T cell subsets and incidence of diabetes in persons with HIV in the ACTG Study A5001

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BACKGROUND

Persons with HIV (PWH) have persistent changes in T cell subsets that can be modified by aging and may contribute to the high burden of comorbid conditions, including type 2 diabetes (DM), observed in older PWH. Here, we examined associations of T cell subsets measured at a uniform time post-ART initiation with incident DM among PWH in the AIDS Clinical Trials Group study A5001 (ALLRT).

METHODS

A5001 enrolled PWH from ACTG clinical trials (parent studies) between 2000 and 2011. This analysis included A5001 participants who were ARV treatment-naïve at entry into their parent study and whose specimens collected 1 year post-ART initiation (baseline) underwent flow cytometry.

DM was defined as: 2 consecutive non-fasting serum glucose measures >200 mg/dl or fasting glucose >126 mg/dl; DM diagnosis; or oral antiglycemic or insulin use for >30 days.

Flow cytometry was conducted using ACTG consensus methods: 5 ml of fresh whole blood either stained and analyzed on the day that it was obtained or collected in potassium EDTA tubes and shipped at room temperature overnight to an ACTG-approved flow laboratory where it was immediately stained and analyzed.

We fit Cox proportional hazards models to evaluate associations of T cell subsets measured 1 yr post-ART initiation with incident DM. PWH with prevalent DM (≤1yr post-ART) were excluded. Multivariable models included known risk factors for diabetes: age, sex at birth (gender not available), self-reported race/ethnicity, smoking status, time-updated BMI, triglyceride, history of cardiovascular disease, and history of hypertension. We explored effect modification by demographic and clinical factors by including interaction terms between each T cell subset and effect modifier in multivariable models.

Alterations that occur in **T cell subsets** among PWH may modify and increase risk for comorbid conditions.

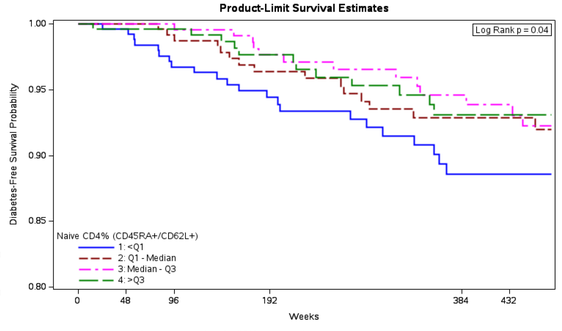
We found that a having a lower proportion of **naïve CD4+ T cells** 1 year after ART initiation **was associated with increased diabetes incidence**, particularly among PWH who were younger, had greater BMI, or were virally non-suppressed.

Table. Characteristics of Study Participants at Baseline (1-Year Post-ART) (N=1015)

Characteristic		Total (N=1015)	No Diabetes (N=953)	Incident Diabetes (N=62)
Female sex at birth	F	179 (18%)	165 (17%)	14 (23%)
Race/Ethnicity	White Non-Hispanic	485 (48%)	457 (48%)	28 (45%)
	Black Non-Hispanic	314 (31%)	292 (31%)	22 (35%)
	Hispanic + Other	216 (21%)	204 (21%)	12 (19%)
Age at ART initiation (yrs)	Median (Q1, Q3)	36 (31, 43)	36 (31, 42)	42 (37, 47)
	≥45	201 (20%)	179 (19%)	22 (35%)
CD4 T cell count (cells/mm^3)	Median (Q1, Q3)	403 (259, 602)	404 (260, 598)	351 (234, 707)
	<200	147 (14%)	137 (14%)	10 (16%)
HIV-1 RNA (copies/ ml)	Median (Q1, Q3)	49 (49, 49)	49 (49, 49)	49 (49, 49)
	≥200	129 (13%)	120 (13%)	9 (15%)
HDL (mg/dl)	Median (Q1, Q3)	45 (37, 54)	45.0 (37.0, 54.3)	39 (35, 49)
	≥40	569 (66%)	545 (67%)	24 (49%)
LDL (mg/dl)	Median (Q1, Q3)	113 (90, 139)	113 (89, 138)	128 (105, 155)
	≥160	122 (15%)	114 (14%)	8 (17%)
Cholesterol (mg/dl)	Median (Q1, Q3)	192 (164, 228)	191 (164, 226)	221.0 (183.0, 243.5)
	≥200	380 (43%)	347 (42%)	33 (63%)
Triglycerides (mg/dl)	Median (Q1, Q3)	140 (94, 220)	138 (92, 212)	204.5 (137.0, 341.0)
	≥200	273 (30%)	243 (29%)	30 (54%)
BMI (kg/m^2)	Median (Q1, Q3)	25.3 (22.6, 28.2)	25.1 (22.4, 27.9)	29.0 (26.3, 32.1)
History of hypertension		157 (15%)	131 (14%)	26 (42%)
Smoking status	Current smoker	335 (33%)	322 (34%)	13 (21%)
	Prior smoker	271 (27%)	255 (27%)	16 (26%)
	Never smoker	405 (40%)	373 (39%)	32 (52%)
CVD		18 (2%)	15 (2%)	3 (5%)

Missing observations: HDL: n=156; LDL: n=180; cholesterol: n=133; triglycerides: n=108; smoking: n=4

Figure 1. Kaplan-Meier curve for incident diabetes by quartile of naïve CD4 %



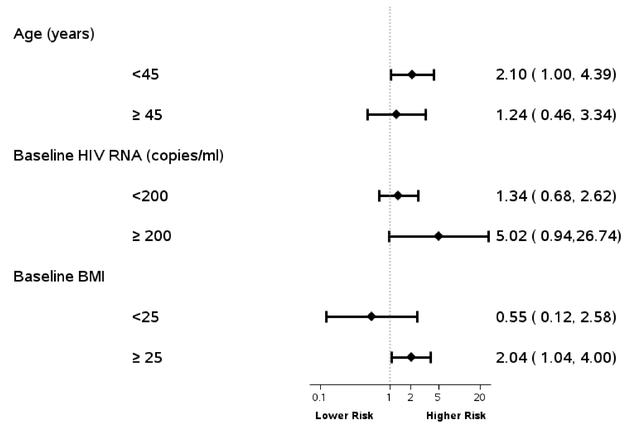
P-value is from logrank test comparing lowest quartile (Q1) to higher quartiles

RESULTS

1015 PWH had ≥1 subset (% activated CD4 or CD8 [HLA-DR+/CD38+], % senescent CD4 or CD8 [CD28-], % memory CD4 [CD45RA-/CD45RO+], % naïve CD4 [CD45RA+/CD62L+]) measured 1yr post-ART initiation. Most participants were male; median age was 36 years (Q1,Q3=31,43). There were 62 DM events. PWH with DM were older, had higher triglycerides, greater BMI, and were more likely to have hypertension or low CD4/CD8 ratio than those without DM. (Table).

PWH in the lowest quartile of % naive CD4 T cells had a higher incidence of DM than those in higher quartiles (Figure 1).Several variables modified this association, including age, viral load, and BMI (Figure 2).

Figure 2. Hazard Ratios (95% CI): naive CD4%(≥ Q1 vs < Q1) and diabetes incidence



CONCLUSIONS

A lower proportion of naïve CD4+ T cells, potentially reflective of reduced naïve cell replenishment or increased memory cell inflation, may be associated with increased diabetes incidence in PWH.

ADDITIONAL KEY INFORMATION

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