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The Impact of Diabetes Mellitus on HIV Virologic Control: Results of the MACS/WIHS Combined Cohort Study

Running title: Diabetes, HIV, and Antiretroviral Adherence

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Abstract

Objective: Diabetes mellitus (DM) is associated with lower antiretroviral (ART) drug exposure among persons with HIV (PWH) compared to PWH without DM. The association between DM and virologic control in PWH, however, remains unknown.

Methods: We included participants in the Multicenter AIDS Cohort Study/Women's Interagency HIV Study Combined Cohort Study (MWCCS) who had initiated ART between 1999 and 2020 and had a suppressed HIV viral load (≤200 copies/mL) within 1 year of ART initiation. We compared the frequency of incident HIV viremia (HIV-1 RNA >200 copies/mL) between adult PWH with and without DM. Poisson regression was used to examine the rate of incident viremia based on the diagnosis of DM among PWH. DM was defined as two consecutive fasting glucose measurements ≥126 mg/dL, use of anti-diabetic medications, pre-existing DM diagnosis, or a confirmed HbA1c >6.5%.

Results: 1,061 women (112 with DM, 949 without DM) and 633 men (41 with DM, and 592 without DM) were included in the analysis. The relative rate (RR) of incident HIV viremia for women with HIV and DM was lower when compared to women without DM (0.85 [95% CI: 0.72-0.99]; p=0.04). The RR of incident viremia for women with uncontrolled DM (HbA1c>7.5%) was higher when compared to women with controlled DM (HbA1c <7.5%) (1.46 [95%CI: 1.03-2.07]; p=0.03). In contrast, the RR of incident viremia for men with HIV and DM was not statistically different compared to men without DM (1.2 [95%CI: 0.96- 1.50]; p=0.12). The results were stratified by adherence levels (100%, 95-99%, and less than 95% based on self-report).

Conclusions: Women with DM who are highly adherent to ART (100% self-reported adherence) have a lower risk of viremia compared to women with HIV without DM. However, women with poorly controlled DM were at higher risk of HIV viremia than women with controlled DM. Further research is necessary to understand the impact of sex, DM, and ART adherence on HIV viremia.

Key Words: HIV, Diabetes mellitus, ART adherence

Introduction

Persons with HIV (PWH) are at increased risk of developing diabetes mellitus (DM). In fact, some studies show that PWH are 4 times more likely to be diagnosed with DM than persons without HIV(1, 2). Furthermore, PWH develop DM at a younger age than the general population (3). Besides traditional risk factors such as age, sex, waist circumference, body mass index (BMI), and genetics, HIV-related risk factors for DM include chronic inflammation (4-6), cumulative antiretroviral (ART) drug exposure (7, 8), and lipodystrophy (9, 10).

DM is a debilitating chronic medical condition with many progressive adverse health effects that can be further complicated by HIV infection. Alone, DM can lead to significant morbidity including infections, blindness, chronic kidney disease, neuropathy, amputations, and cardiovascular complications. Patients suffering from both DM and HIV are susceptible to polypharmacy, drug-drug interactions, and drug-related weight changes(11).

A recent study revealed that PWH with DM receiving tenofovir disoproxil fumarate-based ART have 25% lower concentrations of tenofovir-diphosphate (TFV-DP) in dried blood spots (DBS) –a measure of cumulative adherence to antiretroviral therapy (ART)– when compared to persons without DM, placing them at risk for HIV viral rebound, future viremia and resistance (12-15). Thus, a deeper understanding of the interaction between HIV and DM can improve clinical care and could lead to significant improvement in glycemic and viral outcomes. To date, the association between DM and viral suppression in PWH has not been evaluated. To address this knowledge gap, we evaluated the association of DM with HIV plasma RNA viral load (VL) in PWH receiving ART. We hypothesized that DM is associated with higher rates of HIV viremia.

Methods

Study Sample

We used study visit data collected between 1999 and 2020 from the Multicenter AIDS Cohort Study (MACS)/Women's Interagency HIV Study (WIHS) Combined Cohort Study (MWCCS). The MACS was a multicenter, prospective study of men who have sex with men (MSM) living with and without HIV that began in 1984 (16). The WIHS was a multicenter prospective study of women with and without HIV established in 1993 (17, 18). In 2019, the National Institutes of Health integrated the two cohorts. Enrolled participants attended semi-annual visits where medical information (i.e., ART use), physical examination findings, and laboratory tests (i.e., HIV VL, and hemoglobin A1c) were performed. Study design methods and follow up details have been previously published (16, 19). Participants provided written informed consent and were financially compensated for enrollment. This secondary study was approved by the MWCCS Executive Committee.

