Para 2	20 (30)	11 (32)	
Para 3 or greater	14 (21)	3 (9)	
Race, n (%)			
Black/African American	54 (82)	31 (91)	0.214
Non-Black	12 (18)	3 (9)	
Number of mothers with viral load <20 copies/mL, n, (%)			
1st trimester	48 (73)	25 (74)	0.964
2nd trimester	54 (82)	28 (82)	0.854
3rd trimester	55 (84)	29 (86)	0.791
CD4+ (cells/mm^3), median, IQR			
1st trimester	569 (373-766)	667 (512-973)	0.050
2nd trimester	444 (353-620)	510 (420-722)	0.230
3rd trimester	470 (355-594)	669 (514-750)	0.035
Alcohol use prior to pregnancy, n (%)	1 (2)	2 (5)	0.980
Cocaine use prior to pregnancy, n (%)	5 (8)	0 (0)	0.100
Heroin use prior to pregnancy, n (%)	2 (3)	1 (3)	0.980
Methadone use in pregnancy, n (%)	3 (5)	2 (6)	0.771
Tobacco use prior to pregnancy, n (%)	6 (9)	7 (20)	0.105
Hypertension during pregnancy, n (%)	5 (8)	3 (9)	0.127
Gestational diabetes mellitus, n (%)	2 (3)	2 (6)	0.201
Preterm delivery, n (%)	9 (14)	3 (9)	0.496
Hepatitis B, n (%)	1 (2)	1 (3)	0.629
Hepatitis C, n (%)	3 (5)	0 (0)	0.207
Mode of delivery (n (%)			
Vaginal delivery	41 (62)	17 (50)	0.212
Cesarean delivery	25 (38)	17 (50)	
Cesarean delivery for viral load, n (%)	4 (6)	0 (0)	0.083

Medication adherence in the 1st trimester (76% adherence to TDF versus 83% adherence to a TAF regimen; p=0.282), 2nd trimester (82% adherence to TDF versus 88% adherence to a TAF regimen; p=0.924), and 3rd trimesters (88% adherence to TDF versus 91% adherence to a TAF regimen; p=0.176) of pregnancy were higher in pregnant women living with HIV on TAF compared to those on TDF, but these differences in medication adherence were not statistically significant. Adherence to both medications increased from the first to the third trimesters of pregnancy **(Table 1)**.

There were no significant differences between women on TDF and those on TAF with respect to maternal alcohol and cocaine use; heroin, methadone, and tobacco use; hypertension in pregnancy, preterm delivery, hepatitis B and C infections, and mode of delivery based on maternal viral load. Four women in the TDF arm (6%) were delivered by Cesarean for viral loads >1,000 copies/mL, while none was delivered in the TAF arm solely for a high viral load indication.

Table 2 shows the univariable and multivariable logistic regression analysis of the associations with medication adherence stratified by trimesters of pregnancy (first, second, and third trimesters of pregnancy). In the univariable and multivariable analysis in the first and second trimesters of pregnancy, there were no statistically significant associations between medication adherence and TDF or TAF use, parity, race/ethnicity, cocaine, tobacco, marijuana, and heroin use **(Table 2)**. In the third trimester of pregnancy, multiparous women (parity of >=2) were more likely to be adherent to antiretroviral medications compared to nulliparous women. This finding was statistically significant in both the univariable (odds ratio, OR 1.31, 95% CI 1.12, 1.57; p<0.05) and multivariable (adjusted odds ratio, aOR 1.23, 95% CI 1.08, 1.52; p<0.05) analyses.

Table 2. Parameter estimates and 95% confidence intervals of the crude and adjusted hazard ratios for associations with adherence using logistic regression.

Variable	Unadjusted (crude) OR (95% CI)	Adjusted OR (95% CI) *
First Trimester Medication Adherence		
Antiretroviral		
TDF	Referent	Referent
TAF	2.02 (0.55 - 7.37)	2.35 (0.52 - 10.47)
Parity		
1	Referent	Referent
2 or more	0.99 (0.73 - 1.35)	1.00 (0.72 - 1.40)
Race		
Non-Black	Referent	Referent
Black	1.15 (0.27 - 5.00)	0.84 (0.16 - 4.54)
Cocaine use	0.13 (0.01 - 1.56)	0.25 (0.01 - 6.87)
Tobacco use	0.34 (0.67 - 1.75)	0.14 (0.06 - 3.10)
Marijuana use	0.54 (0.12 - 2.47)	0.43 (0.08 - 2.45)
Heroin use	0.13 (0.01 - 1.56)	0.59 (0.18 - 19.5)
Second Trimester Medication Adherence		
Antiretroviral		
TDF	Referent	Referent
TAF	1.09 (0.17 - 7.00)	0.92 (0.09 - 9.46)
Parity		
1	Referent	Referent

