

RISK FACTORS FOR POOR ADHERENCE TO ANTIRETROVIRAL
THERAPY BY PREGNANCY STATUS IN TWO URBAN COHORTS OF
WOMEN LIVING WITH HIV IN THE UNITED STATES AND SOUTH
AFRICA

by
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A thesis submitted to Johns Hopkins University in conformity with the
requirements for the degree of Master of Science.

Baltimore, Maryland
April, 2016

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Abstract

Introduction: Many women living with HIV around the world are in their reproductive years. Adherence to antiretroviral therapy (ART) and viral suppression are of particular importance before, during, and after pregnancy to maintain maternal health and limit vertical transmission. It is important to understand what factors prevent women from adhering to their medications. Risk factors for poor adherence in pregnant and non-pregnant women were examined in two different contexts.

Methods: Cohorts of HIV-infected women on ART in the United States and in South Africa were examined. Pregnancy experience in the last six months in the United States cohort and becoming pregnant during follow-up in the South African cohort were assessed among various other risk factors for poor adherence. Prevalence of poor adherence at baseline and endline in the South African cohort was examined; estimates were stratified by pregnancy and fertility intentions and compared using equality of proportions tests. Poisson regression models with robust variance (as an approximation of log binomial models) were used to estimate crude (PR) and adjusted (aPR) prevalence ratios and 95% confidence intervals ([,]) of risk factors for poor adherence, separately in each of the cohorts and also stratified by pregnancy status.

Results: Prevalence of poor adherence declined between baseline and endline for the South African cohort of women. The greatest reduction was seen in those who had pregnancy intentions at baseline and were pregnant during follow-up (difference in percentages: 12.5% [8.5, 16.5]). The independent risk factors for poor adherence to ART among the US cohort were low CD4 count and lower level of completed education. From the analyses stratified by pregnancy status, risk factors that were different between those

who experienced a pregnancy outcome and those who did not included age, race, relationship status, parity, and illicit drug use. The main risk factor for the cohort of women from South Africa was trying to conceive (aPrR=1.54 [1.10, 0.94]). Risk factors that were different between those who experienced a pregnancy during follow-up and those who did not were level of education completed, partner HIV status, parity, ability to talk to a provider, and time on HAART.

Conclusions: Risk factors for poor adherence appear to differ between pregnant and non-pregnant women of reproductive age in the United States and South Africa. Self-reported poor adherence was associated with pregnancy intentions in the South African context, and further research should be conducted to assess this relationship and to develop strategies for promoting adherence in this important population.

Advisor: Keri Althoff, PhD

Thesis Reader: Andrea Ruff, MD

Acknowledgements

I have been very fortunate to have the support and guidance of three faculty members in the Department of Epidemiology: Drs. Keri Althoff, Elizabeth Golub, and Sheree Schwartz. This work would not have been possible without their consistent help and high expectations. Throughout the process, they were willing to answer any question, no matter how small, and push me forward to address important challenges in a timely but rigorous manner. Thank you to all of you for working with me to make this happen.

I would also like to acknowledge Dr. Andrea Ruff of the Department of International Health for serving as my thesis reader. Thank you for the work you do and for being so willing to take this on.

Thank you to Bin Liu and Lorie Benning at the WIHS Data Management and Analysis Center (WDMAC) for your patience and help in getting me the data that I needed for this thesis.

To my cohort in the Department of Epidemiology, I cannot thank you all enough for the days spent in the student room “silently” writing together or the nights spent arguing over basic epidemiologic concepts. In you, I have made friends for life.

To my friends and family, thank you for supporting all my decisions in the pursuit of this degree and this thesis, and for teaching me to pursue my work with strength and integrity.

Most importantly, thank you to all the women in Johannesburg and cities around the United States who took part in these two cohorts and spent the time to provide us with this valuable information.

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Chapter 1: Introduction

Close to 37 million people are living with HIV around the world [1]. Despite increasing access to and availability of treatment and a real decline in new infections, close to a 40% decline since 2000, there are still two million new infections every year [1]. Globally, young women, ages 15-24 years, are at particularly high risk, facing almost double the risk of HIV infection as young men of the same age [2]. About half of all individuals living with HIV are women, and AIDS-related deaths continue to be the leading cause of death among women of reproductive age [1].

The majority of women living with HIV around the world are in their reproductive years, highlighting the critical need to better understand the issues of pregnancy and motherhood as they relate to HIV. Adherence to antiretroviral therapy (ART) is important for all HIV-infected individuals in order to maximize clinical benefit and reduce HIV transmission [3]. Adherence and viral suppression are of particular importance before, during, and after pregnancy in order to maintain maternal health and limit vertical transmission (from mother to baby) [4]. While progress has been made to achieve more frequent testing, earlier diagnoses, and better linkage to care, many individuals are not retained in care and fail to adhere [3]. *It is important to understand how pregnancy and other risk factors are associated with women failing to adhere to their medications.*

Pregnant women have been previously shown to be at particular risk of having poor adherence [5]. Very little is known on specific risk factors for poor adherence among pregnant and similar non-pregnant women of reproductive age [5]. As very little information is available on risk factors for poor adherence in this population, a risk factor analysis will serve as an important descriptive tool for identifying important associations

for further exploration, and to begin to identify targets for intervention [6]. In this analysis, *risk factors for self-reported poor adherence in pregnant and non-pregnant women will be examined in two different contexts*: a cohort of women in the United States and a cohort of women in South Africa, as it is of interest to qualitatively examine differences in barriers to ART adherence in low and high-income settings.

1.1 HIV in the United States

In the United States, a resource-rich nation with over 300 million individuals, HIV affects less than 0.1% of the population. There are 1.2 million people living with HIV (PLHIV), with about 50,000 new infections each year [7]. About 25% of PLHIV in the United States are women [7]. Black heterosexual women remain the worst affected, accounting for almost 75% of new infections in women [7]. While more than half of women in the United States have reported being tested at least once for HIV in their lives, only 20% have been tested in the past year [8]. Among those women living with HIV, 20% remain undiagnosed, and just over 30% are virally suppressed [8].

1.2 HIV in South Africa

South Africa has one of the highest national HIV prevalence estimates in the world. Close to 20% of all adults, or 7 million individuals, ages 15-49 are living with HIV [9]. Women of reproductive age bear a disproportionate burden of disease, making up more than half of all HIV cases [9]. With increased national attention and the implementation of The National Strategic Plan 2007-2011, 1 in 4 individuals had been tested in the last year as of 2010 [10]. Increased efforts for the prevention of mother to child transmission (PMTCT) resulted in more testing among women of reproductive age

[10]. While there have been improvements in ART access, only about 42% of those eligible for treatment are on treatment, and fewer are virally suppressed [11]. Even with reductions in maternal to child transmission and increased access of PMTCT services, there has been no change in maternal mortality [11].

Despite these persistent numbers, real improvements in life expectancy and quality of life have been made in the last decade [11]. Because of these advances and the dramatically altered natural history of HIV infections in both high and low income countries, many women living with HIV and their partners are living normal lives, and are either already parents or hope to expand their families in the future [12]. It has been consistently shown that people living with HIV (PLHIV) have comparable pregnancy intentions to individuals not affected by HIV [12].

1.3 Importance of virological suppression during pregnancy

ART reduces the virus' ability to replicate and infect new cells, resulting in virologic suppression, defined as having a plasma HIV viral load below the assay limit of detection [1]. It is important to understand the level of adherence to ART that is required for virological suppression.

In an early study using older protease inhibitor (PIs) combination regimens, it was found that adherence $\geq 95\%$ of the time was required not only for virological suppression, but also for other improvements in health, including increased CD4 count and reduced number of HIV-related infections, hospitalizations, and deaths [13]. More recent studies with efavirenz and other non-nucleoside reverse transcriptase inhibitor (NNRTIs) based regimens suggest that adherence $\geq 80\%$ of the time would be sufficient for achieving viral suppression and immune recovery [14]. It has been shown that different regimens may

allow for different types of non-adherence, with boosted PI-based regimens accommodating intermittent adherence and NNRTI-based regimens accommodating scheduled, longer breaks in treatment [15, 16]. It should be noted, however, that suppression is associated with adherence in a linear dose-response relationship, and therefore it is often recommended that maximum adherence to ART be promoted at all times, especially for pregnant women [5]. Additionally, lower levels of adherence and intermittent use can be associated with drug resistance [15].

Without virologic suppression, pregnancy with HIV can threaten the health of the mother and the child [17]. Some risk of horizontal and vertical transmission will persist in the absence of a cure, but antiretroviral therapy (ART) for the mother and subsequent virological suppression can dramatically reduce these risks [17]. Optimal adherence to ART is critical to the management of HIV infection, and the promotion of the health of the mother, her partner, and her child [3-5].

1.4 Adherence during pregnancy

Nachegea et al., 2012 conducted a systematic review of 51 studies, including 14 from the United States and five from South Africa, to estimate ART adherence during pregnancy and just after pregnancy in settings around the world [5]. The included studies utilized different measures for capturing adherence to ART (e.g. pill count, self-report, and blood drug concentration), and had varying thresholds for defining “good adherence,” (e.g. greater than 80%, greater than 90%, etc.) [5]. A pooled estimate of the proportion of women who were adherent during pregnancy suggested that about 74% (95% CI: [69.3, 77.5]) achieved adherence greater than 80% of the time [5]. The findings

of the study also suggest that reaching adequate adherence levels proves especially challenging during the postpartum period, with only about 53% (95% CI: [32.8, 72.7]) achieving good adherence [5]. In low and middle income countries, like South Africa, women fared better overall with adherence levels at 76% (95% CI: [72.2, 79.7]) as compared with women in high-income settings, where a pooled estimate of 62% (95% CI: [50.1, 73.3]) was observed, but this difference became non-significant with the exclusion of studies examining single-dose nevirapine only regimes [5].

One prospective study conducted in the United States among 500 pregnant women reported 75% of participants not missing any doses on the four days before their study visit; this proportion dropped significantly at 6, 24, and 48 weeks postpartum, to as low as 64% [18]. The women with optimal adherence in this cohort had significantly lower viral loads than those with suboptimal adherence [18]. A study conducted in KwaZulu-Natal, South Africa, examined counseling and clinical notes of 100 Zulu women and found good adherence (defined as >95% adherent) in 61% of women during pregnancy [19].

Despite having disparate measures of adherence and differing thresholds for “good” adherence, these studies suggest that many women are sub-optimally adherent during and just after pregnancy, and that there is a need for strategies to improve adherence in both low and high-income settings.

1.5 Known risk factors for poor adherence during pregnancy

Little information is available on risk factors for poor adherence to ART among pregnant women and other women of reproductive age. An early study conducted in 1997

in the general population reviewed the available literature and broadly outlined younger age, unstable housing, low income and lack of insurance, lack of transportation and child care, mental illness, poor social support, poor knowledge of medications, and illicit drug use as being some potential risk factors that could affect adherence to HIV therapy [20]. Some commonly identified risk factors in resource-rich settings, but not necessarily unique to pregnant women, also include fear of disclosure of HIV status, complex regimens, diminished sense of self-worth, and not accepting their HIV seropositivity [21].

In resource-poor settings, more work has been done to investigate both the barriers to and facilitators of adherence to ART among pregnant women, especially for the purposes of PMTCT treatment adherence. Poor knowledge of HIV and vertical transmission, therapy misconceptions, and psychological issues following HIV diagnosis as additional barriers were all identified as individual-level barriers [22]. Other barriers identified include domestic violence, preference for traditional healers and birth attendants, stigma associated with HIV and parenthood, and issues with disclosure to family [22]. In addition, Gourlay et al., 2013, along with others, have identified some serious health-systems level barriers, including stock-outs of pills, staff shortages, and perceived negative health workers attitudes [22, 23]. There is little to no literature comparing risk factors for poor adherence in pregnant women and other women of reproductive age.

The aims of this thesis were:

1. to examine prevalence of poor adherence in South African women,

2. to identify risk factors for poor adherence and investigate differences in risk factors by pregnancy status in both South Africa and the United States.

First, levels of ART adherence were compared between women who became pregnant and those who did not among a cohort of HIV-infected women in South Africa. Second, risk factors for poor adherence were examined and the effects stratified by whether or not a woman experienced a pregnancy during follow up among the same cohort of HIV-infected women in South Africa. Finally, risk factors for poor adherence were examined and the effects stratified by whether or not a woman experienced a pregnancy outcome as compared with not experiencing a pregnancy outcome among a cohort of HIV-infected women in the United States.

Chapter 2: Methods

2.1 Study design, setting, and populations

The present study was nested in two existing urban cohorts of HIV-infected women on ART: one cohort in the United States and one in South Africa.

The cohort of women studied from the United States was a sample of the Women's Interagency HIV Study (WIHS) and came from six sites: Bronx, New York, Brooklyn, New York, Washington DC, Los Angeles, California, San Francisco, California, and Chicago, Illinois. The WIHS is the largest prospective cohort study of HIV among US women, and includes a structured interview, a clinical examination, and laboratory testing at semi-annual study visits. Details of the WIHS have been published previously [24]. Prior to the analyses presented here, a descriptive study of ART use before, during, and after pregnancy was conducted in the WIHS [25]. This parent study propensity-score matched WHIS participants by whether or not they had reported a pregnancy outcome, defined as a live birth, a termination, a miscarriage, etc., anytime in the six months prior to that visit [25]. Risk factors for poor adherence were measured at the visit prior to the study's baseline (index) visit, or six months before the index visit, and adherence was measured at the index+1 visit, or six months after the index visit (Figure 1). The analyses presented here were nested in this previous WIHS study.

The cohort of women studied from South Africa was part of a clinical cohort based out of four publicly-funded ART health centers: Hillbrow Community Health Centre, South Rand Hospital, Urban Health Clinic, and Rosettenville Primary Health Centre, in Johannesburg, Gauteng between 2009 and 2011. Recruitment was conducted by study staff in clinic waiting rooms. Information was collected at one to three month

clinic visits, and participants were followed for about one year or until the end of pregnancy. Participants were asked questions regarding demographics, reproductive history, fertility intentions, and patient provider relations during a baseline interview. Interviews were conducted in English, Zulu, and Sotho. Pregnancy testing, contraceptive use, and fertility intentions were assessed by study staff at each visit, and patient files were used to obtain additional clinical information. For the cohort of women from South Africa, risk factors for poor adherence were measured at the baseline visit and self-reported adherence was measured at endline (Figure 1).

2.2. Inclusion criteria

For both cohorts, women were included in this study if they were living with HIV, on antiretroviral therapy, and at risk of pregnancy.

Women from the United States were sampled from the parent study describing ART use before, during, and after pregnancy. In the present study, women age ≤ 52 years with at least one male sex partner were included if they had not previously experienced a hysterectomy, oophorectomy, or tubal ligation. Women who were not on treatment in the six months leading up to the index+1 visit were excluded because they could not have had self-reported adherence data at the index+1 visit (Figure 1).

Women from the South African cohort were sampled. Women 18-35 years old, who had been sexually active in the last 12 months, had a negative urine-based pregnancy test at baseline, and were not breastfeeding, had not experienced a tubal ligation, sterilization, or prior infertility diagnosis were eligible for inclusion. Based on the structure of the interviews and the study design, self-reported adherence was only

collected at endline and therefore, only those women with endline data were included in this study.

2.3 Outcome definition

The main outcome of interest was self-reported poor adherence. Self-reported adherence was chosen as the primary outcome of interest rather than viral load suppression, a biologic measure of adherence, because it is possible that for some individuals, suppressed viral load may not be a true indicator of good adherence. Elite controllers in the absence of treatment, as an example, often have viral loads similar to that of those who are adherent to medications [26]. In the absence of other adherence measures, e.g. pill count, pharmacy claims data, etc., self-reported adherence was chosen as the primary outcome. In the United States, women were characterized as having poor adherence if they reported being adherent to antiretroviral medication <95% of the time over the last six months. In the cohort of women from South Africa, women were characterized as having poor adherence if they were adherent to antiretroviral medication <95% of the time, which was captured if they reported missing pills on one or more days in the last two weeks.