We identified PWH 18 years of age and older who had initiated ART between 1999 and 2020. Adult PWH with suppressed HIV VL (≤200 copies/mL) within one year of ART initiation were included in this analysis. The date of ART initiation was set at the midpoint between the last time ART use was not reported and the first visit at which ART use was reported. Viral suppression following ART initiation was established through review of VL levels within one year after ART initiation. The start of follow-up (baseline) was defined as the closest visit that fell one year after ART initiation. The

sample was further limited to persons with at least two VL values after the baseline visit and complete data available on key variables.

Outcome

The outcome of interest was the occurrence of HIV viremia (defined as HIV VL measurements >200 copies/mL) following ART initiation and viral suppression.

Diabetes Mellitus Assessment

DM status was defined by one or more of the following: (1) the first report of anti-DM medication use after the index visit; (2) HbA1c ≥6.5%, with confirmation by fasting glucose (FG) ≥126 mg/dL or anti-DM medication use; (3) an FG ≥126 mg/dL with subsequent confirmation by an FG ≥126 mg/dL, anti-DM medication use, or HbA1c ≥6.5%; or (4) a self-report of DM with confirmation of anti-DM medication use or 2 visits with either an FG ≥126 mg/dL or a combination of HbA1c ≥6.5% and an FG ≥126 mg/dL. Incident DM diagnosis was included, and DM was considered an absorbing state (i.e. once a participant was defined as having DM they maintain that status for the study duration).

Covariates

Participants' chronological age was calculated from date of birth at the index visit. ART adherence was categorized as 100%, 95-99%, and less than 95% based on self-report as previously reported (20). BMI was calculated using weight and height measurements from the closest visit to the baseline. CD4+ T lymphocyte cell counts (cells/mm^3) were assessed using flow cytometry. For the analysis, age was categorized into ≤40 years, >40-55 years, and >55 years, based on the distribution in the sample. BMI was categorized using standard threshold: ≤25 kg/m^2, >25-30 kg/m^2 and >30 kg/m^2. CD4+ T-cell counts was categorized as ≤350 cells/mm^3, >350-500 cells/mm^3 and >500 cells/mm^3.

Statistical analysis

To examine the relationship between DM and the occurrence of HIV viremic episodes, we plotted the empirical Kaplan Meier curves using the time from baseline to the first viral failure following viral suppression. We compared the viral failure-free survival of persons classified as having DM to those without DM. Viral failure for this analysis was defined as the occurrence of two consecutive visits with HIV VL >200 copies/mL; the time of the event was taken at the date of the first occurrence of HIV VL >200 copies/mL with the second occurrence used for confirmation.

Next, we modeled the rate of HIV viremic episodes as a function of DM using Poisson regression and counting all occurrences of HIV VL >200. Models were adjusted for potential confounders including age at visit, BMI category, integrase inhibitor use, ART adherence, and $CD4^+$ T-cell category. The analysis was stratified by cohort given the well-documented differences between the two populations comprising the WIHS and MACS. Hence, we used separate Poisson regression models in WIHS women and MACS men to evaluate potentially different underlying relationships between DM and HIV viremic episodes.

To understand whether control of DM affected the results, we limited the sample to only participants with prevalent or incident DM and defined control of DM as HbA1c< 7.5%. We reran the Poisson

regression amongst this sample, regressing HIV viremic episodes on the dichotomous variable of control/uncontrolled DM, including all previously described covariates and an interaction of controlled/uncontrolled DM with ART adherence.

All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Sensitivity analysis

As data were collected every 6 months in the MACS and WIHS, there was the potential for viremia events to occur between study visits and to be undetected at a subsequent study visit because of a change in ART regimen that reduced the VL prior to the next assessment. Hence, a sensitivity analysis was performed that used ART regimen switches as a proxy for viremic events. ART regimen switches were defined as any change from an NNRTI to either a boosted PI or an integrase inhibitor.

Results

Population Characteristics

Table 1 and Supplementary Table 1, http://links.lww.com/QAD/D290 shows the distribution of demographic and clinical factors by DM status in the MACS and WIHS at baseline. A total of 1,061 women (112 with DM, 949 without DM) and 633 men (41 with DM and 592 without DM) were included in the analysis as shown in Figure 1.

