adherent by DBS. Poor adherence places infants at risk of perinatal HIV acquisition and increases the likelihood of drug resistance, progression of HIV disease, and potential transmission of HIV to sexual partners. Maximizing ARV adherence continues to present a challenge in South Africa and interventions are needed to support pregnant HIV-infected women.

This study has limitations: 1) this cross sectional study only reflects adherence at one time point during pregnancy. Although women were participating in an intervention study and adherence may have be affected by the intervention, this report evaluates crosseccional adherence and congruence among measures, not differences by study condition; 2) DBS data presented refers to the presence of absence of ARV, and no quantification of the exact amount of drug in the blood. This may overestimate adherence as drug may be detectable but at subtherapeutic levels or women may have been adherent only a few days before DBS collection and not for longer period of time; 3) other adherence methods were neglected, e.g., pill count, electronic caps or other biological methods, but the VAS has been reported to provide similar adherence estimates as unannounced pill counts, and is superior to self-reported recalls of missed doses (4); 4) comparing 3 days self-reported adherence to EFV may not correlate with a non detectable level as isolated reports have shown that EFV may be detectable in blood up to 2 weeks, which may have overestimated adherence (10); 5) assessment of viral load would have provided with a measure of the potential risk of perinatal transmission; 6) DBS may be subject to social desirability bias as patients may take their ARVs prior to clinic visits if they are aware that their ARV levels will be examined. Future studies and clinical trials should include alternate biological assessments of adherence such as hair sampling to evaluate ARV uptake over longer periods (e.g., one month), and viral load measuring.

Conclusions

Findings showed that self-report measures of ARV adherence overstimate adherence when compared with biological measures, and interventions to increase adherence to ARV among pregnant women are urgently needed. (6) Future work should include triangulation of multiple adherence assessment methods, and compare them with biological measures, in order to inform adherence interventions in the context of PMTCT and to reduce the risk of HIV transmission to infants.

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Table I

Associations between sociodemographic, alcohol use, HIV related and partner related variables and non-adherence according to antiretroviral dried blood spots (DBS) (N = 379)

	All Mean (SD) n (%)	Unadjusted OR (CI=95%), *p*	Adjusted OR (CI=95%)[a], *p*
Sociodemographics and alcohol use			
Age	28.69 (5.71)	0.98 (0.94–1.02), 0.376	NS
Educational attainment			
<Grade 10	74 (19.5%)	1.00	
Grade 10–11	197 (52.0%)	0.86 (0.48–1.54), 0.609	NS
Grade 12 or more	108 (28.5%)	0.57 (0.57–1.12), 0.102	
Employed (reference=not employed)	69 (18.2%)	0.60 (0.31–1.14), 0.119	NS
Income (South African Rand)			
<310	151 (39.8%)	1.00	
310–949	105 (27.7%)	0.68 (0.38–1.20), 0.181	NS
950 or more	123 (32.5%)	0.74 (0.43–1.26), 0.265	
At least one child (reference=none)	312 (82.3%)	0.74 (0.42–1.32), 0.311	NS
Pregnancy unplanned (ref=planned)	206 (54.4%)	1.16 (0.73–1.83), 0.536	NS
Whether participant has had more than 2 drinks on one occasion in the past 4 weeks (ref=no)	46 (12.1%)	0.75 (0.36–1.57), 0.447	NS
HIV-related variables			
Diagnosed with HIV in this pregnancy (ref=no)	208 (54.9%)	1.06 (0.67–1.68), 0.793	NS
Disclosure of HIV serostatus to anyone (ref=no)	278 (73.4%)	**0.58 (0.35–0.94), 0.029**	0.74 (0.36–1.50), 0.401
Months since ART initiation	13.2 (23.6)	1.01 (0.99–1.01), 0.272	NS
HIV infected children (ref=no or do not know)	16 (5.1%)	1.83 (0.64–5.22), 0.256	NS
Partner-related variables			
Disclosure of HIV serostatus to partner (ref=no)	222 (58.6%)	**0.60 (0.37–0.93), 0.024**	0.80 (0.41–1.59), 0.526
HIV infected partner (ref=no or do not know)	96 (25.3%)	**0.57 (0.32–0.99), 0.048**	0.65 (0.36–1.19), 0.165
Non condom use at last sex (ref=yes)	186 (49.1%)	1.11 (0.70–1.75), 0.654	NS
Male involvement index	7.1 (3.0)	0.96 (0.89–1.04), 0.304	NS

Note. NS = Not significant in bivariate models, and therefore not included in multivariable model. ART = Antiretroviral Therapy.

*** P <0.001;

** P<0.01;

* P<0.05

[a] Hosmer and Lemeshow chi-square = 0.48, $p = 0.924$; Nagelkerke $R^2 = 0.03$.