Among the WIHS women, level of adherence was assessed six to twelve months following the end of a pregnancy or six months after a comparable visit in those who did not report a pregnancy outcome. Among the South African women, level of adherence was assessed at the end of pregnancy or just after the end of pregnancy or at a comparable visit in those who did not experience a pregnancy during follow-up.

2.4 Description of risk factors

Pregnancy was the primary risk factor of interest, defined as pregnancy during follow-up in the South African women, and pregnancy outcome reported at the index visit in the American women. Additional risk factors for poor adherence were considered based on *a priori* knowledge and hypothesized relationships based on a review of the literature. Risk factors for poor adherence from three categories were examined: patient characteristics, reproductive-health related characteristics, and other healthcare-related characteristics. Two separate conceptual frameworks can be found relating the risk factors to poor adherence for each of the two cohorts (Figures 2 & 3).

In the United States, age, income level, education, and race were patient risk factors. Relationship status, pregnancy intentions, and parity were reproductive-health related risk factors. CD4 count, health insurance, depressive symptoms, and illicit drug use were healthcare-related risk factors. Exploratory data analysis and a review of the literature informed the way we modeled the risk factors, to allow for appropriate inference and comparison of our findings with other studies. Age (in years) was categorized into three groups: 18-24, 25-33, and ≥ 34 years. Yearly household income level was dichotomized with reference to the 2008 annual poverty threshold for a family of four (\$24,000) and within the confines of WIHS data collection (household income was categorized as follows: \$6000 or less, \$6001-\$12000, \$12001-\$18000...\$75,000 or more) [27]. Education completed was categorized into three groups: less than high school, high school graduate, or more than high school. Race was classified as Black and non-Black. Relationship status was dichotomized, with women who were either married

or living with a partner categorized as being in a relationship. Whether or not women were currently trying to conceive was dichotomized. Parity was categorized into three groups: no children, one child, or two or more children. CD4 count was categorized into four groups: 0-200, 201-350, 351-500, or ≥ 500 cells/ μ L. Illicit drug use, depressive symptoms, and whether or not women had insurance were all dichotomized (yes/no). Though originally considered for inclusion, any contraceptive use was not included as a risk factor as it was collinear with intention to conceive.

In the South African setting, age, income level, and education were patient-level risk factors. Current partner HIV status, pregnancy intentions, and parity were reproductive-health related risk factors. CD4 count, time on highly active antiretroviral therapy (HAART), and ability to talk to primary healthcare provider other healthcare-related risk factors. Age (in years) was categorized into three groups: 18-24, 25-33, and ≥ 34 years. Monthly household income level was dichotomized to above and below the poverty line, or about \$120 USD per month, which was based on the 2009 poverty threshold for a family of four. The conversion rate from Rand (ZAR) to Dollars (USD) was used from 2009 [28, 29]. Education completed was categorized into three groups: primary or less, some secondary, or secondary or more. Information on the woman's current partner's HIV status was dichotomized into HIV negative (i.e. a serodiscordant partner) and other. The rationale behind this was that those women with a serodiscordant partner have the most to gain from remaining adherent to their medication. Whether or not women were currently trying to conceive was dichotomized (yes/no). Parity was categorized into three groups: no children, one or two children, or more than two children. CD4 count was categorized into four groups: 0-200, 201-350, 351-500, or ≥ 500

cells/ μ L. While it was considered that time on HAART might be collinear with age, in univariate analyses it was shown to have a different effect on poor adherence than age. Time on HAART was therefore included and categorized into three groups: less than 1 year, between 1 and 4 years, and more than 4 years. Whether or not a woman felt that she could talk to her main health care provider was dichotomized (yes/no). Like in the WIHS context, contraceptive use was not included.

Figure 2. Conceptual framework of risk factors for poor adherence in the cohort of women from the United States

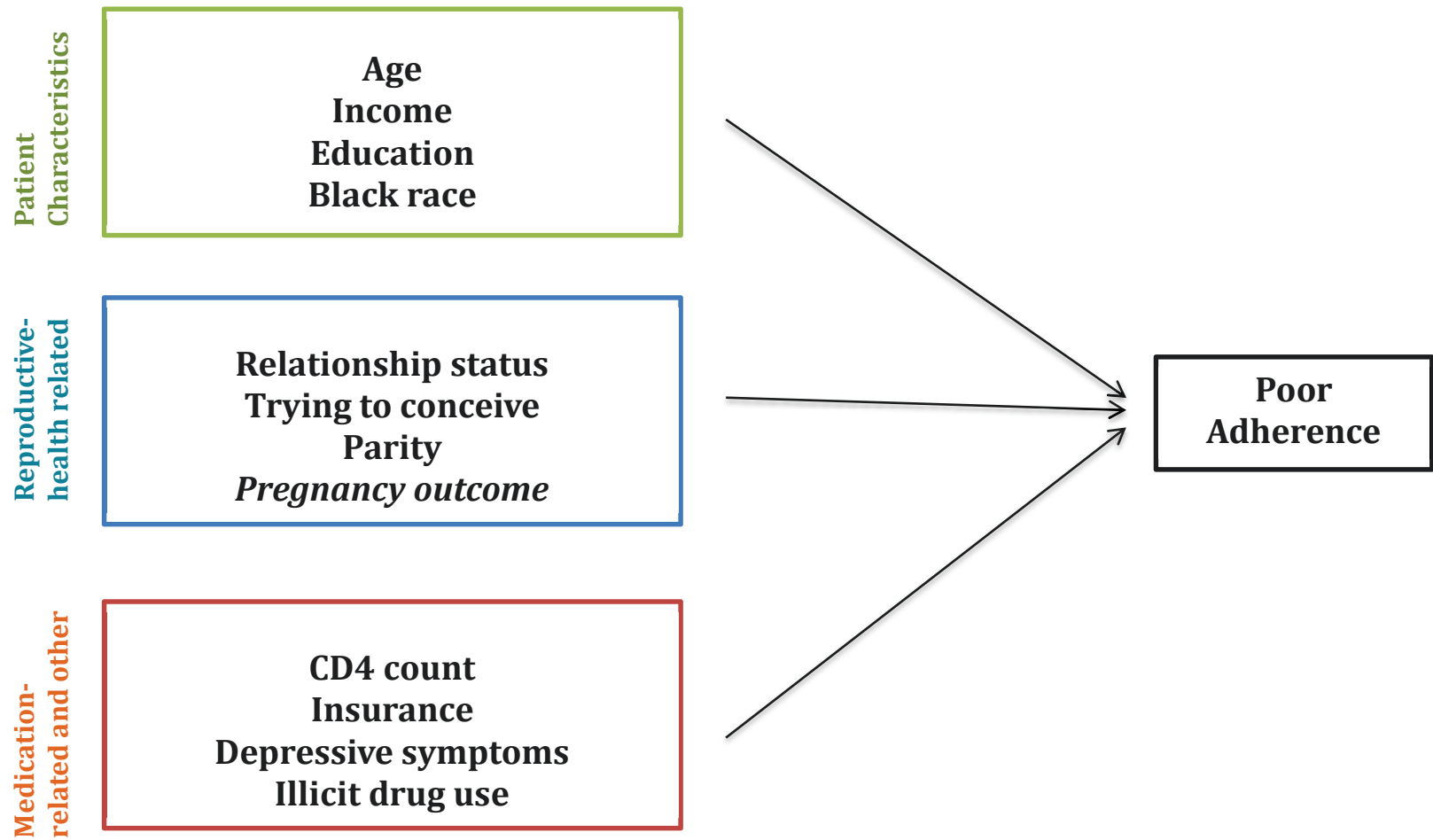
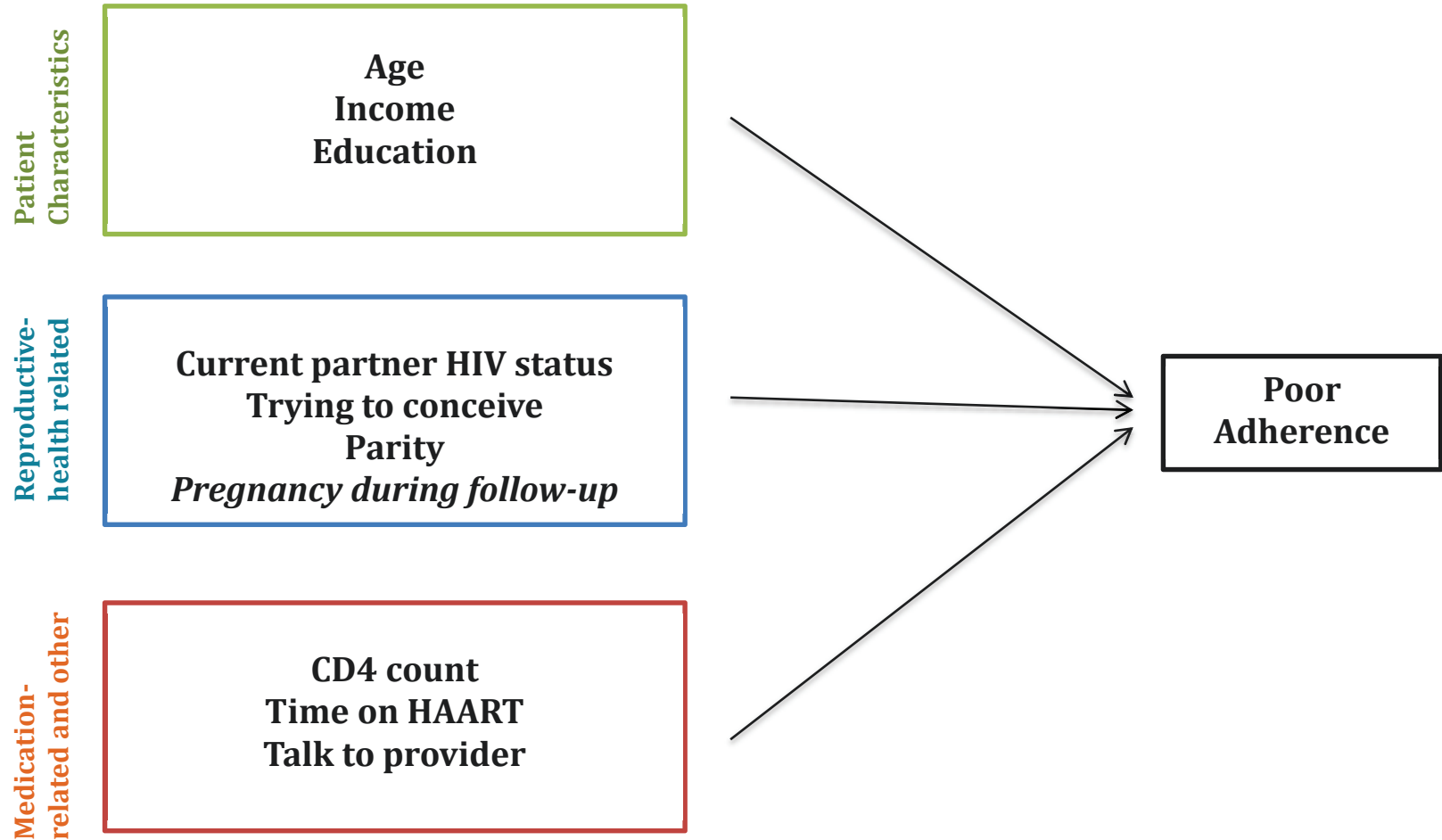


Figure 3. Conceptual framework of risk factors for poor adherence in the cohort of women from South Africa



2.5 Statistical approach

While parsimony was not necessarily a primary goal of this risk factor analysis, factors were included after assessment of univariate associations and collinear relationships.

Data were analyzed using Stata/IC 13.1 for Mac (StataCorp LP, College Station, TX). A p-value of 0.05 was used as a cutoff for statistical significance.

Missing data

Missing data in both cohorts was low. There was less than 2.5% missingness in income (2.4%), relationship status (1.9%), race (1.2%) and insurance (1.2%) for the cohort of women from the United States. There was missingness in only one risk factor, income (2.5%), for the South African cohort. Complete case analysis was used as missingness was thought to be sufficiently low.

Selection bias

Selection bias for both cohorts was examined by comparing characteristics of those in the study prior to application of our inclusion/exclusion criteria (source population), and those included in these analyses (study population, see Appendix). This comparison allowed us to examine the representativeness of the women in our study populations to those in the source populations.

Statistical analyses

A merging of the two datasets was originally considered to assess the importance of cohort, or context, on poor adherence in pregnant and non-pregnant women of

reproductive age, but it was determined that because of the disparate nature of the study questions and study design, the analyses must be stratified by geographical context, thus eliminating the possibility of examining geographical context as a risk factor.

Pearson's chi-square tests for independence were used to explore the associations between various index-1 visit characteristics (age, income, education, race, relationship status, pregnancy intentions, parity, CD4 count, insurance, illicit drug use) and whether or not a woman reported a experiencing a pregnancy outcome at the index visit for the cohort of women from the United States and separately for various baseline characteristics (age, income, education, relationship status, pregnancy intentions, parity, CD4 count, time on HAART, ability to talk to provider) and whether or not a woman experienced a pregnancy during follow-up in the South African cohort. For further detail, age and parity were also examined as continuous variables, and statistical associations were assessed using Wilcoxon-rank sums test for equality of medians.

For Aim 1, the prevalence of women who had poor adherence in the South African cohort was assessed at baseline, or prior to pregnancy, and at endline, during or just after pregnancy or a comparable time for those women who did not become pregnant during follow-up. Because self-reported adherence was not available at the baseline visit, a viral load above the detectable limit (greater than or equal to 50 copies per milliliter) was used as a proxy for poor adherence. The prevalence of poor adherence at baseline was compared with that at endline, and stratified by whether or not the participant experienced a pregnancy during follow-up and by their pregnancy intentions at the start of the study. HIV viral loads used to estimate prevalence of poor adherence were measured at the baseline and closest to the endline interview. Standard errors and

confidence intervals were calculated for the proportions using Clopper-Pearson intervals for binomial proportions. Proportions were compared using tests on the equality of proportions. The prevalence of adherence in the WIHS was not examined because these HIV viral load measurements were not available in our study population [25].

For Aim 2, Poisson regression models with robust variance estimation were used to approximate log binomial models, because the prevalence of the outcome exceeded 10% and prevalence ratios were the most appropriate estimate given the study design. Log binomial models were attempted, but they failed to converge. Crude (PR) and adjusted (aPR) prevalence ratios estimated the association of the risk factors with poor adherence.

Due to the difference in the context, models were stratified by cohort (WIHS women in the US and the South African cohort). Selection of risk factors for the final adjusted model were chosen based on univariate associations and *a priori* knowledge. Our *a priori* belief was that risk factors for poor adherence would be different among pregnant and non-pregnant women. We conducted a stratified analysis, building separate risk factor models stratified by pregnancy in each context.

Sensitivity analyses

A sensitivity analysis was conducted in the South African cohort of women using detectable viral load as the outcome instead of self-reported poor adherence to assess if risk factors changed based on a biologic vs. self-reported outcome. Another sensitivity analysis was conducted in the South African cohort of women in which the cut-off for

self-reported poor adherence was changed from <95% to <85% adherence to assess how risk factors may be influenced by this change in outcome definition.

Chapter 3: Results

3.1 Population characteristics

United States

A total of 902 WIHS HIV-infected women in the United States were included in this study. From the 1305 women in the source population, 403 were excluded because they did not have adherence data at the index+1 visit. Among the 902 women included, median age was 33 years (IQR: 27.8-37.8). More than half (54%) of women completed high school or more; 37% completed some high school and 9% completed less than high school. About 3 in 4 women were living below the poverty line (76%). Less than 20% of women reported any illicit drug use, and 41% had depression symptoms as assessed by a CESD-score. A majority of women included in this study identified as Black (66%).

There was a relatively even distribution for all characteristics measured at the index-1 visit between those women that had reported a pregnancy outcome at the index visit and those that had not, with no statistically significant difference between groups (Table 1).

