Title

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Journal

AIDS, 28(12)

ISSN

0269-9370

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Publication Date

2014-07-31

DOI

10.1097/qad.0000000000000366

Peer reviewed

Published in final edited form as:
AIDS. 2014 July 31; 28(12): 1815–1823. doi:10.1097/QAD.0000000000000366.

Antiretroviral Therapy Modifies the Genetic Effect of Known Type 2 Diabetes-Associated Risk Variants in the Women's Interagency HIV Study

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Abstract

Objective—Type 2 diabetes (DM) incidence is increased in HIV-infected persons. We examined the associations of DM with known DM-risk alleles from the general population in the context of HIV infection and explored effect modification by combination antiretroviral treatment (cART).

Methods—The Women's Interagency HIV Study (WIHS) is a prospective cohort of HIV-infected women. Seventeen European-derived DM-risk polymorphisms were genotyped in eligible WIHS participants. Analyses were run separately for non-African-Americans (Whites, Hispanics, Asians, and other; n=378, 49 with incident DM) and African-Americans (n=591, 49 with incident DM). Cox proportional hazards models were fit to estimate hazard ratios (HRs) for DM overall and within strata of cART.

Results—In non-African-Americans, heterogeneity across cART regimen was observed for 9 of 14 polymorphisms (p_{het}<0.05). One polymorphism was statistically significantly inversely

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CONFLICT OF INTEREST: The authors have no conflict of interest to report.

associated with DM risk among women taking 2 NRTIs+NNRTI. Five polymorphisms were statistically significantly associated with DM among women treated with ≥2 NRTIs + ≥1 PI and one polymorphism was associated with DM among those treated with ≥3 NRTIs ± NNRTI. The HR per risk allele for *IGF2BP2* rs1470579 was 2.67 (95% CI 1.67–4.31) for women taking cART with ≥2 NRTIs+≥1 PI and 2.45 (95% CI 1.08–5.53) in women taking ≥3 NRTIs±NNRTI ($p_{het}=2.50\times10^{-3}$). No such associations were observed in African-Americans.

Conclusions—Genetic susceptibility to DM, based on the variants studied, is substantially elevated among HIV-infected women using cART containing three or more NRTI/PI components. A personalized medicine approach to cART selection may be indicated for HIV-infected persons carrying these DM-risk variants.

Keywords

type 2 diabetes; genetics; HIV; women; antiretroviral therapy

INTRODUCTION

Increased incidence of type 2 diabetes mellitus (DM) among individuals infected with human immunodeficiency virus (HIV) is a major concern given that DM is a risk factor for mortality in the HIV-infected population [1]. Combination antiretroviral therapy (cART) has been consistently implicated in DM risk [2–10]. Two antiretroviral drug classes, nucleoside reverse transcriptase inhibitors (NRTI) and protease inhibitors (PI), have each been linked to elevated DM risk [2–10].

In HIV-uninfected populations, a genetic influence on DM has long been observed with heritability estimates ranging between 20%–70% [11–16]. In 2007, four genome-wide association studies (GWAS) identified multiple alleles associated with DM in predominately European populations [17–21]. Replication studies in independent European, Asian, and Mexican populations have confirmed several of these DM risk variants [22–29]. However, it appears that different signals are observed in African populations due to the greater degree of diversity in linkage disequilibrium (LD) patterns in populations of African descent [25, 30–32].

The interplay among HIV disease, HIV treatment, DM and genetic risk is unclear. The Swiss HIV Cohort (SHC) Study evaluated the main effect of 22 DM-associated variants. Overall, associations were of similar direction and magnitude as demonstrated in HIV-uninfected populations; however, power was limited and the potential modifying effect of cART was not evaluated [8].

The current study aimed to examine the association between selected DM-associated polymorphisms and incident DM in the context of HIV-infection among women. Given the relationship between cART and DM risk, modification of the genetic associations with DM incidence by NRTI and PI use was examined.

METHODS

Study Design

The Women's Interagency HIV Study (WIHS) is a multi-ethnic prospective observational study of HIV-infected and -uninfected women in the United States (U.S.) who have been followed since 1994. Detailed descriptions of the WIHS cohort have been published previously [9, 10, 33]. Participants are seen for in-person visits every six months during which time trained medical interviewers administer an extensive questionnaire, a clinical examination is performed, and biological samples are collected for various laboratory tests, including HIV RNA and CD4+ cell counts. Medications used for HIV treatment and other conditions are recorded at each follow-up visit. Beginning in October 2000 (visit 13), fasting glucose (FG) was measured at each follow-up visit through visit 17 and then annually thereafter. Hemoglobin A1C (A1C) was measured at each follow-up visit through visit 17, annually through visit 23; A1C measurement was suspended from visit 24 through 32 and then was measured annually thereafter.