In both cohorts, all participants were virologically suppressed at baseline according to the eligibility criteria for the study. Similarly, both cohorts had an average $CD4^+$ T-cell counts of over 500 cells/mm^3. Additional demographic factors are reported in Table 1.

HIV Viremia

As shown in Figure 2, women with DM had a lower cumulative incidence of a first viremia event than those without DM. From the Poisson regression, the relative rate (RR) of incident viremia for women with DM was lower when compared to women without DM (0.85 [95%CI: 0.72-0.99]; p=0.04).

In contrast, the Kaplan Meier curves show that for men there was no statistically significant difference in the cumulative incidence of a first viremia event between those with and without DM (Figure 2). From the Poisson regression, there was no significant association between DM and the rate of HIV viremia among men in the MACS cohort. The RR of incident viremia for men with HIV and DM was not statistically different compared to men without DM (1.2 [95%CI: 0.96- 1.50]; p=0.12).

ART Adherence

To evaluate the impact of differences in ART adherence patterns between those with DM and those without DM on the overall findings, we stratified the analysis by adherence level. Women with DM who self-reported 100% ART adherence had a lower RR of incident HIV viremia (0.7 [95%CI: 0.51-0.97]; p=0.03) than those without DM. In contrast, women with a self-reported adherence of 95-

99% (1.19 [95%CI: 0.84-1.69]; p=0.32), and <95% (1.14 [95%CI: 0.85-1.53]; p=0.39), did not demonstrate a significant association between having DM and incident HIV viremia (Figure 3).

Among men, there was not a significant association between having a diagnosis of DM and the rate of HIV viremia episodes across all ART adherence levels: men who reported 100% (1.424 [95%CI: 0.946-2.17]; p=0.08), 95-99% (0.84 [95%CI: 0.5-1.40]; p=0.50) or <95% (1.06 [95%CI: 0.70-1.61]; p=0.7680) adherence (Figure 3).

To further explore the underlying mechanism behind fewer viremic episodes in women with DM, we examined a pre-defined set of health behaviors. We found that women with DM were older (average age 48) and were more likely to report >100% adherence. Furthermore, women with DM were less likely to binge drink (defined as 5 or more drinks at a time in men and 4 or more drinks at a time in women), less likely to be current smokers, and were more likely to have controlled hypertension (defined as systolic blood pressure<140 mmHg, diastolic blood pressure<90 mmHg, and self-report of blood pressure medication use) (Table 2). There were no differences by DM status in self-reported use of injection drugs or lipid control (LDL ≤ 160 mg/dL).

Men with DM were also older (average age 51) than men without DM. In contrast, men with DM had similar drinking and smoking rates and no difference in controlled hypertension levels than men without DM (Table 2 and Supplementary Table 2, http://links.lww.com/QAD/D291).

Diabetes Mellitus Control

Among 1,061WIHS women included in the primary analysis, 204 had DM either at the beginning of baseline visit or developed in the follow-up visits. Since HbA1c was not measured at each visit, we imputed values using carry forward and carry backward methods, resulting in a mean HbA1c of 6.7% (IQR:6.0%~8.4%) among 202 WIHS women who were included in the analysis. The RR of incident viremia for women with uncontrolled DM was higher when compared to women with controlled DM (1.46 [95%CI: 1.03-2.07]; p=0.03). From the interaction term, we found that women with uncontrolled DM who self-reported 100% ART adherence had a higher RR of incident HIV viremia (2.35 [95%CI: 1.30-4.2]; p=0.005) than those with controlled DM; for women with uncontrolled DM who self-reported 95-99% and <95%, the RR of incident HIV viremia was 1.44 [95%CI: 0.76-2.76]; p=0.27) and 0.97 [95%CI: 0.56-1.69]; p=0.92), respectively, compared to controlled DM.

Discussion

In this study, we observed that among women with HIV and 100% self-reported adherence to ART, those with DM have a lower risk of viremia when compared to those without DM. Interestingly, this association was not observed among women with adherence less than 100%, or in men with HIV irrespective of their reported ART adherence. These findings are contrary to our hypothesis, as we anticipated that the presence of DM would increase the risk of viremia based on our previous findings of lower cumulative ART exposure in PWH and DM (12). Women with poorly controlled DM (HbA1c >7.5%), and 100% self-reported adherence, however, were more likely to develop viremia than women

with well-controlled DM (<7.5%). To our knowledge, this is the first report where DM has been found to influence virologic outcomes in PWH on ART.