South Africa

From the original 850 women who were enrolled at baseline in the South African cohort, 730 (86%) women had endline data and were included in this analysis. The median age was 30.5 years old (IQR: 27.5-33.1). Over 90% of women were living below the poverty line, and close to 9% had completed primary school or less. About 93% of women were in a self-reported relationship at baseline, and 12% of them were currently trying to conceive. Most women had been on HAART for less than four years, with only 7% of women on treatment for more than four years. There was no statistically

significant association between any of the baseline characteristics and whether or not the women experienced a pregnancy during follow-up (Table 2).

3.2 AIM 1: Prevalence of poor adherence by pregnancy status in South Africa

Prevalence of poor adherence was measured by detectable viral load during the period of baseline to endline in the South African cohort of women. All women at baseline were at risk of pregnancy and not pregnant yet. Overall, poor adherence as indicated by viral load above the detectable limit at baseline was 25% (95% CI: [22, 28]). Prevalence of poor adherence was significantly lower at endline, 17% (95% CI: [14, 20]). When examining prevalence of poor adherence at either baseline or endline stratified by whether or not a woman experienced a pregnancy during follow-up and whether or not she had pregnancy intentions at baseline, there did not appear to be any statistically significant difference between groups (Figure 6). All four groups experienced a decline in prevalence of poor adherence between baseline and endline (Figure 6). While the difference in prevalence estimates of poor adherence between baseline and endline are very similar for pregnant (difference in percentages: 7% [3, 11]) and non-pregnant women (difference in percentages: 8% [4, 12]), the steepest decline in poor adherence was seen in those women who were pregnant and trying to become pregnant at baseline (difference in percentages: 13% [9, 17]).

3.3 AIM 2: Risk factors for poor adherence by pregnancy status and cohort

United States

In the United States cohort of women, there was no association between having reported a pregnancy outcome and prevalence of self-reported poor adherence in either

univariate (PR=1.00 [0.78, 1.28]) or multivariate analyses (aPR=1.00 [0.78, 1.29]), after adjusting for other risk factors (Table 3).

For patient demographics as risk factors, those who completed more than high school had a significantly lower prevalence of poor adherence than those who completed less than high school (aPR=0.66 [0.47, 0.94]). Age did not appear to be associated with poor adherence. Both black race as compared with other race (aPR=1.12 [0.86, 1.46]) and those with a yearly household income above the poverty line compared with below the poverty line were associated with a higher prevalence of poor adherence, though not statistically significant (Figure 7). When examining stratified estimates, age did appear to be associated with poor adherence, though not significantly. In those women who experienced a pregnancy outcome at the index visit, older age was associated with a higher prevalence of poor adherence, and in those women who did not, older age was associated with a lower prevalence of poor adherence. In those women who experienced a pregnancy outcome, black race was associated with a lower prevalence of adherence, and in those women who did not, black race was associated with a higher prevalence of poor adherence when compared with other races (Figure 10).

For reproductive-health characteristics as risk factors, no factor remained statistically significantly associated with the outcome in multivariate analyses. Though not significant, those who were currently trying to conceive at the index-1 visit had a higher prevalence of poor adherence than those who were not trying (aPR=1.21 [0.73, 2.00]). Those who were in a relationship had a lower prevalence of poor adherence than those who reported being not in a relationship (aPR=0.88 [0.68, 1.13]). Those who

reported having two or more children had a higher prevalence of poor adherence as compared with those with no children (PR=1.17 [0.76, 1.65]) (Figure 8). In those women who experienced a pregnancy outcome, the association between being in a relationship and poor adherence disappears, whereas for those who did not experience a pregnancy outcome, being in a relationship remains protective when compared with being single. Having one living child as compared with having none is associated with higher prevalence of poor adherence in those who experienced a pregnancy outcome, and with lower prevalence of poor adherence in those who did not experience a pregnancy outcome (Figure 11).

For medication-related and other characteristics as risk factors, those with CD4 counts >200, at all levels, had a significantly lower prevalence of poor adherence as compared with those with CD4 counts ≤200. Those who reported using illicit drugs had a higher prevalence of poor adherence as compared with those who did not (aPR=1.21 [0.91, 1.60]), though not statistically significant. Other non-significant relationships include those with depressive symptoms having a lower prevalence of the outcome compared with those without (aPR=0.86, [0.67, 1.10]) and those who had insurance having a higher prevalence of the outcome compared with those without (aPR=1.32 [0.77, 2.27]) (Figure 9). In those women who experienced a pregnancy outcome, using illicit drugs as compared with those not using was associated with lower prevalence of poor adherence, whereas in those women who did not experience a pregnancy outcome illicit drug use was associated with a higher prevalence of poor adherence (Figure 12).

South Africa

In the South African cohort of women, there was a non-significant association between having a pregnancy during follow-up and prevalence of poor adherence, with women who became pregnant during follow-up having a lower prevalence of poor adherence than those who did not become pregnant (aPR=0.85 [0.61, 1.19]) in univariate analysis and in multivariate analysis (aPR=0.81 [0.58, 1.12]), after adjusting for other risk factors (Table 4).

For patient demographics as risk factors, no factor remained statistically significantly associated with the outcome in multivariate analyses. Older age was associated with lower prevalence of poor adherence, with those who were between 25 and 33 years (aPR=0.88 [0.53, 1.46]) and those who were 34 or older (aPR=0.68 [0.41, 1.13]) when compared with those who were younger than 25 years. Education did not appear to be associated with poor adherence. Those with a monthly household income above the poverty line as compared with those below the poverty line had a higher prevalence of poor adherence (aPrR=1.15 [0.76, 1.75]), though not statistically significant (Figure 13). When examining stratified estimates, education did appear to be associated with poor adherence, though not significantly. In those women who experienced a pregnancy during follow-up, some secondary school was associated with a lower prevalence of poor adherence, while secondary school or more was associated with a higher prevalence of poor adherence compared with primary school or less. In those women who did not experience a pregnancy during follow-up, the effects of education were just the opposite, with some secondary being associated with a higher prevalence of poor adherence and secondary or more being associated with a lower prevalence of poor adherence compared with primary school or less (Figure 16).

For reproductive-health characteristics as risk factors, positive pregnancy intentions were significantly associated with poor adherence, with those who were trying to conceive having a higher prevalence of poor adherence than those who were not trying to conceive (aPR=1.54 [1.10, 0.94]). Relationship status did not appear to be associated with the outcome. While not significant, having one child as compared with having no children was associated with a lower prevalence of poor adherence (aPR=0.87 [0.62, 1.23]) (Figure 14). When stratifying by whether or not a woman experienced a pregnancy during follow-up or not, partner HIV status did appear to be associated with the outcome, though not statistically significantly. In women who became pregnant during follow-up, having a current partner that was HIV negative was associated with high prevalence of poor adherence, while among those who did not become pregnant, having a current partner that was HIV negative was associated with a lower prevalence of poor adherence. (Figure 17)

For medication-related and other characteristics as risk factors, no factor remained statistically significantly associated with the outcome in multivariate analyses. CD4 count > 200 and ability to talk to a health care provider did not appear to be associated with the outcome. More than four years on HAART as compared with less than a year was associated with a higher prevalence of poor adherence (aPR=1.45 [0.85, 2.46]) (Figure 15). When stratified by whether or not a woman became pregnant during follow-up, having the ability to talk to a provider was associated with lower prevalence of poor adherence among pregnant women, but there was no association among non-pregnant women. For those who became pregnant, being on HAART for more than four years was associated with a lower prevalence of poor adherence compared with those who were on

HAART for less than one year, while it was associated with a higher prevalence of poor adherence among those who did not become pregnant (Figure 18).

Sensitivity Analyses

When examining risk factors for poor adherence among the South African cohort of women and using detectable HIV viral load as measurement of poor adherence, trying to conceive was no longer observed as an independent risk factor. Having completed secondary school or more was significantly associated with a lower prevalence of poor adherence compared with having completed primary or less (aPR=0.59 [0.36, 0.97]). Higher CD4 count, > 200, was also significantly associated with a lower prevalence of poor adherence (Table 5).

In the sensitivity analysis examining risk factors for poor adherence among the South African cohort of women using a less stringent cutoff for poor adherence, a cutoff of $\geq 85\%$ instead of $\geq 95\%$, those who were 34 years or older had significantly lower prevalence of poor adherence compared with those 18-24 years (aPR=0.40 [0.17, 0.96]) (Table 6).

Chapter 4: Discussion

4.1 Discussion

Overall, prevalence of poor adherence, as measured by detectable viral load, declined over the course of the study for all women in the South African cohort, and the greatest decline was seen in those who were pregnant and trying to get pregnant at the beginning of the study. Risk factors for self-reported poor adherence differed between the two cohorts. The independent risk factors for poor adherence to ART for the cohort of women from the United States were low CD4 count and lower level of completed education. Risk factors that were different between those who experienced a pregnancy outcome and those who did not were age, race, relationship status, parity, and illicit drug use. The main risk factor for the cohort of women from South Africa was trying to conceive. Risk factors that were different between those who experienced a pregnancy during follow-up and those who did not were level of education completed, partner HIV status, parity, ability to talk to a provider, and time on HAART.

Prevalence of poor adherence by pregnancy status in South Africa

The prevalence of poor adherence was not significantly different in those who experienced a pregnancy during follow-up compared with those who did not experience a pregnancy, at both baseline, before any of the women had become pregnant, and at endline, at the end of pregnancy or after pregnancy (Figure 6). While there are very few data available comparing the adherence levels of pregnant women to that of their non-pregnant counterparts, this finding differs from the available literature, which suggests that pregnant women have higher levels of adherence. One study conducted on a group of 165 women living with HIV and attending a multidisciplinary clinic in Puerto Rico found

that when asked about adherence to ART in a three-day adherence questionnaire, pregnant women (n=37) reported higher levels of adherence than non-pregnant women, and that the difference was significant [30]. In a prospective cohort study of 72 pregnant and 79 non-pregnant women, it was shown that a greater proportion of pregnant women met the criteria for 95% adherence, by both pill count and self-report, than non-pregnant women [31]. That being said, these are the results from two small studies in two very different contexts from South Africa: Puerto Rico and Brazil. Part of the difference between the results of these studies and our findings may have to do with differences in populations, differences in when and how women were asked about adherence, or even differences in perceived social desirability of response. For example, it is possible that pregnant women in these studies were differentially more likely to report being more adherent than their non-pregnant counterparts as compared with the women in our South African cohort, or that pregnant women in the South African cohort were differentially less likely to report being adherent [32]. It is also possible that there is a true difference in levels of adherence in these other contexts, but not in South Africa, and this could be due to a number of things including poor knowledge of PMTCT, poor uptake and access of treatment, etc.

There are almost no data available on the difference in adherence levels between women with intended pregnancies and unintended pregnancies, but it was shown here that if the pregnancy is desired, there exists the steepest decline in poor adherence. *This could suggest the need for more research into how the promotion of planned pregnancies and family planning over unintended pregnancies can improve adherence.*

Independent risk factors: WIHS

It was found that those who completed more than high school had a lower prevalence of poor adherence compared with those who had less than a high school education. This association remained significant when examining those who experienced a pregnancy outcome only, but did not hold when restricted to those who did not report a pregnancy outcome at the index visit. Other studies examining risk factors for poor adherence among women did not find any association with education, but did find that those with better understanding of the dosing and complexity of their regimens were more likely to be adherent [33].

Reduced CD4 count was significantly associated with increased prevalence of poor adherence. When examining stratified estimates, this association remained significant when examining those who did not experience a pregnancy outcome only. Higher CD4 count and lack of clinical AIDS has been previously shown to be associated with reduced likelihood of skipping doses of treatment [18, 33].

Although this descriptive analysis begins to explore factors influencing ART adherence during pregnancy, further research is needed to isolate these associations in a longitudinal study design in order to determine if they are causally related to poor adherence in pregnant and non-pregnant women in the US.

Independent risk factors: South Africa

In the South African cohort of women, trying to conceive was significantly associated with higher prevalence of self-reported poor adherence, and remained

significant in stratified analyses for those who did not become pregnant during the study. This is a very interesting finding, as it potentially suggests four things. First, women who are trying to get pregnant are feeling healthy enough to try conceiving a child, and therefore feel less urgency to adhere to ART. Second, women who are trying to get pregnant are prioritizing trying to conceive and other things in their life over ART adherence. Third, women who are trying to get pregnant underreport ART adherence because they are more conscientious of the importance of adherence for viral suppression. Finally, it is possible that women may underreport use because they have been given misinformation that ART is risky during early pregnancy.

Interestingly, the findings from the sensitivity analysis conducted using detectable viral load as a secondary measurement of poor adherence, support the third and fourth hypotheses outlined above. When using detectable viral load rather than self-reported adherence, trying to conceive is no longer significantly associated with poor adherence. When examining this sensitivity analysis, the independent risk factors appear more similar to those of the WIHS cohort of women, including lower educational level and lower CD4 count. There is very little research on the impact of pregnancy intentions on ART adherence in South Africa, and most identified barriers to poor adherence among women of reproductive age are structural in nature, including financial constraints, stock-outs of pills, distance from clinic, migration, service accessibility, etc. [22, 34].

4.2 Limitations

The main limitation of this study is that because of the disparate nature of the study questions and study design, the risk factors for poor adherence in the two cohorts

could not be directly compared. Additionally, while often cited as important barriers, it was not possible to examine perceived or real structural barriers to adherence, because these data were not available in either cohort. Other important risk factors for poor adherence that could not be studied that have been previously identified include side effects of ART, pill burden, maternal knowledge of HIV transmission and PMTCT, stigma associated with living with HIV, etc. Another important limitation of this study is that it utilizes a cross-sectional design, examining risk factors and poor adherence at a single time point, and therefore causal inference is not appropriate. Adherence is difficult to measure and while self-report can be low-cost and easily collected, it assumes that individuals are able to recall their adherence accurately and are also being honest in their reporting. We tried to parse out the accuracy of self-report using detectable viral load as a proxy for poor adherence, but viral load can vary between individuals for reasons others than ART adherence [26]. Finally, although an assessment for selection bias was performed and no appreciable differences were seen between source populations and study populations, there is a potential for selection bias because of the study design and the strict inclusion criteria (Appendix).

4.3 Conclusion

Adherence to ART is of particular importance for women of reproductive age living with HIV. Risk factors for poor adherence may differ in different contexts. Further research is needed to isolate the effect of these factors to evaluate causal relationships; in particular, the effect of pregnancy intention on ART adherence should be considered.

Table 1. Characteristics^a of HIV-infected women on antiretroviral therapy in the United States, stratified by whether or not experienced a pregnancy outcome by the index visit ^b (n=902)

	Overall N= 902	Pregnant N=287	Not pregnant N=615	<i>p</i>
Median age, years (IQR)	32.6 (27.8, 37.8)	32.2 (27.9, 36.7)	32.8 (27.7, 38.4)	0.238
18-24	76 (8.4)	19 (6.6)	57 (9.3)	0.171
25-33	398 (44.1)	138 (48.1)	260 (42.3)	
34+	428 (47.5)	130 (45.3)	298 (48.5)	
Yearly income above poverty line^e	213 (24.2)	73 (26.7)	140 (23.0)	0.234
Education completed				
Less than high school	79 (8.8)	22 (7.7)	57 (9.3)	0.117
Some high school	334 (37.0)	95 (33.1)	239 (38.9)	
High school or more	489 (54.2)	170 (59.2)	319 (51.9)	
Black Race ^g	589 (66.1)	187 (67.8)	402 (65.4)	0.486
In a relationship ^{e,f}	359 (40.6)	118 (43.1)	241 (39.4)	0.310
Currently trying to conceive ^d	36 (4.0)	7 (2.4)	29 (4.7)	0.104
Median parity (IQR)	2 (1, 3)	2 (1, 3)	2 (1, 4)	0.004
None	113 (12.5)	34 (11.9)	79 (12.9)	0.163
One	192 (21.3)	72 (25.1)	129 (19.5)	
Two or more	597 (66.2)	181 (63.0)	416 (67.6)	
CD4 T-Lymphocyte count, cells/μL				
0-200	68 (11.1)	24 (8.4)	68 (11.1)	0.640
201-350	105 (17.1)	53 (18.5)	105 (17.1)	
351-500	138 (22.4)	67 (23.3)	138 (22.4)	
>500	304 (49.4)	143 (49.8)	304 (49.4)	
Has health insurance ^h	829 (93.0)	261 (94.6)	568 (92.4)	0.231
Depressive symptoms	373 (41.4)	121 (42.2)	252 (41.0)	0.736
Illicit drug use	166 (18.4)	50 (17.4)	116 (18.9)	0.603

For continuous variables, p-values estimated using Wilcoxon-rank sums test for equality of medians.