DM Case Definition

The first visit for which FG and A1C measurements were available was defined as the index visit for each participant (visit 13 or later). Participants were followed after the index visit for DM incidence. DM was defined by the first visit for which either FG ≥126 mg/dL, A1C ≥6.5%, or report of anti-diabetic medication with confirmation at the subsequent visit of one or more of these three criteria. This definition conforms to recommendations made by the American Diabetes Association [34] and has been used in the WIHS cohort [10]. Individuals with type 1 diabetes are not likely to be included by this definition, given the age range of our participants, but may include the rare participant with latent autoimmune diabetes of adulthood.

Inclusion and Exclusion Criteria

HIV-infected women consenting to genetic studies with at least one follow-up visit with FG and A1C measurements after the index visit were eligible for the study. Women satisfying the DM definition prior to or at the index visit were excluded from the study due to prevalent DM. To ascertain the most homogenous sample based on the availaibility of treatment with several drug classes, women who reported use of antiretroviral agents prior to the cART era (1995) were excluded. A total of 1,291 women were eligible for this study.

Genotyping and Quality Control

A total of 14 single nucleotide polymorphisms (SNPs) across 13 regions were identified from European-derived GWAS [17–21]. Six of the selected SNPs were genotyped as a subset of a larger panel on Illumina's Golden-Gate platform (San Diego, CA): rs10811661 (*CDKN2A/2B*), rs1470579 (*IGF2BP2*), rs5219 (*KCNJ11*), rs7754840 (*CDKAL1*), rs7903146 (*TCF7L2*), and rs6698181 (*PKN2*). The remaining eight were genotyped using TaqMan (Applied Biosystems, Foster City, CA): rs1801282 (*PPARG*), rs12779790 (*CDC123-CAMK1D*), rs564398 (*CDKN2A/B*), rs8050136 (*FTO*), rs7923837 (*HHEX*), rs864745 (*JAZF1*), rs2237895 (*KCNQ1*), rs2934381 (*NOTCH2)*. Two SNPs in *CDKN2A/2B* were

selected since they have been shown to be independent of each other [25] and do not display LD in White (r^2=0.001), Hispanic (r^2=0.024), or African (r^2=0) populations.

An adequate amount of material for genotyping was available for 80% of eligible participants (n=1,035/1,291). In addition, 66 women were excluded because they had a genotype call rate less than 90% across more than 300 SNPs for which they had been genotyped for another project leaving 969 women for analysis. The SNP call rate for the 14 SNPs was >90%. Duplicates for 53 participants demonstrated 99% concordance. No SNP deviated from Hardy-Weinberg equilibirum at $p<0.05$.

Statistical Analysis

Analyses were stratified by self-reported ethnicity to investigate the suggested heterogeneity of genetic effect across populations [24, 25, 27, 30–32]. As the associations between DM and the SNPs interrogated are generally similar across non-African populations [22–29], we combined self-reported White, Hispanic, Asian, Native American, and Other women as one group ('non-African-Americans'). Analyses were run separately for non-African-Americans (49 DM cases, 329 non-cases) and African-Americans (49 DM cases, 542 non-cases).

Exposure to NRTIs and PIs were evaluated in two ways. First, duration of NRTI and PI use was defined as the cumulative number of years exposed to each drug class beginning at the participant's WIHS enrollment visit. Second, current regimen reported at each visit, a time-dependent variable, was categorized as: 1) no ART, 2) cART containing two drugs from the NRTI class with a non-nucleotide reverse transcriptase inhibitors (NNRTI), 3) cART containing three or more NRTIs, with or without NNRTIs, and 4) cART containing two or more NRTIs and at least one PI (includes boosted regimens). Visits at which the regimen was not in one of these four categories were excluded (e.g. three PIs; two PIs+NNRTI; NRTI+2 PIs; among others), resulting in the loss of 113 person-years in the non-African-American analysis and 119 person-years in the African-American analysis.

