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Background

- ◆ Integrase strand transfer inhibitor (INSTI)-based ART regimens are implicated in weight gain in HIV+ ART-naïve ART initiators^{1,2}
- ◆ However, limited data are available regarding metabolic consequences
- ◆ We therefore examined the impact of initial ART class on incident diabetes mellitus (DM) in a large North American HIV cohort
- ◆ We also examined mediation of this effect by weight change

Methods

- ◆ **Inclusion:** ART-naïve adults (≥18 years old) initiating INSTI-, PI-, or NNRTI-based ART from 2007-2016 in the NA-ACCORD
 - Persons in analyses assessing weight as a mediator also had 12-month (±6-months) weight measurements; persons with incident DM before qualifying 12-month weight measure were excluded
 - Baron & Kenny approach for **total** [both mediated & not mediated by weight] and **direct** [not mediated by weight] effects was used
- ◆ **Outcome:** Incident DM was HgA1c >6.5%, initiation of diabetes-specific medication, or DM diagnosis along with diabetes-related medication (precluding prevalent DM or pre-diabetes)³
- ◆ **Follow-up:** From ART initiation of ≥45 days duration until incident DM, virologic failure (VL ≥400 copies/mL), ART regimen core switch, administrative close, death, or loss to follow-up (≥12 months with no visit or lab measure before cohort close)
- ◆ **Confounders:** Age, Sex, Race, HIV Transmission Risk, Year of ART initiation, and baseline Weight, CD4+ count, and log₁₀ VL
- ◆ **Analysis:** Cox regression, stratified by clinic site & adjusting for above confounders, produced adjusted HRs and 95% CIs; missing baseline data were multiply imputed