Our findings suggest that the presence of well-controlled DM may be linked to lower risk of viremia in highly adherent women with HIV. Although the mechanisms underlying these findings are unclear, several potential explanations can be inferred. Women with DM in the MWCCS were generally older (average age 48 vs 42 years-old in women without DM) and prior studies have shown that older persons are more likely to be adherent to medications.(21, 22) In addition to being more adherent, women with DM in our cohort had higher rates of controlled hypertension and lower rates of smoking and binge drinking compared to women without DM, suggesting a more health-conscious population. Comparatively, while men in the MACS with DM were also more likely to be older, they did not (23)demonstrate lower rates of smoking or binge drinking compared to men without DM.

Women with poorly controlled DM, however, had a higher risk of viremia than women with well controlled DM with high self-reported ART adherence. It is possible that women in the WIHS with poorly controlled diabetes and 100% self-reported ART adherence were overestimating their adherence. On the other hand, elevated glucose levels are known to increase the susceptibility to bacterial infections (e.g. skin and soft tissue, tuberculosis, osteomyelitis, endocarditis) as well as viral infections (e.g. COVID-19)(23, 24). While relatively few studies have evaluated the direct relationship between glycemic control and infectious diseases(24), the Diabetes Control and Complications Trial, however, found that women with well-controlled type 1 DM had a significantly decreased risk of vaginal infections (46% less) than those with poorly controlled DM (25). Our study is the first to find a correlation between poorly controlled diabetes and an increased risk of HIV viremia.

While our study assessed ART adherence, we were unable to assess the impact of adherence to anti-diabetic medication due to the limitations of our data. We suspect that the beneficial effects of improved adherence upon VL control is exclusive to ART as we found that women with poorly controlled DM were at higher risk of viremia than those with well controlled DM. Early work has shown that among PWH with DM there is lower adherence to DM medications compared with antiretrovirals (26). Furthermore, in an analysis of the WIHS, it was established that HIV viral suppression was not correlated with achieving diabetic control, and that HIV treatment is "outpacing that of diabetes."(27) While HIV can often be treated with a one-pill a day regimen, DM management necessitates lifestyle changes and more complex medication regimens hindering glycemic control. Future studies in this population will require a comprehensive assessment of adherence to ART, diabetic medications, and polypharmacy.

While diabetic control and healthy behaviors may provide some explanation for our results, the differences in our findings between men and women argue for additional investigation into sex-related mechanisms. Prior studies have found that women have lower HIV VLs than men (28-32) and factors such as estrogen mediated down-regulation of TNF-alpha (33, 34) and lower CCR5 density on the CD4 cells of women (35, 36) may enhance viral suppression. Higher adipose tissue percentage, and hence elevations in estrogen, could further promote viral suppression among women with DM compared to men (37, 38).

Our study has several limitations. A small number of PWH with DM were included in our analysis. Overall, our participants had well-controlled DM. The median hemoglobin A1c for all participants (in the MACS and WIHS) was 5.4% among those without DM and 6.8% among those with DM. Participants with DM received two or fewer DM medications (with only a small percentage on insulin) in our cohort. Furthermore, there was an even smaller number of participants with HIV viremia or low ART adherence. In addition, several specific DM metrics were not collected including duration of DM, DM complications (e.g., CAD, CKD, retinopathy), and DM physician visits. As the MACS includes only MSM, heterosexual males were not included in our analysis hence limiting the generalizability of our findings. These are all important factors to examine in future studies as DM encompasses a wide spectrum of disease characteristics. Inaccurate self-reported adherence may have influenced our findings. Future studies using tenofovir-diphosphate in dried blood spots in the MWCCS are underway and may elucidate the impact of self-reported adherence on our results. Furthermore, we were not able to assess the number of health-related or physician encounters. While we controlled for multiple co-factors, potential residual confounding factors such as number of physician and follow up appointments may have influenced our results.

Among the strengths of our study are the large, demographically, and racially, ethnically diverse population from a well-established, prospective cohort such as the MWCCS. Furthermore, the MWCCS is a real-life observational cohort study which provides long-term data on underrepresented populations, enhancing the generalizability of our findings. Lastly, we controlled for multiple covariates to minimize confounding.