Cox proportional hazard models were fit to test the association between each SNP and DM using calendar year as the time-scale. Since the prevalence of specific cART regimens changed over the course of this study, calendar time was used to compile risk sets of women who were treated for HIV during the same timeframes. The earliest follow-up began on October 1, 2000 (visit 13); participants entered follow-up at their index visit and were followed through the DM ascertainment visit. Non-cases were censored at their last follow-up visit due to drop-out or death or the end of follow-up for the current analysis (December 31, 2010). Hazard ratios (HR) per allele and 95% confidence intervals (CI) were estimated by modeling the genotypes as an ordinal variable (i.e., a log-additive mode of inheritance). Non-risk allele homozygotes, heterozygotes and risk allele homozygotes were coded as 0, 1, and 2, respectively, based on previously published associations [24].

The potential time-dependent confounders evaluated in the association models included body mass index (BMI), age (18–29, 30–39, 40–49, 50–82), self-reported smoking status (never, current, former), and exposure to antiretroviral drugs. BMI was categorized as < 25, 25–29.9, ≥ 30 kg/m^2 and missing values (6%) were carried forward from the previous visit.

Principal components (PC) analysis was performed to generate genetic ancestry covariates based on 168 ancestry informative markers [35]. A more detailed description on genetic ancestry determination in the WIHS has been published [36]. The top 10 PCs were included in the association models.

Models were applied among women treated with all regimens and then SNP associations were estimated within strata of current cART regimens. P-values for heterogeneity between regimens were calculated using a likelihood ratio test comparing the pooled (all regimens) model and the regimen-stratified model (χ^2 with 3 df).

RESULTS

Characteristics of incident DM cases and non-cases in non-African-American (N=378) and African-American (N=591) women at the index visit are presented in Table 1. In non-African-Americans, the total follow-up time was 2,878 person-years and the median (IQR) follow-up time was 3.5 (3.5) years for cases and 8.8 (2.5) years for non-cases. In African-Americans, the total follow-up time was 4,473 person-years and the median (IQR) follow-up time was 3.5 (4.5) years for cases and 8.7 (3.0) years for non-cases.

The rsIDs, genes, chromosome location, and risk allele frequencies (RAF) in self-reported Whites, Hispanics, and African-Americans are shown in Table 2.

The main effect of the 14 SNPs on DM risk after adjustment for genetic ancestry PCs, BMI, and age in non-African-American participants are presented in Table 3. A statistically significant association was observed with *IGF2BP2* rs1470579, in which each allele was estimated to carry a nearly two-fold increased risk of DM (Table 3, 'all regimens' column). Associations between the other 13 SNPs and DM were much more modest and did not reach statistical significance; however most of these associations trended in the same direction as seen in the general population (Table 3). Adjustment for smoking status, and durations of NRTI and PI exposures did not change these associations. The associations were also similar after employing proportional hazards models with competing risk for mortality.

SNP associations were evaluated within strata of current cART regimen to explore our hypothesis that use of NRTIs and PIs may influence the SNP associations with DM risk (Table 3, columns under cART regimens). Statistically significant heterogeneity in SNP-DM associations across regimens was observed for 9 of the 14 SNPs as indicated by '*' in Table 3. The associations were null among women reporting no treatment (Table 3). Overall, the SNP-DM associations were either restricted to or stronger in women currently treated with ≥3 components from the NRTI and PI classes (Table 3, ≥3 NRTIs ± NNRTI and ≥2 NRTIs + ≥1 PI columns). Adjustment for duration of NRTI and PI exposures did not alter the observed heterogeneity of genetic effects on DM risk across current regimens.

The HR for each copy of the risk allele at *IGF2BP2* rs1470579 among women treated with 2 NRTIs + NNRTI was 0.89 (95% CI 0.37–2.16). Among women treated with at least three components from the NRTI and PI classes, the HR was 2.45 per allele (95% CI 1.08–5.53) among women treated with regimens containing ≥3 NRTIs ± NNRTI and 2.67 per allele

(95% CI 1.67–4.31) among those treated with ≥2 NRTIs + ≥1 PI (p_{het} between all regimens=2.50×10^{-3}).

Four additional SNPs were significantly associated with DM among non-African-American women who were treated with ≥2 NRTIs + ≥1 PI (*CDKAL1* rs7754840 p=0.01, *CDKN2A/B* rs564398 p=0.047, *CDKN2A/B* rs10811661 p=0.03, and *FTO* rs8050136 p=0.04, Table 3). The risk allele at TCF7L2 rs7903146 was inversely associated with DM risk among non-African American women taking cART regimens containing 2 NRTIs + NNRTI. This protective effect was observed across all cART regimen groups (Table 3).