For categorical variables, p-values estimated using Pearson's chi-square test for independence.

IQR=Interquartile range

HAART=Highly active antiretroviral therapy

^a Measured at index-1 visit, between 2002 and 2014.

^b Women asked if they had experienced a pregnancy outcome in the last six months.

^c Categorized as being in a relationship if either married or living with partner.

^d Categorized as not trying if stated not trying or pregnant at index-1 visit

^e Data missing on household income (n= 21); ^f Data missing on relationship status (n=17); ^g Data missing on race (n=11); ^hData missing on insurance (n=11)

Table 2. Characteristics^a of HIV-infected women on antiretroviral therapy in South Africa, stratified by whether or not experienced a pregnancy during duration of follow-up^b (n=730)

	Overall N= 730	Pregnant N=155	Not pregnant N=575	p
Median age, years (IQR)	30.5 (27.5, 33.1)	29.3 (26.7, 32.6)	30.7 (27.8, 33.2)	0.007
18-24	43 (5.9)	9 (5.8)	34 (5.9)	0.124
25-33	288 (39.4)	72 (46.5)	216 (37.6)	
34+	399 (54.7)	74 (47.7)	325 (56.5)	
Monthly income above poverty line^c	59 (8.1)	15 (9.7)	44 (7.7)	0.412
Education completed				0.714
Primary or less	65 (8.9)	13 (8.4)	52 (9.0)	
Some secondary	294 (40.3)	67 (43.2)	227 (39.5)	
Secondary or more	371 (50.8)	75 (48.4)	296 (51.5)	
In a relationship^d	678 (92.9)	147 (94.8)	531 (92.3)	0.285
Currently trying to conceive	86 (11.8)	24 (15.5)	62 (10.8)	0.107
Median parity (IQR)	1 (1, 2)	1 (1, 2)	1(1, 2)	0.530
None	113 (15.5)	24 (15.5)	89 (15.5)	0.872
One to two	538 (73.7)	116 (74.8)	422 (73.4)	
More than two	79 (10.8)	15 (9.7)	64 (11.1)	
CD4 T-Lymphocyte count, cells/μL				0.999
0-200	206 (28.2)	44 (28.4)	162 (28.2)	
201-350	201 (27.5)	42 (27.1)	159 (27.7)	
351-500	156 (21.4)	33 (21.3)	123 (21.4)	
>500	167 (22.9)	36 (23.2)	131 (22.8)	
Time on HAART				0.931
Less than one year	330 (45.2)	72 (46.5)	258 (44.9)	
Between one and four years	350 (48.0)	73 (47.1)	277 (48.2)	
More than four years	50 (6.8)	10 (6.4)	40 (6.9)	
Can talk to main healthcare provider	315 (43.2)	69 (44.5)	246 (42.8)	0.699

For continuous variables, p-values estimated using Wilcoxon-rank sums test for equality of medians.

For categorical variables, p-values estimated using Pearson's chi-square test for independence.

IQR=Interquartile range

HAART=Highly active antiretroviral therapy

^a Measured at baseline study visit, 2009-2010

^b For 12 months or for duration of pregnancy.

^c Data missing on monthly household income (n=18)

^d Categorized as being in a relationship by self-reported relationship status.

Table 3. Crude and adjusted prevalence ratios for risk factors of self-reported poor adherence ^a among a cohort of women in the United States (n=902)

	Crude Prevalence Ratio	95% CI	Adjusted Prevalence Ratio	95% CI
Pregnancy outcome				
No pregnancy outcome reported	Ref		Ref	
Pregnancy outcome reported	1.00	(0.78, 1.28)	1.00	(0.78, 1.29)
Patient characteristics, general				
Age				
18-24	Ref		Ref	
25-33	0.92	(0.60, 1.43)	1.02	(0.64, 1.60)
34+	0.82	(0.64, 1.04)	1.09	(0.69, 1.73)
Income				
Below poverty line	Ref		Ref	
Above poverty line	1.05	(0.80, 1.37)	1.27	(0.96, 1.67)
Education				
Less than HS	Ref		Ref	
HS	1.07	(0.84, 1.38)	1.02	(0.78, 1.33)
More than HS	0.73	(0.54, 0.98)	0.66	(0.47, 0.94)
Race				
Non-Black	Ref		Ref	
Black	1.14	(0.88, 1.47)	1.12	(0.86, 1.46)
Reproductive health-related				
Relationship status				
Single	Ref		Ref	
In a relationship	0.87	(0.68, 1.11)	0.88	(0.69, 1.13)
Currently trying to conceive				
Not currently trying	Ref		Ref	
Trying	1.16	(0.68, 2.00)	1.21	(0.73, 2.00)
Parity				
None	Ref		Ref	
One	0.81	(0.60, 1.10)	0.95	(0.60, 1.49)

Two or more	1.28	(0.98, 1.66)	1.12	(0.76, 1.65)
Medication-related and patient-provider relations				
CD4 count				
0-200	Ref		Ref	
201-350	0.78	(0.56, 1.10)	0.56	(0.37, 0.85)
351-500	0.84	(0.63, 1.13)	0.59	(0.40, 0.87)
>500	1.05	(0.83, 1.32)	0.69	(0.50, 0.96)
Insurance				
No insurance	Ref		Ref	
Has insurance	1.37	(0.79, 2.38)	1.32	(0.77, 2.27)
Depressive symptoms				
No depressive symptoms	Ref		Ref	
Depressive symptoms	0.93	(0.73, 1.18)	0.86	(0.67, 1.10)
Illicit drug use				
No drug use	Ref		Ref	
Yes have used drugs	1.19	(0.90, 1.58)	1.21	(0.91, 1.60)

^a Self-reported poor adherence defined as being adherent less than 95% of the time in the last six months.

Data missing on monthly household income (n= 21); Data missing on race (n=11); Data missing on relationship status (n=17); Data missing on insurance (n=11)

Table 4. Crude and adjusted prevalence ratios for risk factors of self-reported poor adherence ^a among South African women (n=730)

	Crude Prevalence Ratio	95% CI	Adjusted Prevalence Ratio	95% CI
Pregnancy during follow-up				
Not pregnant during follow-up	Ref		Ref	
Pregnant during follow-up	0.85	(0.61, 1.19)	0.81	(0.58, 1.12)
Patient characteristics, general				
Age				
18-24	Ref		Ref	
25-33	1.21	(0.94, 1.56)	0.89	(0.54, 1.48)
34+	0.78	(0.61, 1.01)	0.68	(0.41, 1.13)
Income				
Below poverty line	Ref		Ref	
Above poverty line	0.49	(0.17, 1.42)	1.16	(0.76, 1.76)
Education				
Primary or less	Ref		Ref	
Some secondary	1.09	(0.84, 1.41)	1.00	(0.64, 1.58)
Secondary or more	0.89	(0.69, 1.16)	0.92	(0.58, 1.44)
Reproductive health-related				
Current partner HIV status				
Single or regular partner HIV positive/unknown	Ref		Ref	
Regular partner, HIV negative	1.07	Ref	1.11	Ref (0.82, 1.50)
Currently trying to conceive				
Not currently trying	Ref		Ref	
Trying	1.59	(1.16, 2.18)	1.56	(1.12, 2.17)
Parity				
None	Ref		Ref	
One to two	0.81	(0.62, 1.07)	0.87	(0.62, 1.23)
More than two	1.11	(0.75, 1.64)	1.08	(0.65, 1.80)
Medication-related				
CD4 count				
0-200	Ref		Ref	

201-350	1.12	(0.85, 1.49)	1.13	(0.79, 1.64)
351-500	1.01	(0.74, 1.37)	1.06	(0.70, 1.61)
>500	0.98	(0.72, 1.34)	0.95	(0.61, 1.48)
Time on HAART				
Less than one year	Ref		Ref	
Between one and four years	1.00	(0.78, 1.30)	1.08	(0.79, 1.47)
More than four years	1.26	(0.81, 1.96)	1.44	(0.85, 2.44)
Patient-provider relations				
Provider talk				
Cannot talk to provider	Ref		Ref	
Can talk to provider	0.95	(0.73, 1.23)	0.95	(0.73, 1.23)

ART= Antiretroviral therapy

HAART= Highly active antiretroviral therapy

^a Self-reported poor adherence defined as being adherent less than 95% of the time in the last fourteen days

Data missing on monthly household income (n=18)

Table 5. Sensitivity Analysis: Crude and adjusted prevalence ratios for risk factors of poor adherence defined as having a viral load below the detectable limit ^a among South African women (n=730)

Risk factors	Crude Prevalence Ratio	95% CI	Adjusted Prevalence Ratio	95% CI
Pregnancy during follow-up				
Not pregnant during follow-up	Ref		Ref	
Pregnant during follow-up	1.05	(0.71, 1.56)	1.05	(0.70, 1.56)
Patient characteristics, general				
Age				
18-24	Ref		Ref	
25-33	0.75	(0.39, 1.42)	0.77	(0.39, 1.50)
34+	0.81	(0.44, 1.51)	0.78	(0.40, 1.51)
Income ^b				
Below poverty line	Ref		Ref	
Above poverty line	1.13	(0.64, 1.97)	1.29	(0.72, 2.33)
Education				
Primary or less	Ref		Ref	
Some secondary	0.77	(0.48, 1.26)	0.83	(0.51, 1.35)
Secondary or more	0.55	(0.33, 0.90)	0.59	(0.36, 0.97)
Reproductive health-related				
Current partner HIV status				
Single or regular partner HIV positive/unknown	Ref		Ref	
Regular partner, HIV negative	1.23	(0.86, 1.77)	1.28	(0.89, 1.83)
Currently trying to conceive				
Not currently trying	Ref		Ref	
Trying	0.97	(0.58, 1.62)	0.97	(0.58, 1.63)
Parity				
None	Ref		Ref	
One to two	0.81	(0.52, 1.25)	0.89	(0.57, 1.39)
More than two	1.36	(0.79, 2.34)	1.52	(0.85, 2.71)
Medication-related				
CD4 count				
0-200	Ref		Ref	
201-350	0.62	(0.41, 0.96)	0.56	(0.35, 0.89)
351-500	0.80	(0.53, 1.23)	0.74	(0.45, 1.20)

>500	0.54	(0.33, 0.87)	0.46	(0.26, 0.80)
Time on HAART				
Less than one year	Ref		Ref	
Between one and four years	1.00	(0.78, 1.30)	1.04	(0.70, 1.56)
More than four years	1.26	(0.81, 1.96)	1.71	(0.89, 3.28)
Patient-provider relations				
Provider talk^c				
Cannot talk to provider	Ref		Ref	
Can talk to provider	0.80	(0.57, 1.12)	0.81	(0.57, 1.14)

ART= Antiretroviral therapy

HAART= Highly active antiretroviral therapy

^a Poor adherence defined as detectable viral load (greater than or equal to 50 copies per milliliter)

^b Data missing on monthly household income (n=18)

^c Self-reported ability to talk to provider about health issues.

Table 6. Sensitivity Analysis: Crude and adjusted prevalence ratios for risk factors of self-reported poor adherence ^a among South African women (n=730)

Risk factors	Crude Prevalence Ratio	95% CI	Adjusted Prevalence Ratio	95% CI
Pregnancy during follow-up				
Not pregnant during follow-up	Ref		Ref	
Pregnant during follow-up	0.63	(0.30, 1.31)	0.60	(0.30, 1.22)
Patient characteristics, general				
Age				
18-24	Ref		Ref	
25-33	0.51	(0.23, 1.12)	0.55	(0.24, 1.25)
34+	0.37	(0.17, 0.81)	0.40	(0.17, 0.96)
Income ^b				
Below poverty line	Ref		Ref	
Above poverty line	0.89	(0.33, 2.38)	0.95	(0.36, 2.51)
Education				
Primary or less	Ref		Ref	
Some secondary	0.64	(0.30, 1.36)	0.64	(0.29, 1.37)
Secondary or more	0.53	(0.25, 1.12)	0.55	(0.26, 1.17)
Reproductive health-related				
Current partner HIV status				
Single or regular partner HIV positive/unknown	Ref		Ref	
Regular partner, HIV negative	0.93	(0.50, 1.72)	1.01	(0.54, 1.88)
Currently trying to conceive				
Not currently trying	Ref		Ref	
Trying	1.66	(0.87, 3.18)	1.51	(0.79, 2.89)
Parity				
None	Ref		Ref	
One to two	0.60	(0.33, 1.09)	0.74	(0.39, 1.42)
More than two	0.55	(0.20, 1.48)	0.75	(0.25, 2.22)
Medication-related				
CD4 count				
0-200	Ref		Ref	
201-350	0.90	(0.46, 1.76)	0.98	(0.46, 2.06)
351-500	0.78	(0.37, 1.65)	0.90	(0.39, 2.08)

>500	0.94	(0.47, 1.89)	1.06	(0.43, 2.64)
Time on HAART				
Less than one year	Ref		Ref	
Between one and four years	0.84	(0.49, 1.42)	0.94	(0.49, 1.81)
More than four years	0.98	(0.36, 2.68)	1.17	(0.35, 3.91)
Patient-provider relations				
Provider talk ^c				
Cannot talk to provider	Ref		Ref	
Can talk to provider	0.81	(0.48, 1.37)	0.84	(0.49, 1.43)

ART= Antiretroviral therapy

HAART= Highly active antiretroviral therapy

^a Self-reported poor adherence defined as being adherent less than 85% of the time in the last fourteen days

^b Data missing on monthly household income (n=18)

^c Self-reported ability to talk to provider about health issues.

