# Hemoglobin A1c is a poor predictor of fasting glycemia in HIV-infected men with low CD4 count, high mean corpuscular hemoglobin and red cell volume : the Multicenter AIDS Cohort Study (MACS)


**Laurence Slama[1,2], Frank J. Palella[2], Alison G. Abraham[3], Xiuhong Li[3], Corinne Vigouroux [1,4,5,6], Gilles Pialoux[1], Lawrence Kingsley[7], Jordan E. Lake[8], Todd T. Brown[3]**

1. APHP, Hôpital Tenon, Maladies Infectieuses et Tropicales, F-75020, Paris, France, 2. Northwestern University, Chicago, IL, 3. Johns Hopkins University, Baltimore, MD, 4. APHP, Hôpital Tenon, Biochimie et Hormonologie, F-75020, Paris, France, 5. UPMC Univ Paris 06, UMR_S938, F-75005, Paris, France, 6. INSERM UMR_S938, Centre de Recherche Saint-Antoine, Faculté de Médecine Pierre et Marie Curie, Site Saint-Antoine, F-75012, Paris, France, 7. University of Pittsburgh, Pittsburgh, PA, 8. University of California, Los Angeles, CA


## Introduction

- Diabetes mellitus is common in HIV-infected persons and, as in the general population, is associated with comorbidities such as hypertension, dyslipidemia, cardiovascular disease and renal impairment.
- In order to reduce the risk of diabetic macrovascular and microvascular complications, adequate glycemic control is necessary.
- In the general population, hemoglobin A1c (HbA1c) measures the percentage of hemoglobin A that is glycated.
- Among HIV-infected patients, HbA1c may underestimate glycemia, which may be a result of low grade hemolysis.
- Factors that have been associated with inaccurate HbA1c in HIV-infected person include high MCV, low serum haptoglobin, certain antiretroviral therapies (AZT, abacavir), and diabetes medications.
- We sought to determine whether HbA1c underestimates fasting glucose in HIV-infected compared to HIV-uninfected men and to determine factors associated with HbA1c discordance (the difference between observed and expected HbA1c) among HIV-infected men.

## Methods

- The MACS is an ongoing multi-center prospective observational study of U.S. men who have sex with men established by the NIH in 1984.
- MACS sites include Baltimore MD/Washington DC, Chicago IL, Los Angeles CA, and Pittsburgh PA.
- Participants are seen at semi-annually visits at which interviews, physical examination and collection of biological specimen are performed .
- We included all men with at least one fasting glucose (FG)-HbA1c pair measurement between 1999 and 2012 and the first visit at which a FG-HbA1c pair was available was defined as the baseline visit.
- All pairs from each participant were used in this analysis.

### Statistical Methods

- Median regression was used to determine the HbA1c-FG association by HIV-status and predict the expected HbA1c among HIV-infected as a function of FG; bootstrapping was used to estimate 95% confidence intervals (CI) for effect estimates.
- Logistic regression with generalized estimating equations was used to assess the association between clinical factors and clinically significant HbA1c discordance, defined as observed HbA1c - expected HbA1c ≤ -0.5%.
- An HbA1c discordance of -0.5% was chosen as a cut-point since this is the minimum change of HbA1c that the International Diabetes Foundation considers to be clinically relevant.
- We used a nested modeling strategy to determine the factors associated with HbA1c discordance among the HIV-infected men, as follows:
  - Model 1 : Demographics : Age, Race, BMI
  - Model 2: model 1 + HIV-infection -related parameters (CD4 cell count, current ART use with or without HIV-RNA < 50 copies/ml, HCV, history of AIDS).
  - Model 3 : model 2 + Hematologic parameters (Hemoglobin, MCV, MCH)
  - Model 4 : model 3 + all ART variables of interest (use of PI, NNRTI, NRTI), restricted to men who had a HIV-RNA<50 cop/mL