The two *CDKN2A/B* SNPS were jointly modeled among regimens containing at least three components from the NRTI and PI classes (n=33 cases) to determine if the genetic effects were independent of each other (results not shown). The individual associations were attenuated when modeled together, however the magnitude of the association at both loci remained elevated (rs564398 HR=1.57, 95% CI 0.83–2.97; rs10811661 HR=1.90, 95% CI 0.74–4.84).

A statistically significant protective effect (p=0.02) was observed between the *JAZF* rs864745 allele and risk of DM in the pooled sample of African-Americans and modestly significant associations (p=0.04) were observed among women who were not receiving ART or were treated with 2 NRTIs + NNRTI (Table 4). No other statistically significant associations were observed in African-Americans across the remaining interrogated SNPs.

DISCUSSION

Carrying known European-derived DM risk alleles was associated with substantially increased risk of DM among non-African-American HIV-infected women treated with cART containing at least three components from the NRTI and PI classes (e.g. 3 NRTIs or 2 NRTIs + ≥1 PI). While these variants are associated with a modest 10–35% increased risk of DM among White and Hispanic general populations, the magnitude of increased risk was 60%–170% per risk allele among HIV-infected non-African-American women taking these cART regimens. These findings suggest that more personalized approaches to HIV treatment might be beneficial among individuals with an underlying genetic predisposition to DM.

To our knowledge, we are the first to evalauate the genetic effects of confirmed DM-risk alleles among persons prescribed different regimens of cART. Statistically significant differential effects of DM-risk alleles across cART regimens were observed for the majority of SNPs tested. The strongest departure from homogeneity across regimens was observed with the risk allele at *IGF2BP2* rs1470579 ($p_{het}=2.50 \times 10^{-3}$).

The probability of false positive associations in our study is unlikely, given that the interrogated SNPs are confirmed susceptibility loci in the HIV-uninfected European and Hispanic populations. The alleles that were significantly associated with DM in non-African-Americans treated with regimens containing at least three components from the NRTI and PI classes have achieved genome-wide significance in the non-African general population ($p< 1.0 \times 10^{-8}$). In a recent meta-analysis comprising over 14,000 cases of

European descent, *CDKAL1* rs7754840, *CDKN2A/B* rs10811661, and *IGF2BP2* rs1470579 were some of the top signals for DM risk ($p<1.0 \times 10^{-15}$) [24]. Additionally, elevated risk has been reported for both *CDKAL1* rs7754840 and *IGF2BP2* rs4402960 ($r^2=0.87$ with rs1470579) in a large subset of Hispanics (n=2,200 cases) [22].

Our *a priori* hypothesis that antiretroviral regimen may modify the genetic influence on DM was based on evidence that NRTIs and PIs increase DM risk [2–10]. The interaction between NRTIs and PIs with variants in *CDKAL1*, *CDKN2A/B*, and *IGF2BP2* is biologically plausible owing to the common mechanism of abberant glucose metabolism [23, 28, 37–40]. Both NRTIs and PIs have been shown to affect normal glucose homeostasis in muscle, fat, and liver, thereby leading to insulin resistance and altered insulin secretion by the pancreas [37]. Functional studies of *CDKAL1* rs7754840, *CDKN2A/B* rs10811661 and rs564398, and *IGF2BP2* rs1470579/rs4402960 have demonstrated altered insulin secretion and other phenotypes of insulin resistance [23, 28, 38–40]. We observed differential SNP associations across cART regimens, suggesting that NRTI/PI-mediated and SNP-induced insulin resistance are likely to interact and to substantially increase risk of DM in HIV-infected individuals treated with at least three drugs from the NRTI and PI classes. The mechanism for a biological interaction between NRTIs/PIs and these genes has not been studied and is a next step of interest for our group.

Interestingly, estimates of genetic risk of DM were null in those who were currently untreated for HIV-infection. These data could suggest that DM-risk alleles in the general population are not implicated in DM risk in the context of HIV infection. Alternatively, the competing risk of mortality in those who are untreated, and thus may have uncontrolled viral replication, may lead to an artificially low incidence of DM and no ability of the risk alleles to express themselves. However, we considered models of competing risks and the results were similar to those using standard survival models. Thus, the reason for the lack of association in HIV-infected women not currently taking antiretrovirals is unclear and may simply be due to the small effect estimates in the absence of cART with at least three drugs from the NRTI and PI classes. The SHC, the only additional study to examine the association between these DM risk variants in an HIV-infected population, reported modest main effect associations, but did not explore the modifying effect of antiretroviral treatment [8]. It is therefore unclear whether the associations in the SHC were restricted to individuals taking specific types of regimens as suggested by our data.