Figure 4. Comparison of study design and cohort characteristics for two urban cohorts of women from the United States and South Africa

	USA	South Africa
STUDY DESIGN		
Number of sites	6 study sites	4 Primary health centers
Time period	2002-2014	2009-2011
Frequency of study visits	Every 6 months	1-3 month intervals
Follow-up time	12 months	12 months or duration of pregnancy
Pregnancy status	Pregnancy outcome observed at index visit	Pregnancy during follow up
COHORT CHARACTERISTICS		
Age	≤52	18-35
Total number of participants	902	850
Number retained (retention rate)	902 (100%)	730 (85.9%)
Number of women who experienced pregnancy/pregnancy outcome (% of total)	287 (31.8%)	161 (22.1%)
Living with HIV	YES	YES
On antiretroviral therapy	YES	YES
Male partner?	YES	YES
Excluded if not at risk of pregnancy	YES	YES

Figure 5. Definition of poor adherence by cohort and level of analysis: self-reported adherence and viral load as a proxy for adherence

COHORT	ANALYSIS	COLLECTED	Poor adherence defined as
USA	Primary	Self-report: How often did you take ARVs over the past 6 months? 100% of the time 95-99% of the time 75-94% of the time <75% of the time	Taking ARVs <95% of the time.
South Africa	Primary	Self-report: How many days in the last two weeks have you missed taking your ARV pills for any reason?	Missed pills on one or more days (<95%).
South Africa	Sensitivity	Self-report: How many days in the last two weeks have you missing taking your ARV pills for any reason?	Missed pills on three or more days (<85%).
South Africa	Sensitivity	Viral load as proxy	Having a detectable viral load (50 copies/mL or more)

Figure 6. Prevalence of detectable viral load, comparing HIV-infected women on antiretroviral therapy by whether or not they experienced a pregnancy and pregnancy intentions in South Africa, 2009-2011 (n=730)

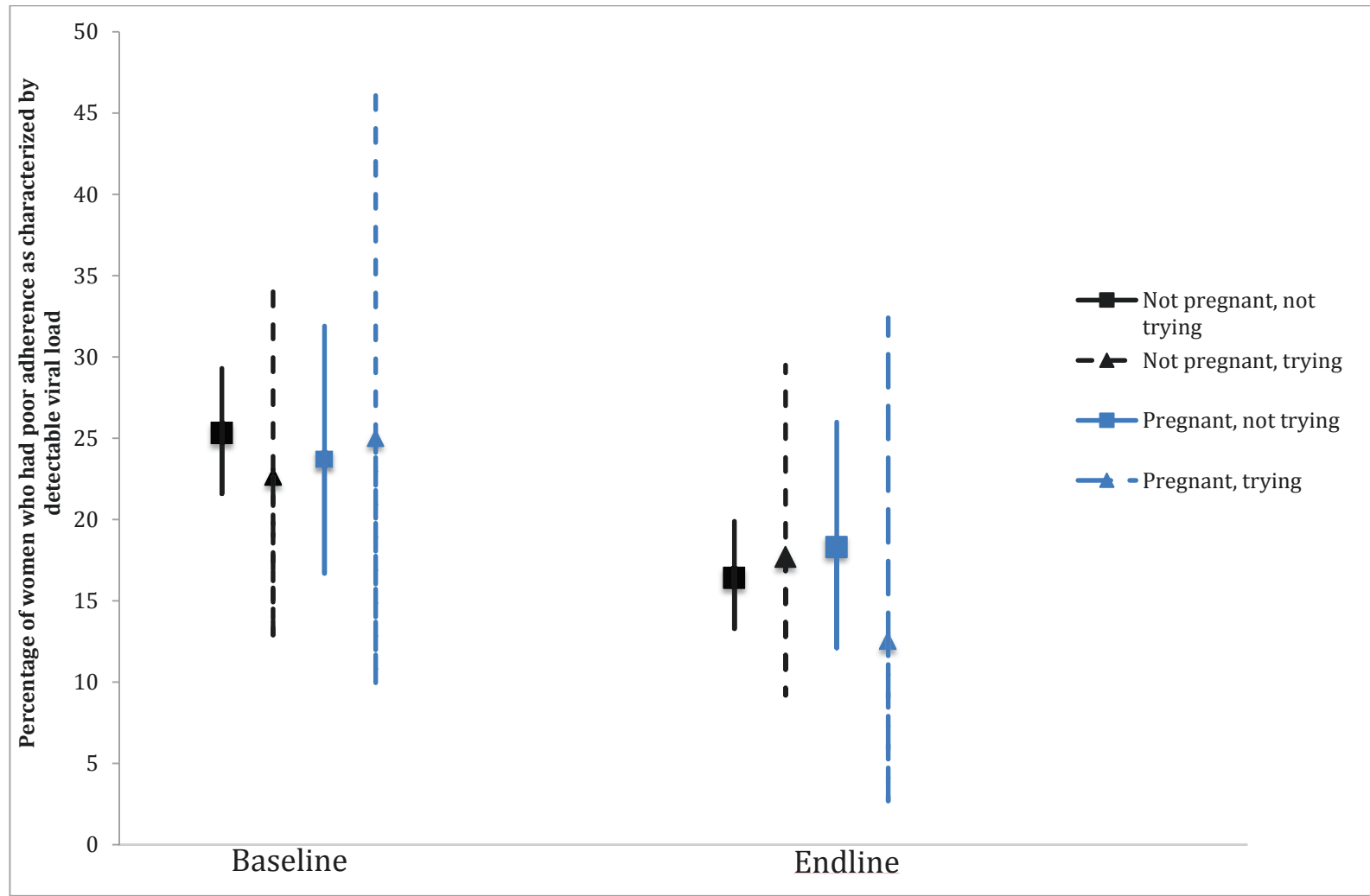
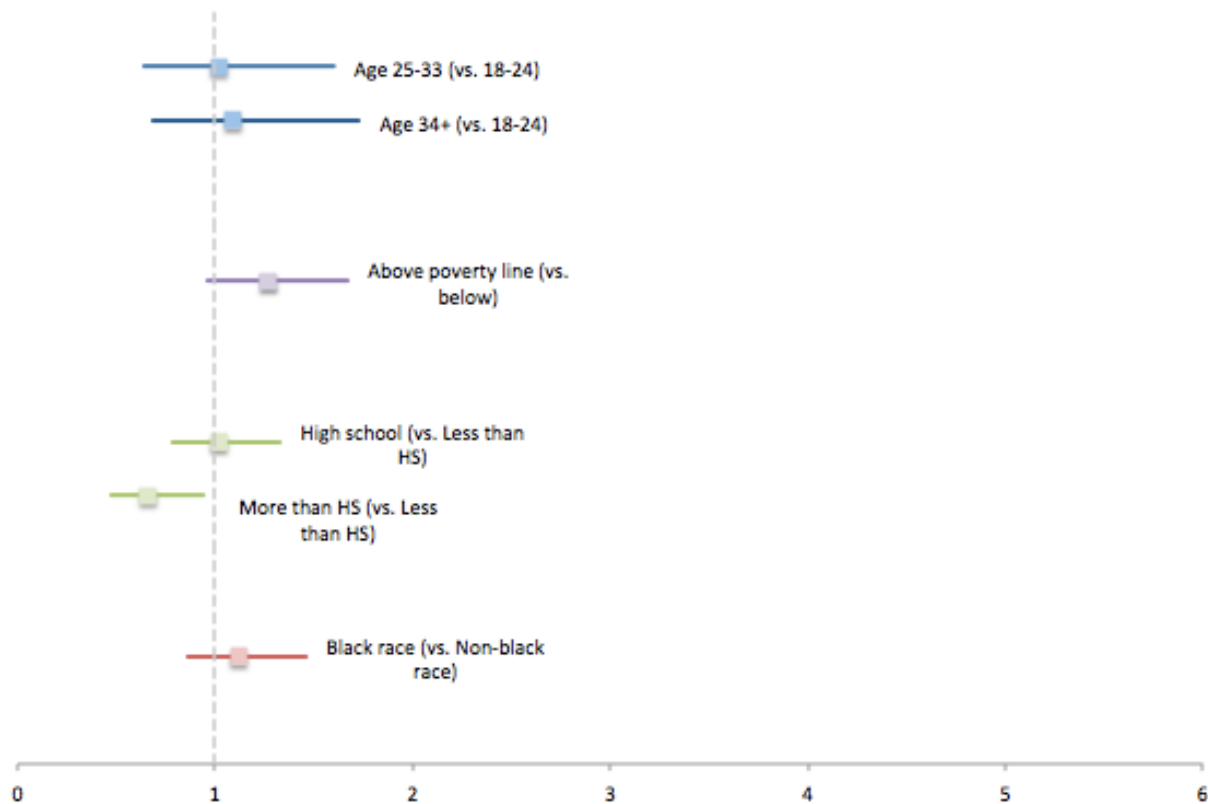
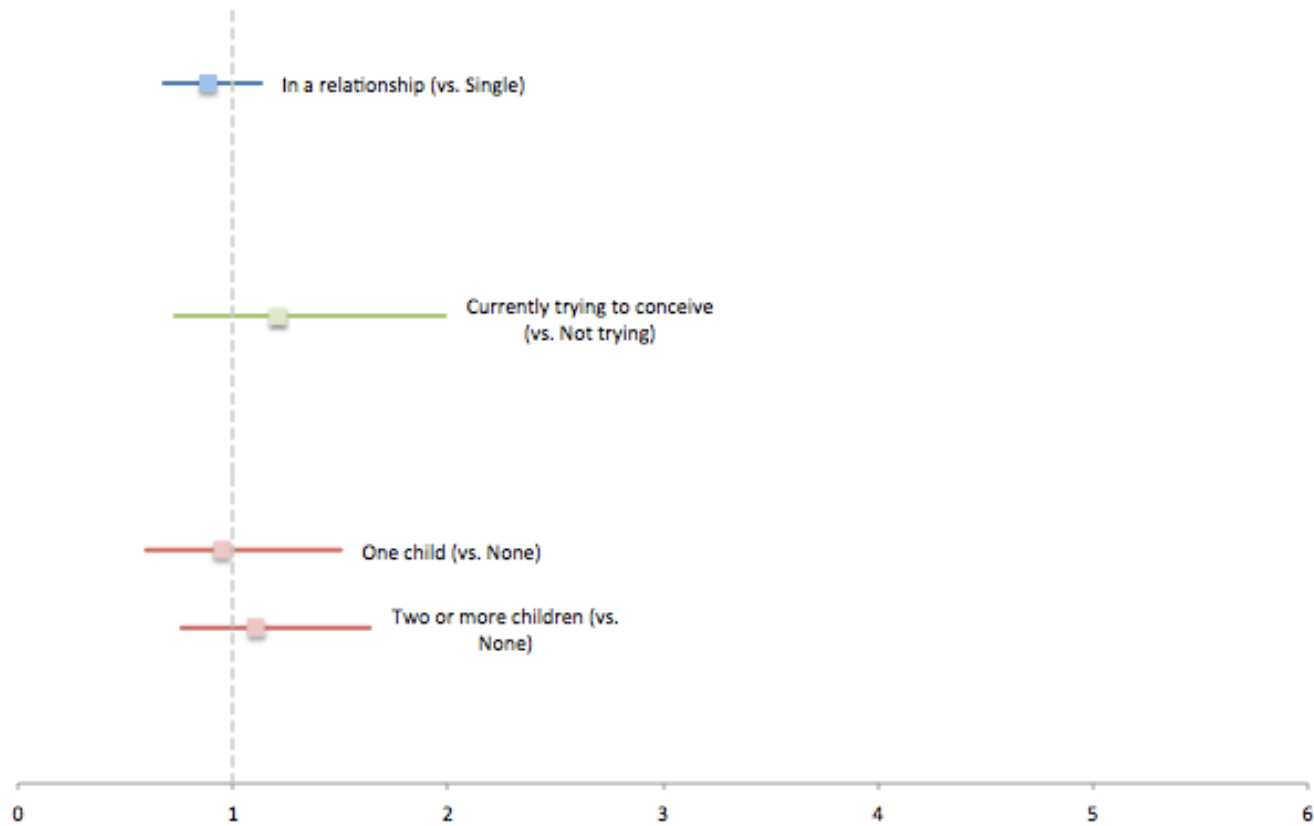


Figure 7. Forest plot of patient demographics as predictors of poor adherence among HIV-infected women on antiretroviral therapy in the United States, overall (n=902)



Variable	aPR	95% CI
Age 25-33 (vs. 18-24)	1.02	(0.64, 1.60)
Age 34+ (vs. 18-24)	1.09	(0.69, 1.73)
Above poverty line (vs. Below poverty line)	1.27	(0.96, 1.67)
High school (vs. Less than high school)	1.02	(0.78, 1.33)
More than high school (vs. Less than high school)	0.66	(0.47, 0.94)
Black race (vs. Non-black race)	1.12	(0.86, 1.46)

Figure 8. Forest plot of reproductive-health characteristics as predictors of poor adherence among HIV-infected women on antiretroviral therapy in the United States, overall (n=902)



Variable	aPR	95% CI
In a relationship (vs. Single)	0.88	(0.68, 1.13)
Currently trying to conceive (vs. Not trying)	1.21	(0.73, 2.00)
One child (vs. No children)	0.95	(0.6, 1.49)
Two or more children (vs. No children)	1.17	(0.76, 1.65)

Figure 9. Forest plot of medication-related characteristics as predictors of poor adherence among HIV-infected women on antiretroviral therapy in the United States, overall (n=902)

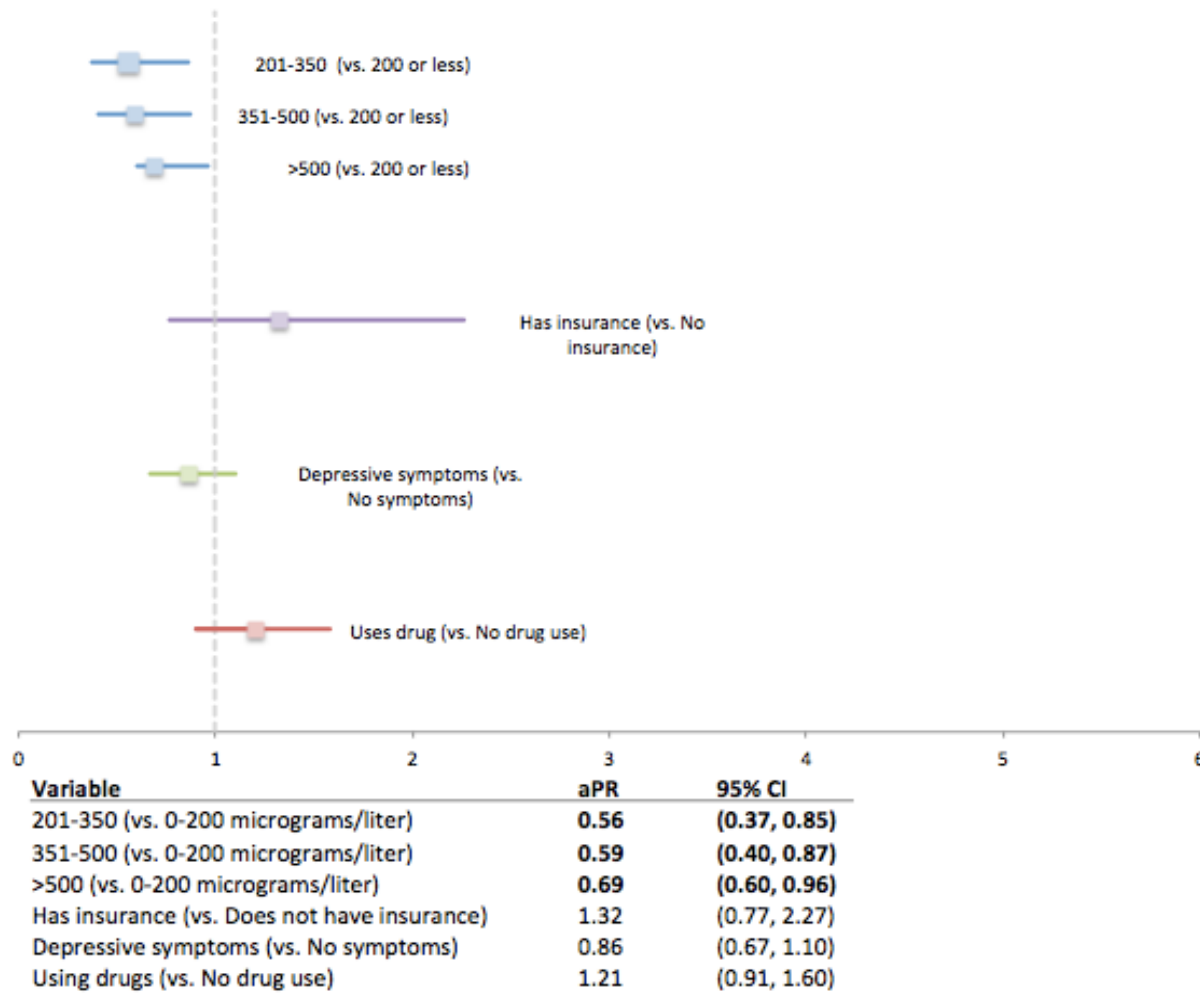
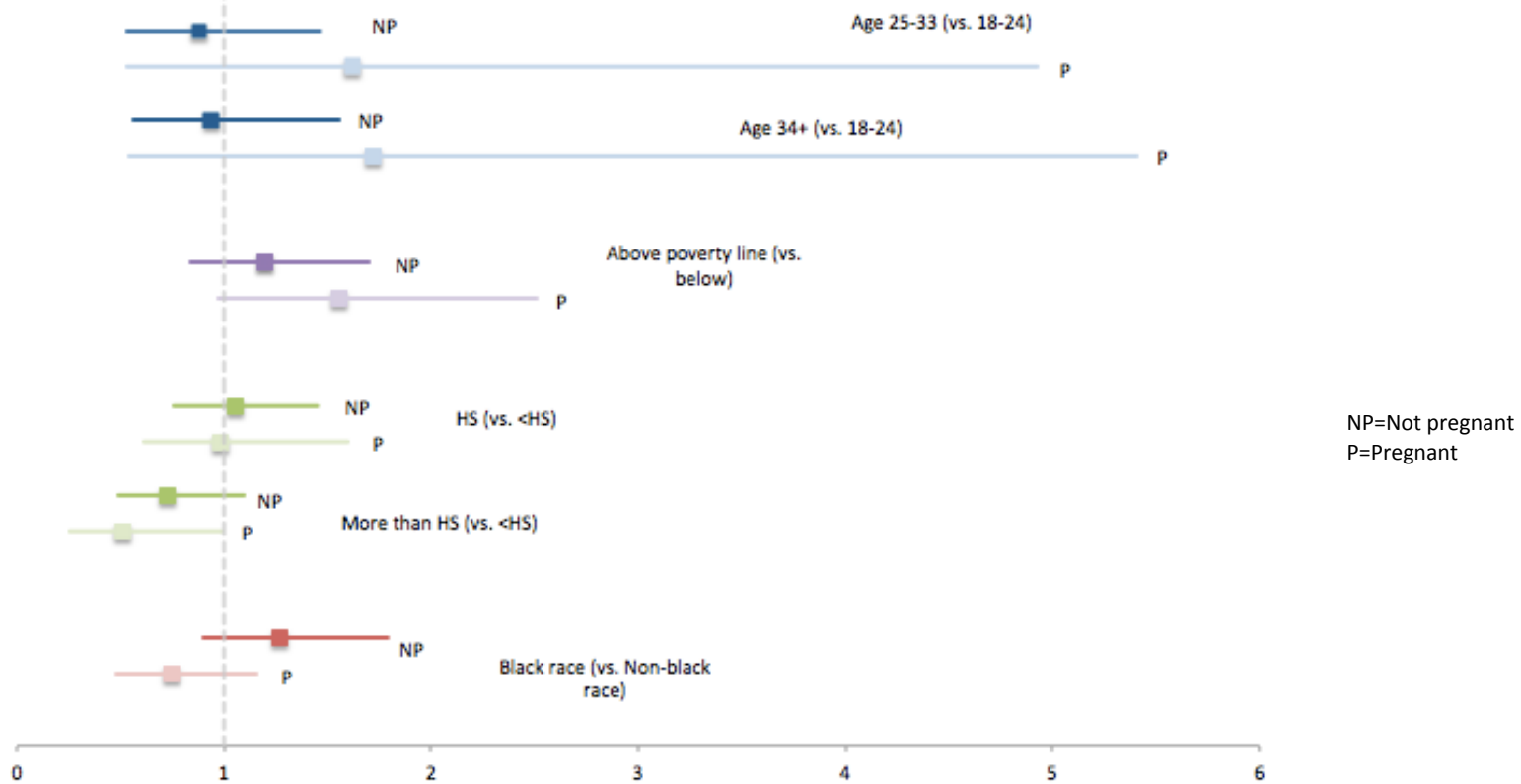