2 or more	0.96 (0.56 - 1.65)	0.90 (0.46 - 1.75)
Race		
Non-Black	Referent	Referent
Black	3.60 (0.53 - 24.4)	3.40 (0.29 - 39.8)
Cocaine use	0.06 (0.03 - 1.21)	0.07 (0.01 - 4.99)
Tobacco use	0.18 (0.03 - 1.30)	0.41 (0.22 - 7.41)
Marijuana use	0.25 (0.04 - 1.68)	0.17 (0.02 - 1.79)
Heroin use	0.06 (0.03 - 1.21)	0.97 (0.01 - 92.1)
Third Trimester Medication Adherence		
Antiretroviral		
TDF	Referent	Referent
TAF	1.03 (0.99 - 1.07)	0.86 (0.66 - 1.08)
Parity		
1	Referent	Referent
2 or more	1.31 (1.12 - 1.57) **	1.23 (1.08 - 1.52) **
Race		
Non-Black	Referent	Referent
Black	0.79 (0.52 - 1.27)	0.83 (0.41 - 1.48)
Cocaine use	0.34 (0.03 - 3.87)	0.24 (0.01 - 3.57)
Tobacco use	0.62 (0.06 - 7.07)	0.58 (0.05 - 6.68)
Marijuana use	0.19 (0.01 - 2.33)	0.14 (0.03 - 1.89)
Heroin use	0.93 (0.74 - 1.39)	0.87 (0.59 - 1.07)

DISCUSSION

This retrospective cohort study found that medication adherence levels to TDF and TAF are overall, high in pregnant women living with HIV. Although medication adherence was higher for women using TAF when compared to compare to TDF, the differences in adherence were not statistically significant. In the third trimester of pregnancy, multiparous women were more likely to be adherent to TDF/TAF antiretroviral medications compared to nulliparous women, a statistically significant finding.

Nulliparity was identified as a risk factor for poor antiretroviral medication adherence in this study. While it can be difficult to explain why adherence was better in multiparous women in this cohort of pregnant women living with HIV, a possible explanation why multiparous women had better adherence in our study is that nulliparous pregnant women sometimes forget to take their medications, partly because, as their first pregnancy, nulliparous pregnant women might be scared of taking medications, or due to adverse effects of the medications compared to the more experienced multiparous women who would take medications more consistently in their prior pregnancies.

Changes in medication adherence can occur at any time during pregnancy [23,24]. Although medication adherence generally increases as pregnancy increases from the first to the third trimesters of pregnancy [23], adherence can be modified by a woman's' medication dosing regimen complexity, pill burden, social support systems, among other predisposing factors [25]. While many pregnant women are motivated to increase medication adherence during pregnancy, keep their disease under control, and reduce the chances of perinatal transmission of HIV, the proportion of women who are poorly adherent to medications during pregnancy, especially in the first trimester of pregnancy, do so for fear and anxiety of potential harm to the fetus [23]. In this study, adherence to HIV medications increased from the first to the third trimester of pregnancy, consistent with findings from other studies [23].

There remains a critical, unmet need for objective, quantitative measures of adherence to antiretroviral

medications among women living with HIV [19]. Non-pharmacological adherence measures such as patient self-report, pillbox checks and counts of pill days, and electronic apps are limited by response bias, as participants can respond to questions about adherence inaccurately, incompletely, or falsely. In addition, these subjective methods do not measure adherence directly [26,27]. Multiple studies have examined tenofovir diphosphate (TFV-DP), the active form of tenofovir in peripheral blood mononuclear cells (the site of action) as an objective measure of cumulative adherence [19,28,29]. Data from the MTN 001 trial [30] demonstrated that TFV-DP concentrations in peripheral blood mononuclear cells (PBMCs) could be used as objective measures of adherence [30]. While plasma tenofovir (TFV) did not correlate well with medication adherence in the MTN 001 trial, measurement of TFV-DP in PBMCs was an authentic and valid process of assessing TFV adherence [30]. Other methods to assess medication adherence include use of dried blood spots [31,32] and maternal hair [33]. Although TFV-DP in dried blood spots (DBS) can be used to measure accumulated drug, they represent drug exposures over 4-6 weeks (hair) or 6-8 weeks (DBS) [34,35] and might not efficiently capture current adherence patterns in pregnant women given the rapidly changing physiology of pregnancy. So, objective methods of adherence assessment, while better than subjective methods of adherence have limitations as well.

This study had some limitations. First, is the strict method in which we classified adherence (<100% versus 100% adherence). There have been less strict ways to classify medication adherence in literature (as <95% versus ≥95%; <90% versus ≥90%; or <80% versus ≥80%). However, despite our strict method of classifying adherence, there were no TDF or TAF groups in the first, second or third trimesters of pregnancy that were less than 75% adherent in this study. A second limitation of this study is that the comparatively small sample size of the study did not allow for sub-group analyses. With an increased sample size, it may have been possible to show other statistically significant differences in medication adherence patterns between women who used TDF compared to those who used TAF during pregnancy. Finally, although women subjectively reported medication adherence, it was difficult to objectively ascertain adherence to TDF/TAF medications in this study. This is important because non-pharmacologic adherence measures have limitations and may overestimate or underestimate TDF or TAF adherence [9,19].

The strengths of this study include the comparatively high number of pregnant women living with HIV managed at this single center - much more than the numbers currently managed at several other centers within the United States and other developed countries. Finally, because TAF use was part of routine obstetric care at this institution, the results of this study may be more generalizable to many obstetric practices within and outside the United States.

CONCLUSION

Our results suggest that there are no differences in optimal adherence to TDF versus TAF based antiretroviral therapy in pregnant women living with HIV except for maternal parity. Utilizing objective methods of adherence are important, as objective methods of medication adherence are less prone to bias. Larger studies are required to describe intracellular PBMC TFV-DP concentrations, and establish TAF medication adherence benchmarks in pregnancy and postpartum in pregnant and postpartum women living with HIV.

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