An inverse association with DM risk was observed with the risk alelle at *TCF7L2* rs7903146 in our female HIV-infected non-African American population, even though rs7903146 was the most signicant signal in European GWAS meta-analyses [25, 29]. and this association has been replicated in several independent European and Asian populations [21–29]. The SHC Study reported elevated risk in European HIV-infected carriers of the risk allele at rs7903146 (RR=1.43, 95% CI 0.93–2.21) [8]. One potential difference in the SHC Study compared to the WIHS that might account for this discrepancy is the absence of Hispanics in the SHC [8]. The majority of the non-African-American cases in our study are Hispanic women (56%) and the effect of rs7903146 in HIV-uninfected populations is more modest in Hispanics than in Europeans [22, 25]. In fact, rs7903146 was not a top signal in two recent GWAS in Mexican populations [41, 42]. Although we controlled for population

stratification in our analysis, it is possible that there is true heterogeneity of effect across racial/ethnic groups. The lack of association in our data might be explained by disparate LD between the causal allele and rs7903146 in the Hispanic genome.

Associations between DM and known risk variants in WIHS African-American women were not observed. This is not surprising given that the SNPs genotyped in this study were selected based on index SNPs with strong signals in European GWAS. While most common European-derived SNPs are present in African-Americans, the allele frequencies vary across populations. Subsequent GWAS have identified different susceptibility alleles in the African-American general population, with the exception of signals at *TCF7L2* [30–32]. This disparity between DM-associated alleles in African and non-African populations is partly accounted for by the diverse LD patterns that occur across populations, by which an index SNP in the European population may not be in the same LD block as the true signal in the African population [31, 32]. Ultimately, we were not able to address the modifying effect of cART on DM-risk variants among WIHS African-American women with the markers we genotyped and additional work in this area is warranted.

Further follow-up of the genetic influence on DM risk in the HIV-infected population is needed. Study of individual PIs is important since there are inherent differences in their ability to stimulate insulin resistance; for instance newer PIs are more metabolically neutral [37, 43]. We controlled for the temporal effect of the clinical atmosphere by using calendar time for the time-scale to account for regimen trends over time, but we did not have sufficient power to assess the role of specific drugs. Identification of modification of genetic associations by specific antiretroviral drugs may be possible in the future as follow-up and DM incidence accrues in the ongoing WIHS. The majority of enrollees in the WIHS are African-American; now that DM risk variants in African-Americans have been identified [43, 44], we can evaluate the potential modifying effect of regimens on African-American derived risk variants. This effort is critical given that African-Americans have a high rate of DM diagnoses, as well as HIV in the U.S. [44].

HIV disease is the perfect context in which to implement a personalized medicine approach and the potential clinical impact of these data could be profound. Genetic screening could be used to preferentially prescribe specific cART regimens to those who harbor these DM-risk variants. The U.S. guidelines for cART initiation in HIV-infected individuals recommend an initial regimen of 2 NRTIs + NNRTI (efavirenz) or 2 NRTIs + PIs [45]. Our results suggest the NNRTI-based regimen may be preferred for non-African-Americans with genetic predisposition for DM, given that the alternative regimen of two NRTIs and one or more PIs substantially increases DM risk in those with an underlying genetic predisposition.

ACKNOWLEDGEMENTS

Melissa A. Frasco: Design, data generation, analysis, interpretation. Manuscript preparation.

Roksana Karim: Analysis and interpretation. Manuscript preparation.

David Van Den Berg: Data generation and manuscript preparation.

Richard M. Watanabe: Interpretation and manuscript preparation.

Kathryn Anastos: WIHS overall design and data collection. Interpretation and manuscript preparation.

Mardge Cohen: WIHS overall design and data collection. Interpretation and manuscript preparation.

Stephen Gange: WIHS overall design and data collection. Interpretation and manuscript preparation.

Deborah Gustafson: Interpretation and manuscript preparation.

Chenglong Liu: Interpretation and manuscript preparation.

Phyllis C. Tien: Interpretation and manuscript preparation.

Wendy J. Mack: Design, analysis, interpretation. Manuscript preparation.

Celeste Leigh Pearce: Design, data generation, analysis, interpretation. Manuscript preparation.

Data in this manuscript were collected by the Women's Interagency HIV Study (WIHS) Collaborative Study Group with centers (Principal Investigators) at New York City/Bronx Consortium (Kathryn Anastos); Brooklyn, NY (Howard Minkoff); Washington DC, Metropolitan Consortium (Mary Young); The Connie Wofsy Study Consortium of Northern California (Ruth Greenblatt); Los Angeles County/Southern California Consortium (Alexandra Levine); Chicago Consortium (Mardge Cohen); Data Coordinating Center (Stephen Gange).