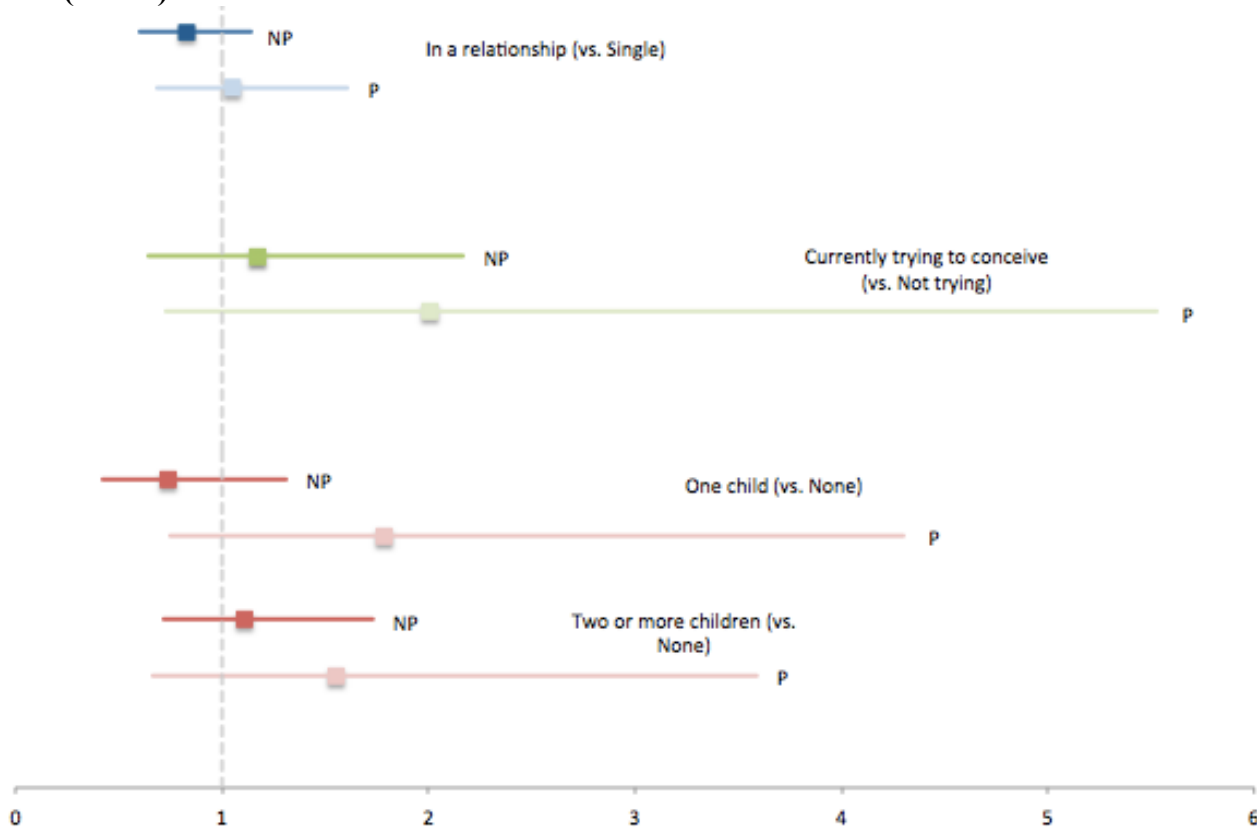
Figure 10. Forest plot of patient demographics as predictors of poor adherence among HIV-infected women on antiretroviral therapy in the United States stratified by whether or not they experienced a pregnancy outcome by the index visit (n=902)



NP=Not pregnant
P=Pregnant

Variable	aPR (Non-pregnant)	95% CI	aPR (Pregnant)	95% CI
Age 25-33 (vs. 18-24)	0.88	(0.53, 1.46)	1.62	(0.53, 4.93)
Age 34+ (vs. 18-24)	0.94	(0.56, 1.56)	1.72	(0.54, 5.41)
Above poverty line (vs. Below poverty line)	1.20	(0.84, 1.70)	1.56	(0.97, 2.51)
High school (vs. Less than high school)	1.05	(0.76, 1.45)	0.98	(0.61, 1.60)
More than high school (vs. Less than high school)	0.73	(0.49, 1.10)	0.51	(0.26, 0.99)
Black race (vs. Non-black race)	1.27	(0.90, 1.79)	0.75	(0.48, 1.16)

Figure 11. Forest plot of reproductive-health characteristics as predictors of poor adherence among HIV-infected women on antiretroviral therapy in the United States stratified by whether or not they experienced a pregnancy outcome by the index visit (n=902)



NP=Not pregnant
P=Pregnant

Variable	aPR (Non-pregnant)	95% CI	aPR (Pregnant)	95% CI
In a relationship (vs. Single)	0.83	(0.60, 1.14)	1.05	(0.69, 1.61)
Currently trying to conceive (vs. Not trying)	1.17	(0.64, 2.17)	2.01	(0.73, 5.53)
One child (vs. No children)	0.74	(0.42, 1.31)	1.79	(0.75, 4.30)
Two or more children (vs. No children)	1.11	(0.72, 1.73)	1.55	(0.67, 3.59)

Figure 12. Forest plot of medication-related characteristics as predictors of poor adherence among HIV-infected women on antiretroviral therapy in the United States stratified by whether or not they experienced a pregnancy outcome by the index visit (n=902) (→ indicates upper bound of confidence interval beyond 6.0)

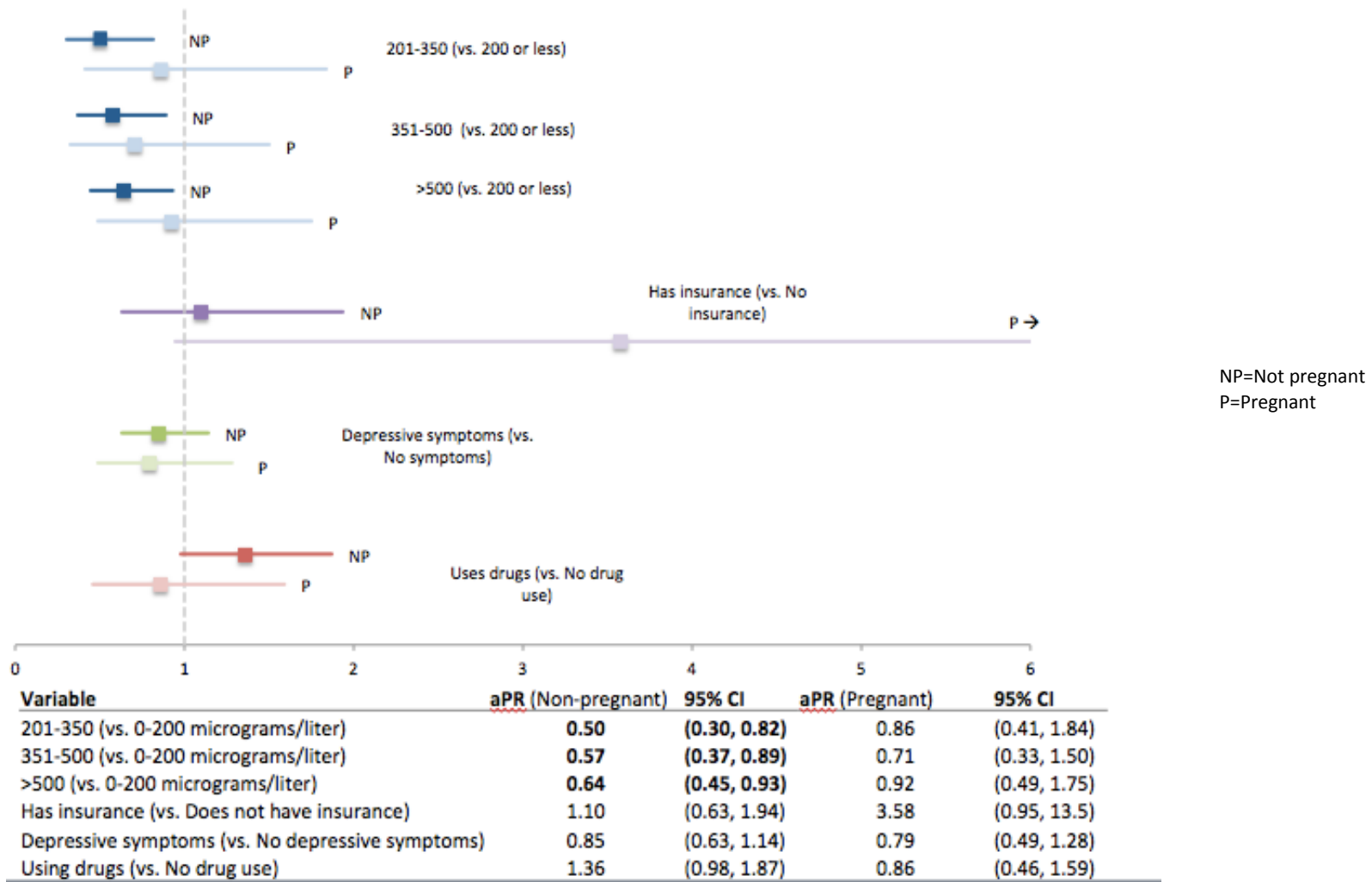
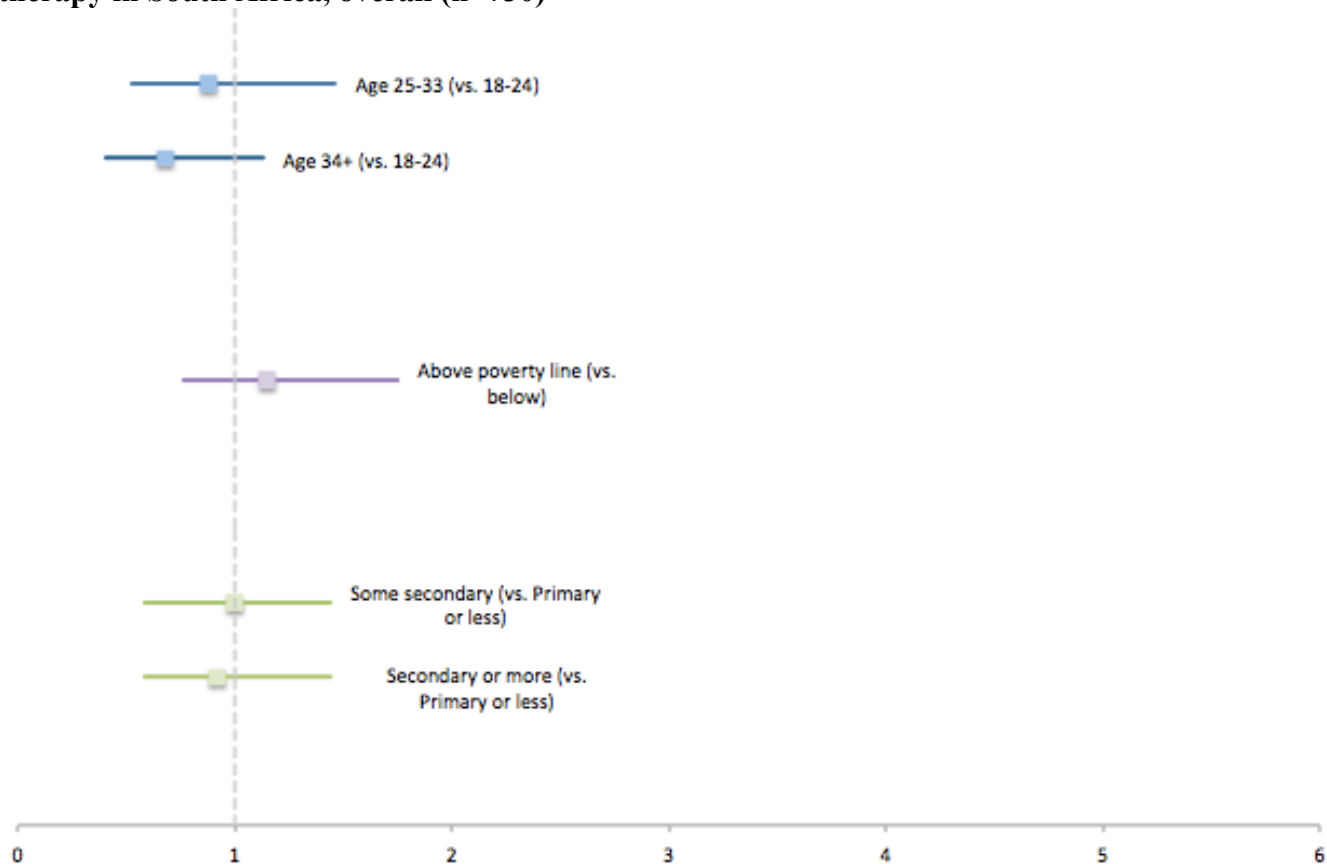