## Results

**Table 1: Characteristics of 2857 MACS participants at baseline**

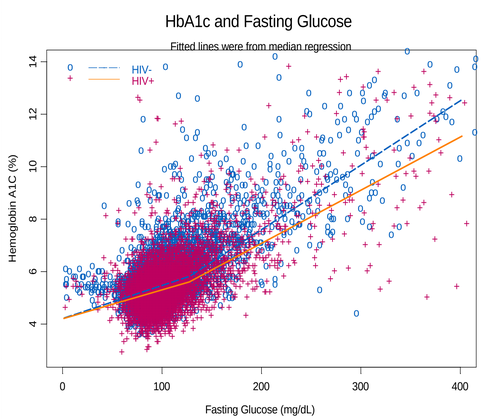
| | HIV-uninfected N=1500 | HIV-infected N=1357 |
|---|---|---|
| Age (years), median (IQR) | 46 (40-53) | 43 (37-49) |
| Caucasian, % | 68% | 54% |
| Education ≥ College degree, % | 57% | 42% |
| BMI, median (IQR) | 26 (23-29) | 25 (23-27) |
| Current diabetes, % | 5% | 8% |
| HCV-infected, % | 5% | 11% |
| HBV-infected, % | 2% | 7% |
| Fasting glucose* (mg/dL), median (IQR) | 90 (82-98) | 91 (83-99) |
| Hemoglobin A1c (%)** | 5.2 (4.9-5.5) | 5.0 (4.6-5.4) |
| Hemoglobin (gm/dL) median (IQR)** | 15 (14-16) | 15 (14-16) |
| MCV (fL), median (IQR)** | 91 (88-94) | 100 (91-111) |
| MCH (pg/cell), median (IQR)** | 31 (30-32) | 34 (31-38) |
| CD4 cell count (cells/ul), median (IQR) | | 486 (320-679) |
| HIV-RNA < 400 copies/mL, n (%) | | 57% |
| Treatment exposure, % | | |
| ART-naive | | 19% |
| Past ART | | 9% |
| Current ART (in last 6 months) | | 69% |
| PI - containing regimen (%) | | 60% |
| NNRTI - containing regimen (%) | | 49% |
| Zidovudine - containing regimen (%) | | 42% |
| Abacavir - containing regimen (%) | | 26% |
| Lamivudine - containing regimen (%) | | 74% |
| Tenofovir - containing regimen (%) | | 19% |

- Diabetes was defined as FG≥126 mg/dL or self-reported diabetes with use of hypoglycemic medications
- Hepatitis C virus (HCV) infection was defined as having a positive serum antibody to HCV or positive HCV RNA
- Hepatitis B virus (HBV) infection was defined as having a positive serum HBV surface antigen (HBV Ag)
- MCV : mean corpuscular volume; MCH : mean corpuscular hemoglobin
- Specific ART% were calculated among ART- treated men in the previous 6 months.

**The mean number of visits for each participants was 11 ( range 1-26)**

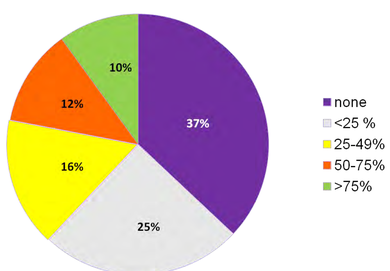
*** p= 0.013**
**** p<0.001**

**Relationship between Hemoglobin A1c and fasting glucose in HIV-infected and HIV-uninfected men using median regression with a knot at 125 mg/dL**




•At a fasting glucose at 125 mg/dL, the HbA1c was 0.21% lower among the HIV-infected men compared to HIV-uninfected men (p<0.001). This difference became larger when the FG was 126 mg/dL and above (p=0.018).

**Percentage of HIV-infected men with visits with A1c discordance**



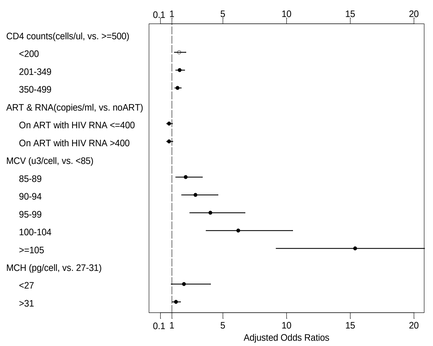

Of the 1378 HIV- infected men, 871 (63%) had at least one visit with clinically significant HbA1c discordance (observed HbA1c – expected HbA1c )≤ -0.5%)