The WIHS is funded by the National Institute of Allergy and Infectious Diseases (UO1-AI-35004, UO1-AI-31834, UO1-AI-34994, UO1-AI-34989, UO1-AI-34993, and UO1-AI-42590) and by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (UO1-HD-32632). The study is co-funded by the National Cancer Institute, the National Institute on Drug Abuse, and the National Institute on Deafness and Other Communication Disorders. Funding is also provided by the National Center for Research Resources (UCSF-CTSI Grant Number UL1 RR024131). The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

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Table 1

Characteristics of incident type 2 diabetes (DM) cases and non-cases in non-African-Americans and African-Americans at the index visit.

	Non-African-American[1]		African-American	
	DM cases N (%)	Non-cases N (%)	DM cases N (%)	Non-cases N (%)
N	49	329	49	542
Site				
Bronx, NY	11 (22)	57 (17)	10 (20)	101 (18)
Brooklyn, NY	1 (2)	37 (11)	13 (27)	160 (29)
Washington DC	2 (4)	24 (7)	6 (12)	96 (18)
Los Angeles, CA	14 (29)	132 (40)	0	34 (6)
San Francisco, CA	12 (25)	55 (17)	4 (8)	58 (11)
Chicago, IL	9 (18)	24 (7)	16 (33)	93 (17)
Race/ethnicity				
White	17 (36)	93 (28)	--	--
Hispanic	28 (56)	204 (62)	5 (9)	20 (4)
Asian/Other	4 (8)	32 (10)	--	--
Cohort				
1995–1996	35 (72)	185 (56)	31 (64)	287 (53)
2000–2001	14 (28)	144 (44)	18 (36)	255 (47)
Smoking status				
Never	14 (28)	129 (39)	9 (18)	165 (31)
Current	18 (37)	121 (37)	28 (57)	280 (52)
Former	17 (35)	77 (24)	12 (25)	93 (17)
Missing	0	2	0	4
BMI category, kg/m^2				
< 25, normal	13 (26)	137 (41)	9 (18)	193 (36)
25–29.9, overweight	15 (31)	105 (32)	12 (25)	158 (29)
≥30, obese	21 (43)	87 (27)	28 (57)	191 (35)
Mean (SD) BMI kg/m^2	29.4 (6.6)	27.4 (6.4)	32.9 (8.5)	28.8 (7.5)
Mean (SD) age in years	41.5 (9.2)	38.1 (8.5)	41.2 (8.0)	38.3 (8.6)
Mean (SD) CD4+ cells/ul	569 (386)	493 (334)	608 (372)	476 (292)
Naïve to antiretroviral therapy through follow-up	7 (14)	16 (5)	11 (20)	50 (9)

[1] Self-reported Non-Hispanic White, Hispanic, Asian, Native American, and Other

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Table 2

Risk allele frequencies by self-reported race/ethnicity in participants included in this study.

Gene	Chr Position (NCBI 37)	SNP	Risk / Non-risk Allele[1]	Risk Allele Frequency[2]		
				White	Hispanic	African-American
CAMK1D	10p13	rs12779790	G/A	0.18	0.16	0.14
CDKAL1	6p22	rs7754840	C[3]/G	0.28	0.33	0.58
CDKN2A/B	9p21	rs564398	T/C	0.62	0.80	0.93
CDKN2A/B	9p21	rs10811661	T/C	0.80	0.86	0.93
FTO	16q12	rs8050136	A/C	0.49	0.26	0.45
HHEX	10q23	rs7923837	G/A	0.65	0.63	0.92
IGF2BP2	3q27	rs1470579	C[3]/A	0.34	0.37	0.78
JAZF1	7p15	rs864745	T/C	0.50	0.64	0.73
KCNJ11	11p15	rs5219	T/C	0.30	0.31	0.07
KCNQ1	11p15	rs2237895	C/T	0.46	0.38	0.20
NOTCH2	1p12	rs2934381	A/G	0.09	0.09	0.34
PKN2	1p22	rs6698181	T/C	0.34	0.36	0.14
PPARG	3p25	rs1801282	C/G	0.90	0.92	0.98
TCF7L2	10q25	rs7903146	T/C	0.29	0.25	0.27

[1] Established risk allele in European populations; minor allele is underlined.