Figure 13. Forest plot of patient demographics as predictors of poor adherence among HIV-infected women on antiretroviral therapy in South Africa, overall (n=730)



Variable	aPR	95% CI
Age 25-33 (vs. 18-24)	0.88	(0.53, 1.46)
Age 34+ (vs. 18-21)	0.68	(0.41, 1.13)
Above poverty line (vs. below)	1.15	(0.76, 1.75)
Some secondary (vs. Primary or less)	1.00	(0.59, 1.44)
Secondary or more (vs. Primary or less)	0.92	(0.59, 1.44)

Figure 14. Forest plot of reproductive-health characteristics as predictors of poor adherence among HIV-infected women on antiretroviral therapy in South Africa, overall (n=730)

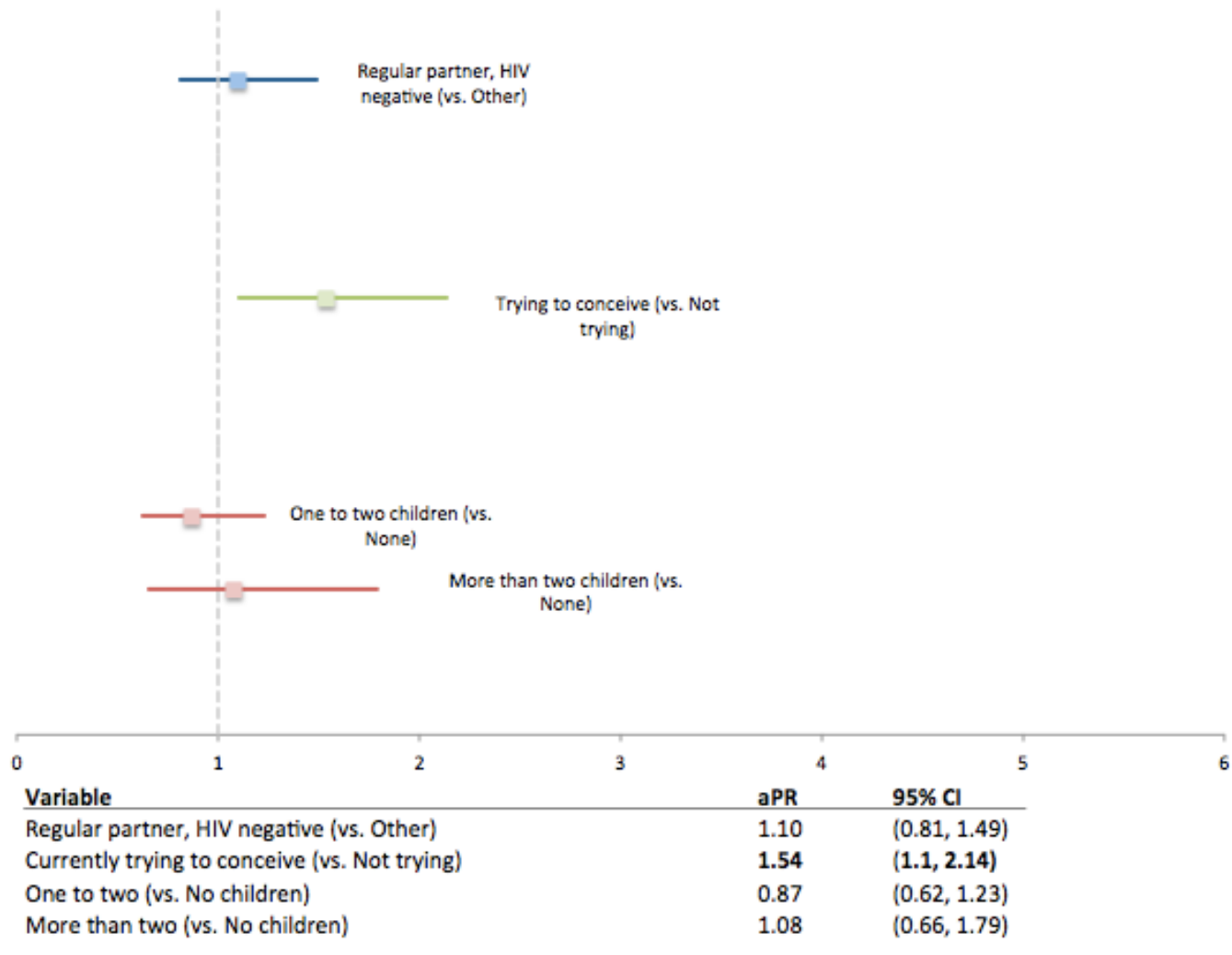


Figure 15. Forest plot of medication-related characteristics as predictors of poor adherence among HIV-infected women on antiretroviral therapy in South Africa, overall (n=730)

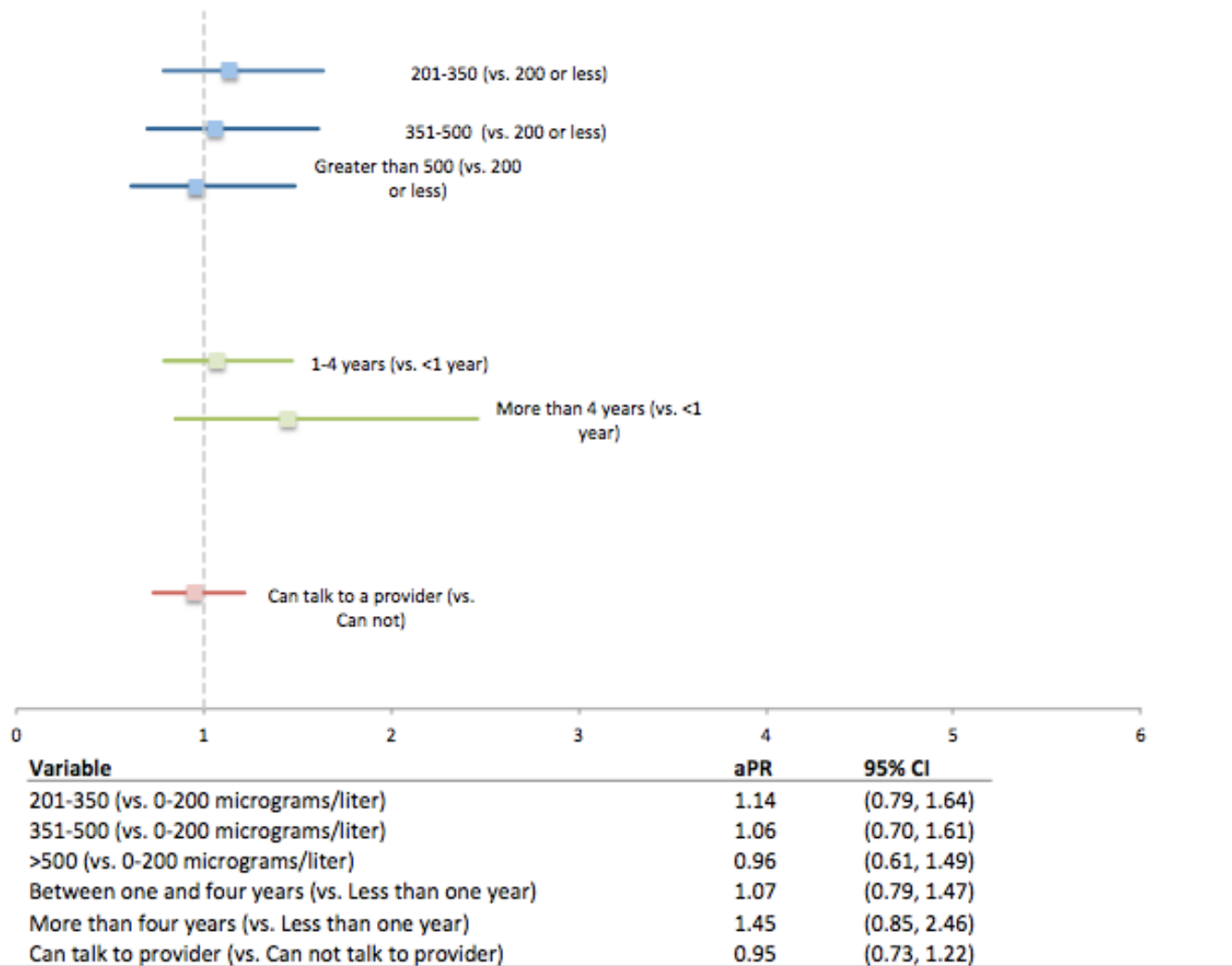
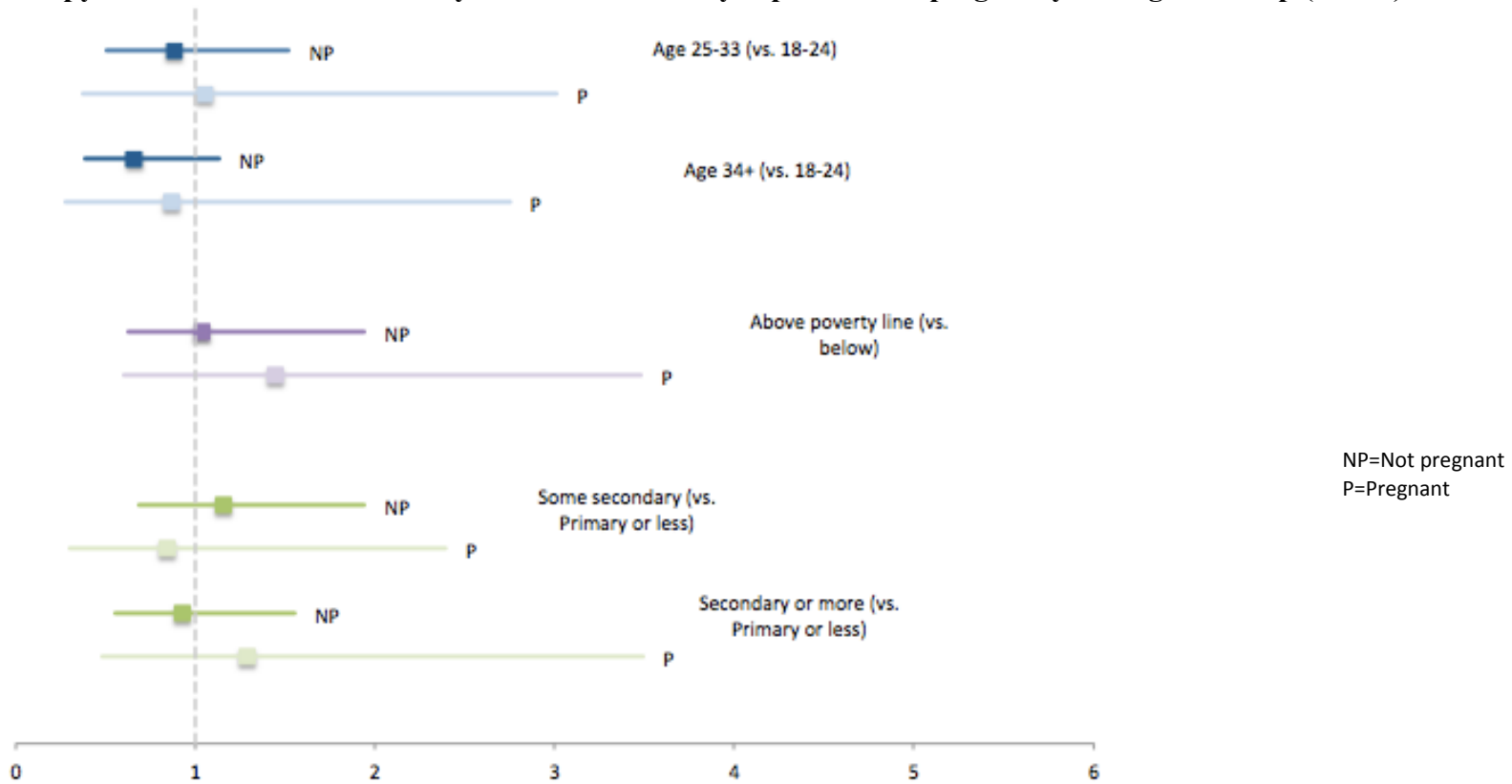


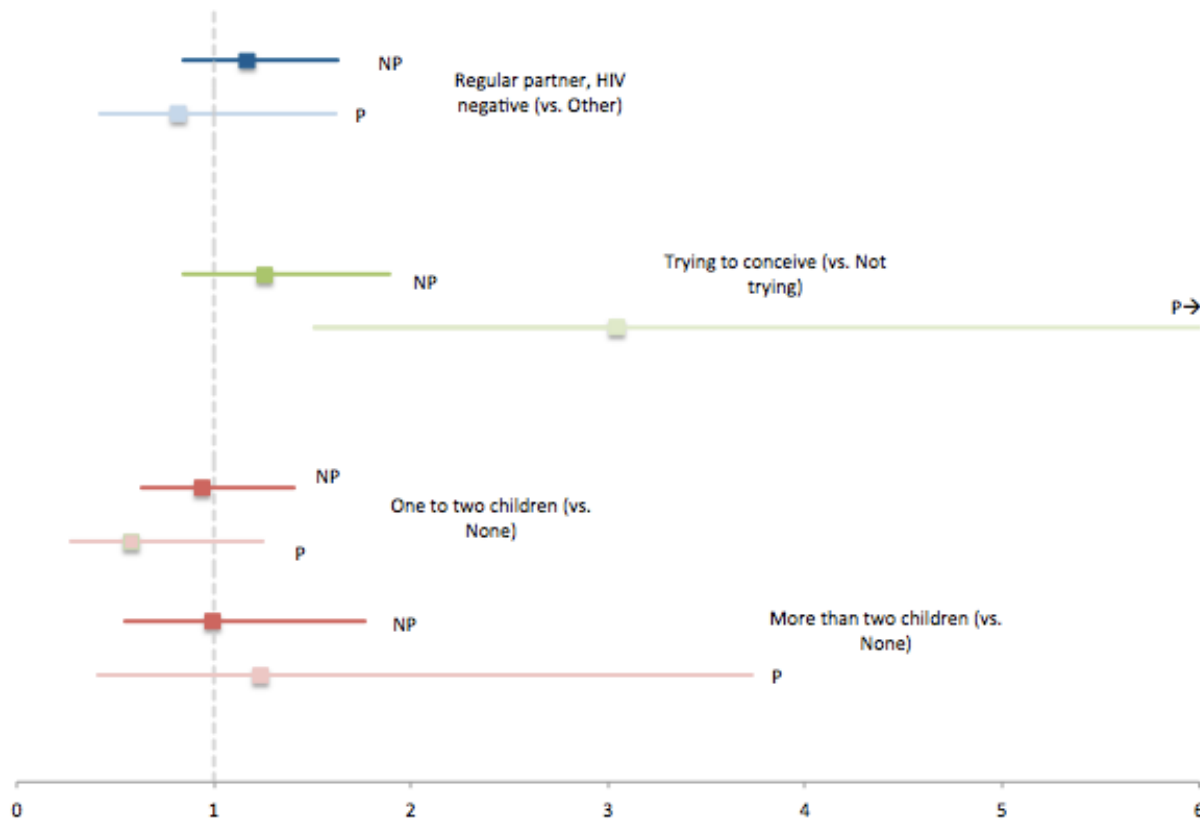
Figure 16. Forest plot of patient demographics as predictors of poor adherence among HIV-infected women on antiretroviral therapy in South Africa stratified by whether or not they experienced a pregnancy during follow-up (n=730)



NP=Not pregnant
P=Pregnant

Variable	aPR (Non-pregnant)	95% CI	aPR (Pregnant)	95% CI
Age 25-33 (vs. 18-24)	0.88	(0.51, 1.52)	1.05	(0.37, 3.01)
Age 34+ (vs. 18-21)	0.66	(0.38, 1.13)	0.86	(0.27, 2.75)
Above poverty line (vs. below)	1.03	(0.63, 1.94)	1.44	(0.60, 3.48)
Some secondary (vs. Primary or less)	1.15	(0.68, 1.94)	0.84	(0.30, 2.39)
Secondary or more (vs. Primary or less)	0.92	(0.55, 1.55)	1.29	(0.48, 3.49)