**Model 2 : HbA1c-discordance (observed HbA1c – expected HbA1c) ≤ -0.5 % among HIV-infected men: Demographic and HIV Parameters**

| Factors | Multivariate model 2 OR ( 95% CI) | p value |
|---|---|---|
| Age (per1 year) | 0.98 (0.97,0.99) | <0.001 |
| Race (vs. white) | | |
| Black | 0.6 (0.47,0.76) | <0.001 |
| Hispanic or other | 0.51 (0.39,0.67) | <0.001 |
| BMI (kg/m², vs. 18.5-24.9) | | |
| <18,5 | 0.96 (0.52,1.80) | 0.921 |
| 25-29 | 1.03 (0.86,1.22) | 0.762 |
| ≥30 | 0.65 (0.49,0.86) | 0.003 |
| Current CD4 cell counts ( cells/ul, vs. ≥500) | | |
| <200 | 1.38(1.06,1.79) | 0.016 |
| 200-349 | 1.41 (1.16,1.71) | <0.001 |
| 350-499 | 1.29 (1.1,1.51) | 0.001 |
| Current ART and HIV-RNA level (copies/mL vs. No ART) | | |
| On ART with HIV-RNA ≤400 | 1.92 (1.51,2.42) | <0.001 |
| On ART with HIV-RNA > 400 | 1.74 (1.34,2.26) | <0.001 |
| HCV-infected, yes vs.no | 1.17 (0.92,1.5) | 0.203 |
| AIDS, yes vs.no | 1.1 (0.88,1.41) | 0.363 |

•Lower CD4 cell counts, ART treatment, with or without a suppressed viral load, were independently associated with a lower observed than expected HbA1c value.
•In contrast, a higher than expected HbA1c value was associated with older age, non-caucasian race and obesity.

**Model 3 : HbA1c-discordance (observed HbA1c – expected HbA1c) ≤ -0.5 % among HIV-infected men: Hematologic Parameters***




*also adjusted for covariates in Model 2

**Model 4 : HbA1c-discordance (observed HbA1c – expected HbA1c) ≤ -0.5 % among HIV-infected men: Hematologic , HIV Parameters and ART variables***

| Factors | Multivariate OR ( 95% CI) | p value |
|---|---|---|
| MCV (fL, vs.<85) | | |
| 85-89 | 1.21 (0.6,2.42) | 0.602 |
| 90-94 | 1.67 (0.92,3.06) | 0.093 |
| 95-99 | 2.3 (1.21,4.38) | 0.011 |
| 100-104 | 2.85 (1.47,5.52) | 0.02 |
| ≥105 | 5.71 (2.93,11.1) | <0.001 |
| On ART with HIV RNA ≤ 400 copies/mL | 0.83 (0.43,1.61) | 0.59 |
| PI, yes vs.no | 1.39 (1.08,1.78) | 0.010 |
| NNRTI, yes vs.no | 1.17 (0.92,1.49) | 0.212 |
| AZT, yes vs.no | 1.38 (1.06,1.81) | 0.019 |
| 3TC, yes vs.no | 0.74 (0.56,0.99) | 0.041 |
| FTC, yes vs.no | 0.36 (0.26,0.49) | 0.000 |
| ABC, yes vs.no | 0.73 (0.58,0.91) | 0.005 |
| TDF, yes vs.no | 0.91 (0.7,1.18) | 0.477 |

- PI and AZT use were associated with clinically signifncant HbA1c discordance .
- Abacavir and FTC use appears to be protective against clinically significant HbA1c discordance.
- An attenuation of the MCV effect was noted with the inclusion of ART variables in the model

## Summary & Conclusions

- This is the largest study to date which has evaluated the relationship between HbA1c and fasting glucose among HIV-infected persons.
- HbA1c underestimated fasting glycemia in HIV-infected men.
- This underestimation was most pronounced in men with CD4 cell counts below 500 cells/mm$^3$, higher MCV and MCH.
- PI and zidovudine exposure was associated with increased odds of HbA1c discordance.
- Caution should be exercised when using HbA1c to diagnose DM in HIV-infected persons.
- A lower HbA1c level treatment target should be considered to prevent long term diabetes complications in those HIV-infected patients with diabetes and risk factors for inaccurate HbA1c.