Conclusion

This study is the first study to assess the relationship between DM and incident HIV viremia among PWH. We observed that women with HIV and high ART adherence and DM had a lower rate of HIV viremia. Notably, women with high self-reported ART adherence and poorly controlled DM were at a higher risk of HIV viremia. This relationship was not found among men with HIV and DM. These data suggest that DM control as well as health-conscious behavior, such as decreased rates of smoking and binge drinking, may be associated with HIV viremia in women with DM. As women with HIV age and develop obesity, they are more susceptible to DM and potentially increased rates of HIV viremia. Further investigation into the relationship between sex, DM, health behaviors, physician visits, and HIV viremia is necessary to elucidate the mechanisms mediating viral suppression among PWH and DM. These findings could lead to the development of sex specific DM prevention and intervention efforts which could, in turn, be coupled with HIV adherence counselling to improve the outcomes of PWH with DM.

Notes

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Figure 1 Inclusion diagram

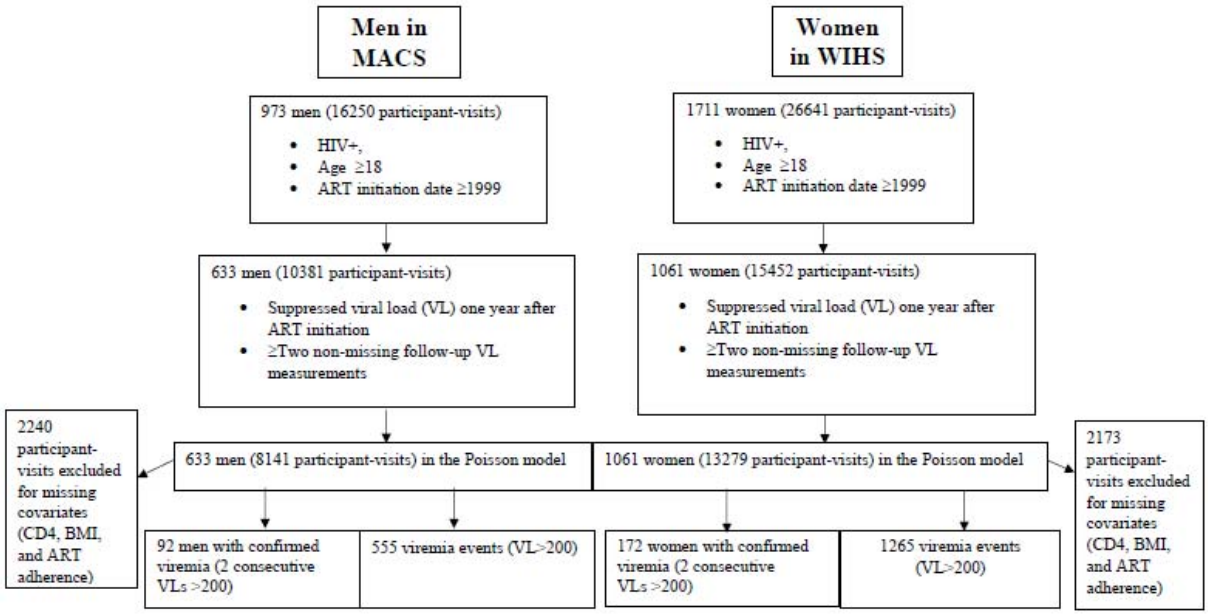

Figure 2 KM.