[2] Asian, Native American, and other not shown

[3] Common allele in African-Americans

AIDS. Author manuscript; available in PMC 2015 July 31.

Table 3

Associations between the risk allele of GWAS-derived single nucleotide polymorphisms (SNP) and incident type 2 diabetes (DM) in all self-reported non-African-Americans1 and stratified by regimen.

					cART regimens		
Gene	**SNP**	**Risk Allele[2]**	**All Regimens 49 DM / 2,844 PY HR† (95% CI)**	**No Treatment 11 DM / 804 PY HR† (95% CI)**	**2 NRTIs + NNRTI[3] 5 DM / 781 PY HR† (95% CI)**	**≥3 NRTIs ± NNRTI[4] 7 DM / 239 PY HR† (95% CI)**	**≥2 NRTIs PI[5] 26 DM / 1,020 PY HR† (95% CI)**
CAMK1D	rs12779790	G	1.31 (0.77–2.23)	1.64 (0.81–3.22)	0.27 (0.04–1.90)	0.84 (0.11–6.52)	1.87 (0.94–3.71)
CDKAL1	rs7754840*	C	1.30 (0.85–1.99)	0.97 (0.47–1.99)	0.41 (0.11–1.56)	1.37 (0.46–4.05)	**1.93 (1.21–3.08)**
CDKN2A/B	rs564398*	T	1.23 (0.74–2.03)	0.86 (0.45–1.63)	0.70 (0.64–2.66)	1.30 (0.64–2.66)	**1.68 (1.01–2.80)**
CDKN2A/B	rs10811661*	T	1.63 (0.84–3.16)	1.28 (0.62–2.66)	0.98 (0.43–2.24)	1.84 (0.83–4.09)	**2.07 (1.06–4.03)**
FTO	rs8050136*	A	1.21 (0.80–1.84)	0.86 (0.43–1.71)	0.58 (0.22–1.52)	1.65 (0.71–3.81)	**1.59 (1.02–2.49)**
HHEX	rs7923837*	G	1.24 (0.80–1.94)	1.05 (0.59–1.86)	0.74 (0.36–1.53)	1.59 (0.77–3.29)	1.57 (0.98–2.52)
IGF2BP2	rs1470579*	C	**1.76 (1.13–2.75)**	0.95 (0.43–2.10)	0.89 (0.37–2.16)	**2.45 (1.08–5.53)**	**2.67 (1.67–4.31)**
JAZF1	rs864745*	T	1.07 (0.69–1.67)	0.89 (0.49–1.61)	0.55 (0.24–1.25)	1.27 (0.59–2.75)	1.39 (0.87–2.23)
KCNJ11	rs5219	T	1.00 (0.64–1.58)	0.82 (0.38–1.74)	0.51 (0.17–1.55)	1.71 (0.66–4.39)	1.21 (0.71–2.05)
KCNQ1	rs2237895*	C	0.92 (0.61–1.38)	0.79 (0.40–1.54)	0.29 (0.08–1.05)	1.06 (0.44–2.55)	1.24 (0.80–1.94)
NOTCH2	rs2934381	A	1.15 (0.58–2.27)	0.44 (0.06–3.16)	0.57 (0.08–4.22)	1.29 (0.34–4.83)	1.81 (0.78–4.20)
PKN2	rs6698181	T	0.85 (0.55–1.31)	0.90 (0.45–1.80)	0.41 (0.13–1.22)	0.89 (0.32–2.51)	1.00 (0.61–1.66)
PPARG	rs1801282*	C	0.92 (0.44–1.95)	0.73 (0.33–1.63)	0.53 (0.21–1.34)	1.02 (0.44–2.36)	1.12 (0.52–2.41)
TCF7L2	rs7903146	T	0.61 (0.36–1.03)	0.53 (0.21–1.32)	**0.13 (0.02–0.95)**	0.43 (0.11–1.69)	0.90 (0.51–1.59)

*P-value < 0.05 for likelihood ratio test between pooled sample and stratified by regimen type (χ^2 with 3 df)

†Model is adjusted for time-dependent BMI category (< 25, 25–29.9, ≥ 30), age (18–29, 30–39, 40–49, 50–82), and genetic ancestry PC 1–10

1Self-reported Non-Hispanic White, Hispanic, Asian, Native American, Other

2Established risk allele in European populations; not necessarily the minor allele

3Two nucleotide reverse transcriptase inhibitors (NRTI) and one non-nucleotide reverse transcriptase inhibitor (NNRTI)

4Three or more NRTIs with or without NNRTI (≥3 NRTIs=154 PY, ≥3 NRTIs + 1 NNRTI=85 PY)