Results

Table. Characteristics of study population, by initial ART class, 2007-2016

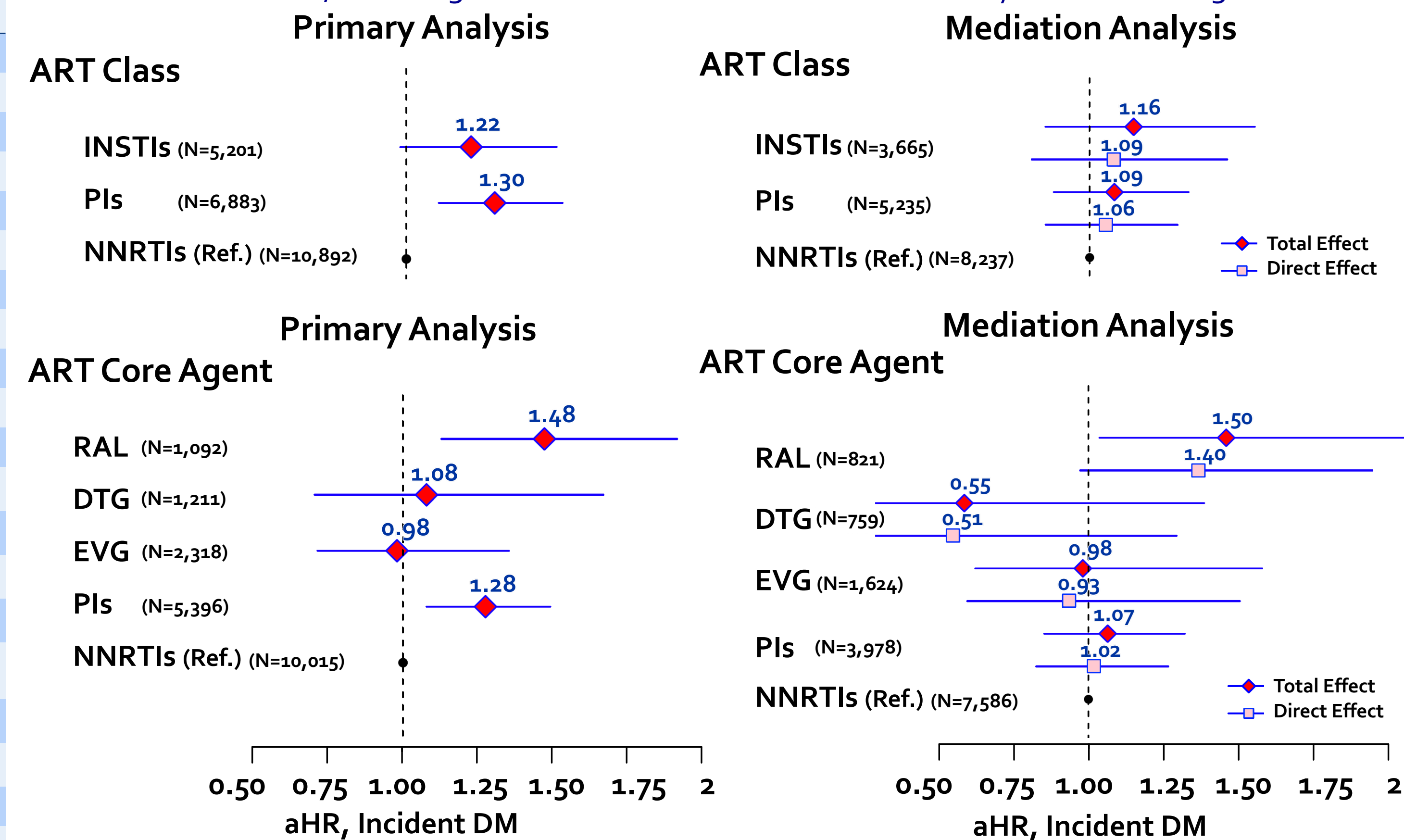
	N	NNRTI-based N = 10,892 (47.4%)	PI-based N = 6,883 (30.0%)	INSTI-based N = 5,201 (22.6%)	P-value
Sex assigned at birth	22,976				<0.001 ¹
Male		0.90 (9,827)	0.80 (5,529)	0.86 (4,478)	
Female		0.10 (1,065)	0.20 (1,354)	0.14 (723)	
Race/Ethnicity	21,886				0.033 ¹
White, non-Hispanic		0.39 (4,064)	0.37 (2,445)	0.39 (1,964)	
non-White		0.61 (6,238)	0.63 (4,084)	0.61 (3,091)	
HIV transmission risk	22,976				<0.001 ¹
MSM		0.40 (4,410)	0.31 (2,146)	0.51 (2,646)	
IDU, including MSM/IDU		0.11 (1,236)	0.14 (997)	0.08 (395)	
Heterosexual		0.15 (1,635)	0.20 (1,407)	0.18 (957)	
Other/Unknown		0.33 (3,611)	0.34 (2,333)	0.23 (1,203)	
Age (years)	22,976	31 42 51	31 41 50	28 37 48	<0.001 ²
Baseline Weight (kg)	19,033	68 78 89	66 76 87	67 77 89	<0.001 ²
Weight 1 year after ART (kg)	17,651	70 80 91	69 79 91	70 80 93	0.049 ²
Baseline BMI (kg/m²)	18,218	22 25 28	22 25 28	22 25 29	<0.001 ²
Baseline CD4+ count (cells/μL)	19,485	182 314 453	105 260 406	190 363 535	<0.001 ²
Baseline log₁₀ HIV-1 RNA	18,410	4.0 4.6 5.1	4.1 4.7 5.2	4.1 4.6 5.2	<0.001 ²
Year of ART initiation	22,976	2008 2010 2012	2008 2010 2012	2013 2014 2016	<0.001 ²
Incident diabetes mellitus	22,976				0.01 ¹
No		0.96 (10,475)	0.96 (6,609)	0.97 (5,045)	
Yes		0.04 (417)	0.04 (274)	0.03 (156)	
Follow-up time (years)	22,976	1.21 3.05 5.25	0.94 2.31 4.16	0.83 1.64 3.00	<0.001 ²

Numbers after proportions in parentheses are frequencies.
^a a , b , c represents the lower quartile a , the median b , and the upper quartile c for continuous variables.
¹ N is the number of non-missing values.
 Tests used: ¹Pearson χ^2 test; ²Kruskal-Wallis test

Conclusions

- ◆ Initiating ART with PI-based or INSTI-based (particularly those containing RAL) vs. NNRTI-based regimens may confer greater risk of incident DM
- ◆ This increased risk is only partially due to 12-month weight gain after initiation
- ◆ Work elucidating metabolic changes following INSTI initiation is ongoing

Figures. Adjusted Hazard Ratios (aHR) for the association between initial ART class or core agent and incident DM, including total & direct effects when mediated by 12-month weight



RAL: raltegravir; DTG: dolutegravir; EVG: elvitegravir
 All models adjusted for Age, Sex, Race, HIV Transmission Risk, Year of ART initiation, and baseline Weight, CD4+ count, and log₁₀ VL
 Continuous covariates were modeled using restricted cubic splines with 5 knots to relax linearity assumptions
 Missing baseline data were multiply imputed and all models were stratified by site

- ◆ Among ART initiators, 847 (4%) developed DM (4% each for PI- and NNRTI-initiators, 3% for INSTI-initiators)
- ◆ Mediation analysis revealed an INSTI-DM association only slightly attenuated by 12-month weight in the model

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