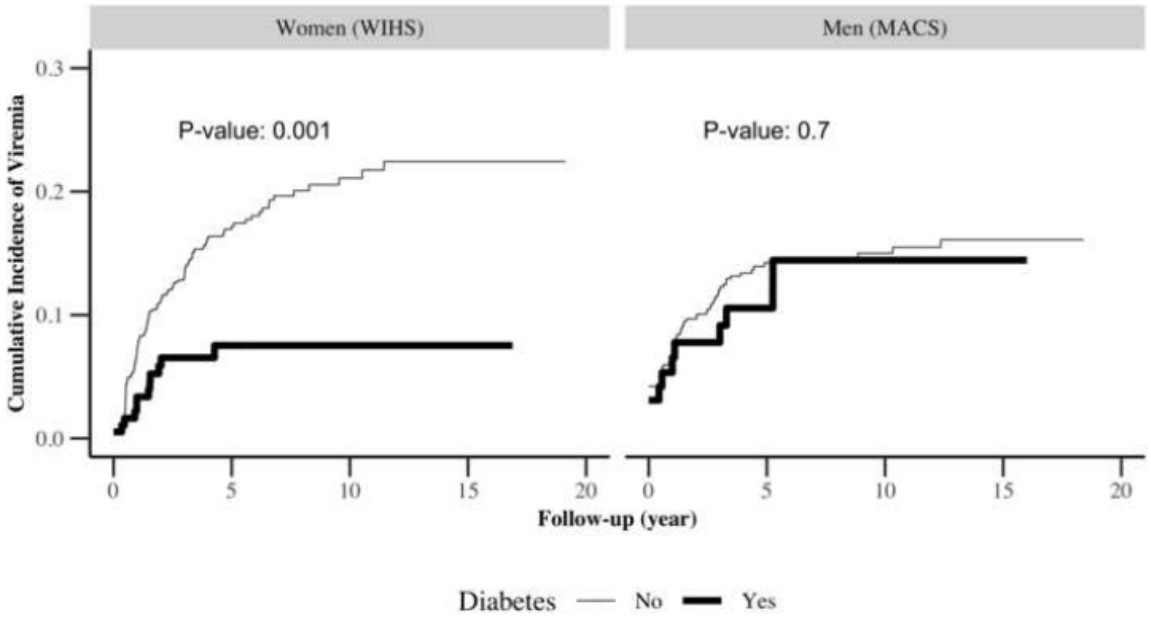

Figure 3 IR.