[5] At least two NRTIs and one or more protease inhibitors (PI) (≥2 NRTIs + 1 PI=564 PY, ≥2 NRTIs + two or three PIs=456 PY)

Table 4

Associations between the risk allele of GWAS-derived single nucleotide polymorphisms (SNP) and incident type 2 diabetes (DM) in self-reported African-Americans and stratified by regimen.

					cART regimens		
Gene	**SNP**	**Risk Allele[1]**	**All Regimens 49 DM / 4,348 PY HR† (95% CI)**	**No Treatment 19 DM / 1,828 PY HR† (95% CI)**	**2 NRTIs + NNRTI[2] 9 DM / 868 PY HR† (95% CI)**	**≥3 NRTIs ± NNRTI[3] 4 DM / 282 PY HR† (95% CI)**	**≥2 NRTIs [4] 17 DM / 1,370 PY HR† (95% CI)**
CAMK1D	rs12779790	G	0.88 (0.48–1.63)	0.52 (0.16–1.67)	0.97 (0.31–3.02)	2.23 (0.55–8.95)	0.98 (0.40–2.39)
CDKAL1	rs7754840	C	0.94 (0.62–1.43)	0.91 (0.55–1.50)	0.99 (0.55–1.80)	1.10 (0.52–2.35)	0.91 (0.54–1.53)
CDKN2A/B	rs564398	T	1.99 (0.65–6.12)	1.91 (0.61–5.99)	1.82 (0.56–5.91)	2.46 (0.72–8.42)	2.05 (0.66–6.37)
CDKN2A/B	rs10811661	T	0.70 (0.35–1.39)	0.67 (0.32–1.38)	0.64 (0.30–1.39)	0.81 (0.34–1.93)	0.73 (0.36–1.51)
FTO	rs8050136	A	1.16 (0.77–1.77)	1.06 (0.62–1.81)	1.14 (0.61–2.13)	1.25 (0.45–3.50)	1.28 (0.77–2.13)
HHEX	rs7923837	G	1.09 (0.46–2.59)	1.03 (0.42–2.52)	1.03 (0.41–2.57)	1.27 (0.47–3.48)	1.18 (0.48–2.87)
IGF2BP2	rs1470579	C	0.85 (0.52–1.38)	0.80 (0.46–1.38)	0.73 (0.39–1.35)	1.10 (0.54–2.24)	0.91 (0.53–1.56)
JAZF1	rs864745	T	0.60 (0.40–0.91)	0.59 (0.37–0.97)	0.54 (0.29–0.98)	0.77 (0.35–1.72)	0.63 (0.38–1.04)
KCNJ11	rs5219	T	0.89 (0.38–2.11)	1.58 (0.57–4.42)	2.20 (0.51–9.53)	--	--
KCNQ1	rs2237895	C	0.88 0.50–1.57)	0.31 (0.07–1.25)	1.41 (0.65–3.08)	1.18 (0.21–6.61)	1.05 (0.48–2.34)
NOTCH2	rs2934381	A	1.00 (0.66–1.52)	0.91 (0.53–1.56)	0.52 (0.20–1.35)	1.68 (0.70–4.02)	1.32 (0.77–2.25)
PKN2	rs6698181	T	0.59 (0.29–1.20)	0.19 (0.03–1.40)	0.29 (0.04–2.06)	1.38 (0.21–9.18)	0.98 (0.44–2.19)
PPARG	rs1801282[5]	C	--				
TCF7L2	rs7903146	T	0.91 (0.57–1.43)	0.96 (0.52–1.78)	0.70 (0.27–1.79)	0.68 (0.11–4.02)	1.08 (0.56–2.07)

† Model is adjusted for time-dependent BMI category (< 25, 25–29.9, ≥ 30), age (18–29, 30–39, 40–49, 50–82), and genetic ancestry PC 1–10

[1] Established risk allele in European populations; not necessarily the minor allele

[2] Two nucleotide reverse transcriptase inhibitors (NRTI) and one non-nucleotide reverse transcriptase inhibitor (NNRTI)

[3] Three or more NRTIs with or without NNRTI (≥3 NRTIs=187 PY, ≥3 NRTIs + 1 NNRTI=95 PY)

[4] At least two NRTIs and one or more protease inhibitors (PI) (≥2 NRTIs + 1 PI=827 PY, ≥2 NRTIs + two or three PIs=543 PY)

[5] Not tested in African-Americans due to low non-risk allele (G) frequency (2%)