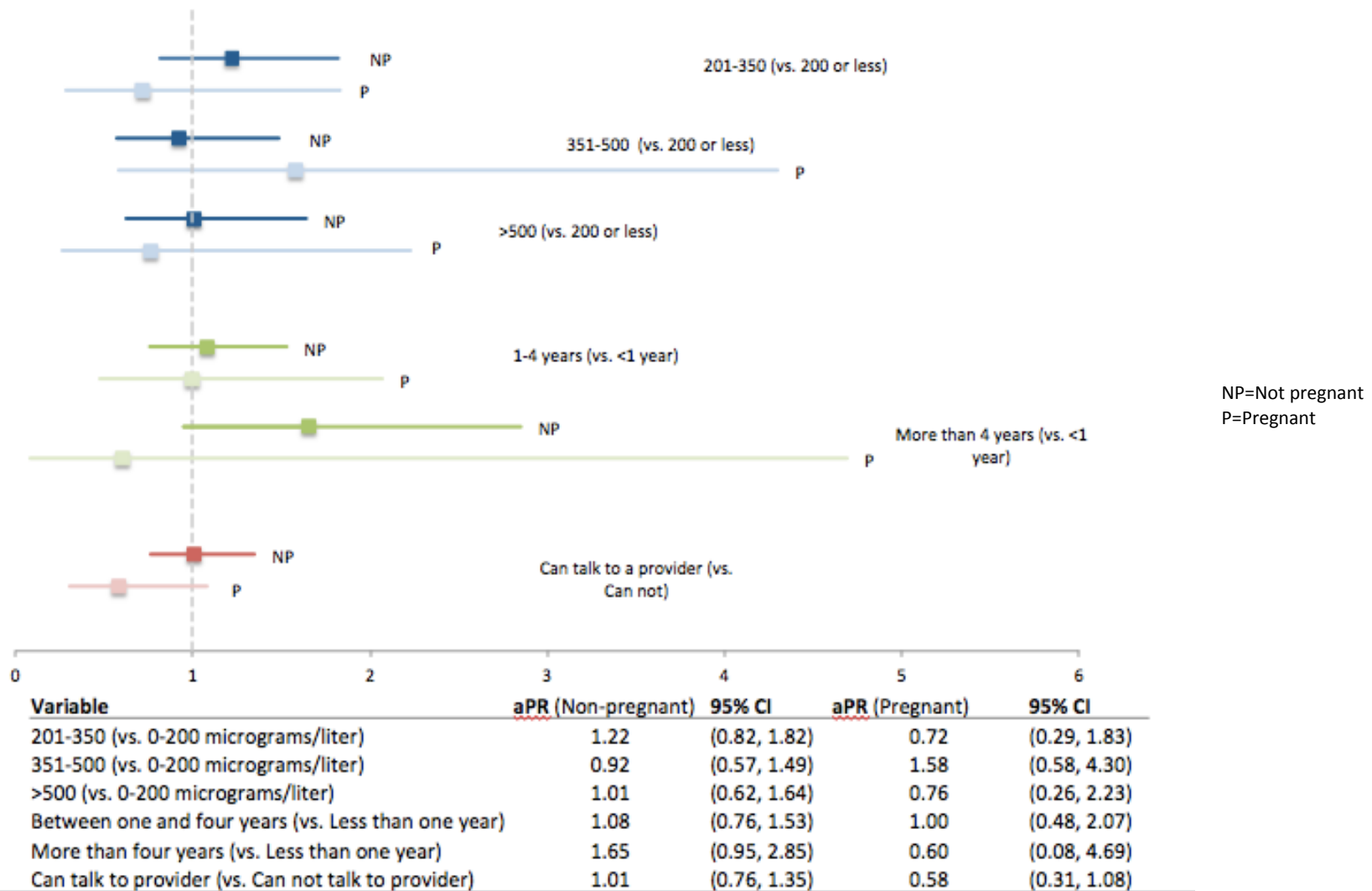
Figure 17. Forest plot of reproductive-health characteristics as predictors of poor adherence among HIV-infected women on antiretroviral therapy in South Africa stratified by whether or not they experienced a pregnancy during follow-up (n=730) (→ indicates upper bound of confidence interval beyond 6.0)



NP=Not pregnant
P=Pregnant

Variable	aPR (Non-pregnant)	95% CI	aPR (Pregnant)	95% CI
Regular partner, HIV negative (vs. Other)	1.17	(0.84, 1.63)	0.82	(0.42, 1.62)
Currently trying to conceive (vs. Not trying)	1.26	(0.84, 1.89)	3.04	(1.51, 6.14)
One to two (vs. No children)	0.94	(0.63, 1.41)	0.58	(0.27, 1.25)
More than two (vs. No children)	0.99	(0.55, 1.77)	1.24	(0.41, 3.73)

Figure 18. Forest plot of medication-related characteristics as predictors of poor adherence among HIV-infected women on antiretroviral therapy in South Africa stratified by whether or not they experienced a pregnancy during follow-up (n=730)



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APPENDIX

Table 1a. Characteristics ^a of 1305 HIV-infected women on antiretroviral therapy in the United States, stratified by whether or not experienced a pregnancy outcome by the index visit ^b

	Overall N= 1305	Pregnant N=444	Not pregnant N=861	p
Median age, years (IQR)	32.7 (28.0, 37.7)	32.4 (28.3, 37.0)	32.8 (27.8, 38.1)	0.633
18-24	107 (8.2)	28 (6.3)	79 (9.2)	0.086
25-33	574 (44.0)	210 (47.3)	364 (42.3)	
34+	524 (47.8)	206 (46.4)	418 (48.6)	
Yearly income above poverty line				0.252
Yes (vs. No) (USD) ^e	306 (24.2)	109 (26.1)	197 (23.2)	
Education completed				0.147
Less than high school	109 (8.4)	34 (7.7)	75 (8.7)	
Some high school	469 (35.9)	146 (32.9)	323 (37.5)	
High school or more	727 (55.7)	264 (59.5)	463 (53.8)	
Race ^g				0.291
Black (vs. Non-Black)	835 (65.0)	284 (67.0)	551 (64.0)	
Relationship status ^{e, f}				0.837
In a relationship (vs. Single)	368 (43.2)	178 (42.6)	368 (43.2)	
Currently trying to conceive ^d				0.020
Yes (vs. No)	53 (4.2)	10 (2.4)	44 (5.1)	
Median parity (IQR) ⁱ	2 (1, 3)	2 (1, 3)	2 (1, 4)	0.006
None	166 (12.9)	52 (12.2)	114 (13.2)	0.178
One	289 (22.4)	109 (25.5)	180 (20.9)	
Two or more	834 (64.7)	267 (62.4)	567 (65.9)	
CD4 T-Lymphocyte count, cells/μL				0.640
0-200	130 (10.0)	38 (10.0)	92 (10.7)	
201-350	225 (17.2)	75 (17.2)	150 (17.4)	
351-500	303 (23.2)	110 (23.2)	193 (22.4)	
>500	647 (49.6)	221 (49.8)	426 (49.5)	
Insurance ^h				0.138
Has insurance (vs. no insurance)	1186 (92.3)	398 (93.9)	788 (91.5)	
Depression				0.664
Has symptoms (vs. no symptoms)	533 (40.8)	185 (41.7)	348 (40.4)	
Illicit drug use				0.548
Uses drugs (vs. no drug use)	229 (17.6)	74 (16.7)	155 (18.0)	

For continuous variables, p-values estimated using Wilcoxon-rank sums test for equality of medians.

For categorical variables, p-values estimated using Pearson's chi-square test for independence.

IQR=Interquartile range

HAART=Highly active antiretroviral therapy

^a Measured at index-1 visit, between 2002 and 2014.

^b Women asked if they had experienced a pregnancy outcome in the last six months.

^c Categorized as being in a relationship if either married or living with partner.

^d Categorized as not trying if stated not trying or pregnant at index-1 visit

^e Data missing on household income (n= 39); ^f Data missing on relationship status (n=35); ^g Data missing on race (n=20); ^hData missing on insurance (n=20); ⁱData missing on parity (n=16)

Table 2a. Characteristics^a of 850 HIV-infected women on antiretroviral therapy in South Africa, stratified by whether or not experienced a pregnancy during duration of follow-up^b

	Overall N= 850	Pregnant N=161	Not pregnant N=689	p
Median age, years (IQR)	30.0 (27.4, 33.0)	29.1 (26.7, 32.6)	30.5 (27.7, 33.1)	0.01
18-24	62 (7.3)	10 (6.2)	52 (7.6)	0.115
25-33	581 (68.4)	121 (75.2)	460 (66.8)	
34+	207 (24.4)	30 (18.6)	177 (25.7)	
Monthly income above poverty line Yes (vs. No) ^c	70 (8.2)	16 (9.9)	56 (8.1)	0.436
Education completed				0.789
Primary or less	78 (9.2)	13 (8.1)	65 (9.4)	
Some secondary	353 (41.5)	70 (43.5)	283 (41.1)	
Secondary or more	419 (49.3)	78 (48.5)	341 (49.5)	
Relationship status ^d				0.386
In a relationship (vs. Single)	789 (92.8)	152 (94.4)	637 (92.5)	
Currently trying to conceive Yes (vs. No)	105 (12.4)	25 (15.5)	80 (11.6)	0.174
Median parity (IQR)	1 (1, 2)	1 (1, 2)	1 (1, 2)	0.937
None	141 (16.6)	25 (15.5)	116 (16.8)	0.759
One to two	614 (72.2)	120 (74.5)	494 (71.7)	
More than two	95 (11.2)	16 (9.9)	79 (11.5)	
CD4 T-Lymphocyte count, cells/μL				0.974
0-200	258 (30.4)	47 (29.2)	211 (30.6)	
201-350	230 (27.1)	43 (26.7)	187 (27.1)	
351-500	181 (21.3)	35 (21.7)	146 (21.2)	
>500	181 (21.3)	36 (22.4)	145 (21.0)	
Time on HAART				0.942
Less than one year	397 (46.7)	77 (47.8)	320 (46.4)	
Between one and four years	397 (46.7)	74 (46.0)	323 (46.9)	
More than four years	56 (6.6)	10 (6.2)	46 (6.7)	
Provider talk Can talk to provider (vs. Cannot talk)	344 (40.5)	71 (44.1)	273 (39.6)	0.297

For continuous variables, p-values estimated using Wilcoxon-rank sums test for equality of medians.

For categorical variables, p-values estimated using Pearson's chi-square test for independence.

IQR=Interquartile range

HAART=Highly active antiretroviral therapy

^a Measured at baseline study visit, 2009-2010

^b For 12 months or for duration of pregnancy.

^c Data missing on monthly household income (n=20)

^d Categorized as being in a relationship by self-reported relationship status.

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Location of Birth: Boston, Massachusetts

PROFILE

Master of Science Candidate in Epidemiology with focus on linkage between sexual and reproductive health and HIV. Specific interests in prevention of mother to child transmission of HIV (PMTCT), family planning, expansion and improvement of HIV testing and treatment services.

EDUCATION

Master of Science (ScM) in Epidemiology, Expected 2016

Johns Hopkins Bloomberg School of Public Health (JHSPH), Baltimore, MD

Honors: Global Health Established Field Placement, Master's Tuition Scholarship

Bachelors of Science (BS) in Human Biology, Health, and Society, 2014

Cornell University, Ithaca, NY

Minor: Inequality Studies

Honors: Human Ecology Alumni Association Outstanding Senior

RESEARCH EXPERIENCE

Research/Field Assistant, Dr. Stefan Baral

April 2015-Current

JHSPH Department of Epidemiology, Port Elizabeth South Africa

Study examining the coverage of health services, including PMTCT and other reproductive-health related services, among female sex workers and their children in Port Elizabeth.

- Provided on-site technical assistance in data management and quality assurance to partner organizations. Helped train and manage study staff. Assisted in setup of study site and recruitment of participants. Ongoing qualitative data coding and analysis.
- Currently evaluating quantitative association between prior HIV diagnosis, future pregnancy intentions and knowledge of methods for safer conception.
- Evaluated overall physical and mental health needs of sex workers and their children.
- Ongoing efforts to expand mobile clinic reach to include better HIV testing and linkage to care for children of sex workers.

Intern, Dr. Prabhu Pingali

May 2014-August 2014

Tata Cornell Agriculture and Nutrition Initiative (TCi), Hyderabad India

TCi is a research initiative working to design and evaluate interventions linking agriculture, food systems, human nutrition, and poverty in India.

- Conducted surveys with women head of households. Worked on analysis to test the validity and ease of use of a Minimum Nutrition Dataset for Agricultural surveys in four villages in South India
- Worked with other interns to conduct focus-group discussions, generate survey items, and pilot test the survey.

Intern, Center for Health Policy and Inequalities Research

May 2013-August 2013

Duke University, Durham, North Carolina

The Center for Health Policy and Inequalities Research conducts health policy and health disparities research as part of the Duke Global Health Institute.

- Designed a pilot study to assess incident HIV and substance abuse prevalence among youth in juvenile detention centers in East Africa
- Worked primarily on data entry, cleaning, and analysis on existing surveys.
- Maintained website and sent monthly newsletters to relevant stakeholders.

Research Assistant, Laboratory for Rational Decision-Making

August 2012-May 2014

Cornell University, Ithaca, New York

- Developed and tested an intervention using Fuzzy Trace Theory to help women correctly weigh the benefits of a potentially life-saving mammogram against the distress of receiving a false-positive result.
- Administered survey to participants and conducted initial analyses of data using SPSS.

Research Assistant, Cornell Health International

January 2011

Kigali, Rwanda

- Assessed the structural successes and failures of universal healthcare coverage in Rwanda through a series of structured observations.

Research Assistant, KidRisk Inc.

June 2009-August 2009

Boston, Massachusetts

- Evaluated health ministers' willingness to pay for ongoing polio vaccination. Helped review survey structure. Organized and sent surveys to various ministries of health.

PUBLIC HEALTH VOLUNTEER WORK

Online Hotline Volunteer

Rape Abuse & Incest National Network, Washington D.C.

- Provide support to victims of sexual assault and their friends and family members.
- First line of anonymous, secure crisis support and linking those who turn to the hotline to important next step resources.

Sex Educator, Safe sex and STI prevention

Sexual Health Awareness Group, Cornell University

- Worked as a peer-educator and provided interactive hour-long presentations to various student groups with the intent on decreasing the stigma associated with sexual transmitted diseases, testing, and contraception.
- Oversaw recruitment of new peer-educators and development of presentations.

TEACHING EXPERIENCE

Teaching Assistant, Epidemiologic Methods 2 (EPI 752).

JHSPH Epidemiology Department

Teaching Assistant, Public Health Nutrition (NS 4500)

Cornell Division of Nutritional Sciences

Teaching Assistant, Maternal and Child Nutrition (NS 3220).

Cornell Division of Nutritional Sciences

Teaching Assistant, Introductory Biology (BIOG 1105).

Cornell Biology Department

PUBLICATIONS and PROFESSIONAL DEVELOPMENT

MANUSCRIPTS IN PREPARATION:

Rao, A., Baral, S., Phaswanamafuya, N., Lambert, A., Kose, Z., Mcingana, M. Ketende, S., Holland, C. Schwartz, S. Future pregnancy intentions and safer pregnancy knowledge among Female Sex Workers in Port Elizabeth, South Africa.

PRESENTATIONS:

Brust-Renck, P., Reyna, V., Wilhelms, E., **Rao, A.**, Blitsman, K. A fuzzy-trace theory intervention to reduce distress from positive mammography screening results. Poster session presented at: Society for Medical Decision Making; 2014 October 18-22.

LEADERSHIP EXPERIENCE

Student Coordinator, General Epidemiology & Methodology Journal Club

Master's Representative, Epidemiology Student Org. JHSPH

VP Administration, Cornell University Class Council