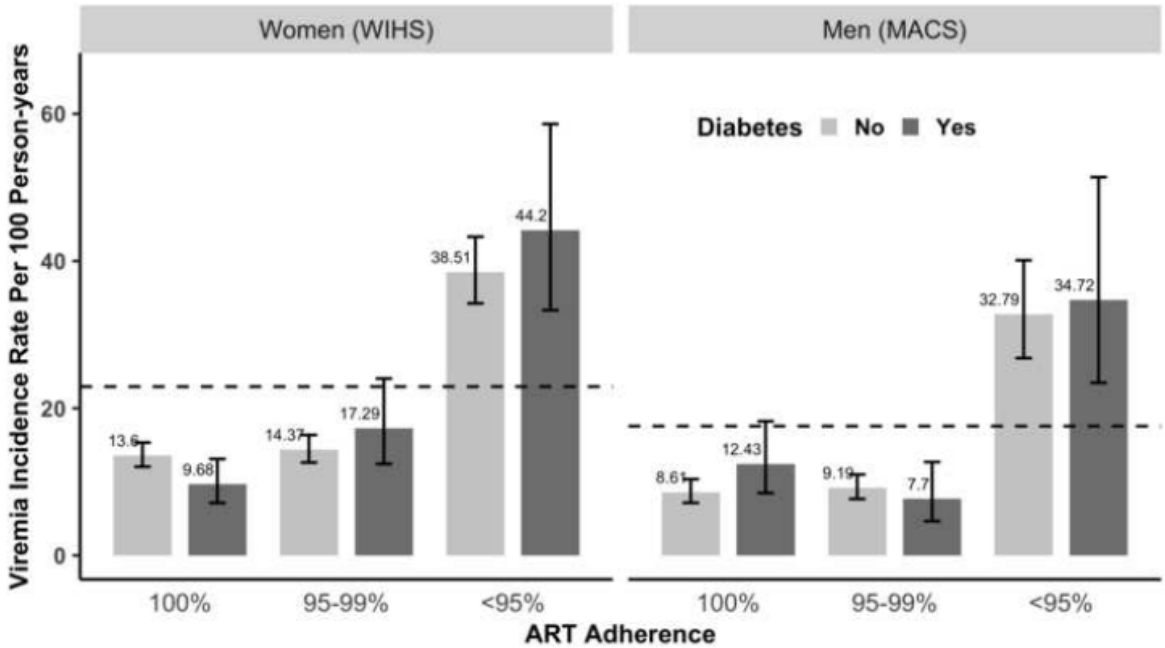

Table 1: Baseline Factors of Women in WIHS and Men in MACS

	Women in WIHS (1061)		Men in MACS (633)	
Characteristics	**DM (112)**	**No DM (949)**	**DM (41)**	**No DM (592)**
Age	48 (42, 53)	42 (35, 49)	51 (46, 57)	42 (34, 49)
Body Mass Index (kg/m2)	36 (30, 44)	29 (25, 35)	28 (23, 34)	25 (23, 29)
18.5-24.9	5.90%	26.10%	31.40%	47.70%
25-29.9	21.60%	28.30%	37.10%	35.80%
≥30	72.50%	45.60%	31.40%	16.50%
Race				
Black	67.90%	64.00%	43.90%	31.00%
White	12.50%	11.80%	43.90%	55.30%
Other	19.60%	24.20%	12.20%	13.70%
Hispanic				
Yes	15.20%	15.40%	12.20%	20.30%
No	84.80%	84.60%	87.80%	79.70%
Education				
≤High school graduate	63.40%	64.20%	43.90%	27.70%
Some post high school	32.10%	27.70%	34.10%	30.90%
College graduate	4.50%	8.00%	22.00%	41.40%
Depression	37.50%	34.80%	31.60%	31.10%
CD4 Count (cells/mm3)	536 (359, 841)	542 (369, 735)	571 (437, 750)	603 (432, 781)
CD4 Nadir (cells/mm3)	243 (105, 358)	245 (130, 364)	315 (213, 498)	321 (212, 446)
Fasting Glucose (mg/dl)	140 (106, 194)	87 (82, 95)	126 (105,159)	94 (88, 101)
HbA1C (mg/dl)	7.4(6.4, 9.5)	5.5(5.2, 5.8)	6.5(5.8, 7.3)	5.3(4.9, 5.5)
DM Medication				
Yes	85.70%	0.10%	51.20%	0.20%
No	14.30%	99.90%	48.80%	99.80%
Metformin use				

Yes	52.40%	0.20%	31.70%	0.20%
No	47.60%	99.80%	68.30%	99.80%
Insulin use				
Yes	18.80%	0	19.00%	0
No	81.30%	100.0%)	81.00%	100.00%
Number of DM medications	1 (1, 2)	0	0 (0, 1)	0
Antiretroviral Therapy				
NRTI-based	0.90%	4.60%	2.60%	4.10%
NNRTI-based	46.80%	44.50%	48.70%	49.70%
PI-based	24.30%	31.80%	33.30%	26.20%
II-based	27.90%	18.60%	10.30%	15.30%
Mono or Combination	0	0.50%	5.10%	4.30%
Other	0	0	0	0.40%

The median and IQR are represented as "median (IQR)."

Depression is defined as CESD $\geq$16.

NNRTI= non-nucleoside reverse transcriptase inhibitor. NRTI= Nucleoside reverse transcriptase inhibitor. PI = Protease Inhibitor. II= Integrase Inhibitor.

Corresponding p-values as well as categories with large quantity of missing data (Hepatitis C) are available in the supplement.

Table 2: Comorbidities and Healthy Behaviors

	Women in WIHS (1061)			**Men in MACS (633)**		
Characteristics	**DM (112)**	**No DM (949)**	**P-value**	**DM (41)**	**No DM (592)**	**P-value**
Hypertension						
Uncontrolled	25.0%	16.1%	<.0001	31.7%	18.2%	0.0048
Controlled	37.5%	15.7%		14.6%	5.9%	
No Hypertension	37.5%	68.2%		53.7%	75.8%	
Adherence						

100%	61.6%	54.2%	0.305	43.9%	38.9%	0.6832
≥95%	25.9%	32.3%		39.0%	44.4%	
75-94%	10.7%	7.9%		9.8%	7.6%	
<75%	1.8%	3.0%		0	1.9%	
Smoking						
Current smoker	32.1%	41.3%	0.063	39.0%	37.8%	0.1278
Former smoker	25.9%	17.9%		43.9%	30.7%	
Never smoked	40.2%	39.2%		17.1%	29.6%	
Binge Drinking	3.6%	9.3%	0.042	9.8%	11.8%	0.6428
Injection Drug Use	0%	1.2%	0.252	2.4%	2.0%	0.8782

Controlled hypertension was defined as systolic blood pressure<140 mmHg, diastolic blood pressure<90 mmHg, and self-report of blood pressure medication use.

Binge drinking defined as defined as 5 or more drinks at a time in men and 4 or more drinks at a time in women since last visit. Injection drug use defined as injected drugs since last visit.

Categories with a large quantity of missing data (cholesterol) are available in the supplement.