

Integrase strand inhibitors (INSTI) related changes in BMI and risk of diabetes

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BACKGROUND

- Despite a good overall safety profile and high tolerability, studies have found Integrase strand inhibitor (INSTI) use in people living with HIV (PLWH) to be associated with increased body mass index (BMI)^{1,2}
- BMI increases have also been associated with a higher risk of diabetes mellitus (DM)³
- This study compared INSTI and non-INSTI based regimens in terms of the association between BMI and risk of incident DM.

METHODS

- Study baseline: latest of cohort entry, combination antiretroviral (ART) use, or first BMI.
- Study follow-up: Baseline to date of first DM, final follow-up, or 31st December, 2019.
- RESPOND⁴ participants were included if they had CD4 and HIV RNA 12 months before baseline and >2 BMI measurements during follow-up. Those with DM prior to baseline were excluded.
- DM was defined as having a random blood glucose measurement > 11.1 mmol/L, HbA1c>6.5%/48 mmol/L or use of antidiabetic medication or clinical diagnosis.
- Poisson regression assessed the association between time updated log BMI, current INSTI/non-INSTI and TDF/TAF use, and their interactions, on DM risk.

RESULTS

- 20865 RESPOND participants were included.
- 785 (4%) incident DM events:
 - Random blood glucose >11.1 mmol/L : 254 (32%)
 - HbA1c >6.5%/48 mmol/mol : 239 (30%)
 - Use of anti-DM medication/clinical diagnosis: 292 (37%)
- 107641 person years of follow-up (PYFU)
- Crude DM rate: 7.30/1000 PYFU (95% confidence interval(CI) 6.80-7.80)

Table 1: Participant characteristics at baseline

	Total participants n (%)	Participants diagnosed with DM n (%)
Total	20865 (100)	785 (4)
Sex		
Male	15529 (74)	617 (79)
Female	5336 (26)	168 (21)
Age (years)		
Median (IQR)	45 (37 - 52)	50 (44 - 57)
Risk group		
Heterosexual contact	7158 (34)	307 (39)
MSM	9358 (45)	306 (39)
IDU	3108 (15)	118 (15)
Other	507 (2)	23 (3)
Unknown or missing	734 (4)	31 (4)
Ethnicity		
White	15161 (73)	546 (70)
Black	1510 (7)	93 (12)
Other	699 (3)	27 (3)
Unknown	3495 (17)	119 (15)
CD4 count (cells/μL)		
Median (IQR)	551 (380 - 750)	562 (380 - 783)
HIV viral load (copies/mL)		
<200	160967 (77)	649 (83)
≥200	4769 (23)	136 (17)
BMI (kg/m²)		
Median (IQR)	24 (22-26)	27 (23 - 30)
Glucose (mmol/L)		
Median (IQR)	5.1 (4.7-5.6)	5.9 (5.1-6.7)
ART naive	3184 (15)	72 (9)
ART use		
TDF	12157 (58)	462 (59)
TAF	1175 (6)	27 (3)
no TDF/no TAF	7533 (36)	296 (38)
INSTI use		
No	15590 (75)	623 (79)
Yes	5275 (25)	162 (21)

MSM: men who have sex with men; IDU: injecting drug use; HIV: human immunodeficiency virus; BMI: Body mass index; ART: anti-retroviral treatment, TDF:Tenofovir disoproxil fumarate ; TAF: Tenofovir Alafenamide; INSTI: Integrase strand inhibitor

Figure 1. Factors associated with DM

	No. of DM events/ PYFU	Crude rate/ 1000PYS	IRR (95% CI)	p-value
Sex				
Male	617/79277	7.80	Reference	
Female	168/28364	5.90	0.69 (0.57, 0.85)	<0.001
Risk group				
Heterosexual contact	307/38220	8.00	Reference	
MSM	306/48081	6.40	0.86 (0.71, 1.04)	0.117
IDU	118/15205	7.80	1.26 (1.00, 1.58)	0.049
Other	23/2646	8.70	1.34 (0.87, 2.05)	0.181
Unknown/missing	31/3490	8.90	1.01 (0.69, 1.46)	0.969
Ethnicity				
White	546/79196	6.90	Reference	
Black	93/8153	11.40	1.78 (1.40, 2.28)	<0.001
Other	27/3551	7.60	1.81 (1.22, 2.68)	0.003
Unknown	119/16739	7.10	1.09 (0.89, 1.34)	0.389
CD4 (cells/μL)				
≤200	52/3541	14.70	2.24 (1.69, 2.98)	<0.001
201-350	69/9869	7.00	0.96 (0.75, 1.23)	0.762
≥350	664/94230	7.00	Reference	
ART				
TDF	298/47399	6.30	Reference	
TAF	151/18902	8.00	1.01 (0.82, 1.25)	0.912
no TDF/no TAF	336/41339	8.10	1.13 (0.96, 1.33)	0.143
INSTI use				
No	414/68656	6.00	Reference	
Yes	371/38984	9.50	1.48 (1.29, 1.71)	<0.001
High BP				
No	335/64147	5.20	Reference	
Yes	311/29159	10.70	1.43 (1.22, 1.67)	<0.001

Note: Analyses was adjusted for natural log of age (IRR 7.28) and natural log of BMI (16.54). MSM: Men who have sex with men; IDU: Injecting drug use; BP: blood pressure
Interaction of ln BMI and INSTI-use: IRR 0.57, 95% CI (0.27, 1.18), p-value 0.130

Figure 2. Predicted risk of DM by current INSTI use and BMI

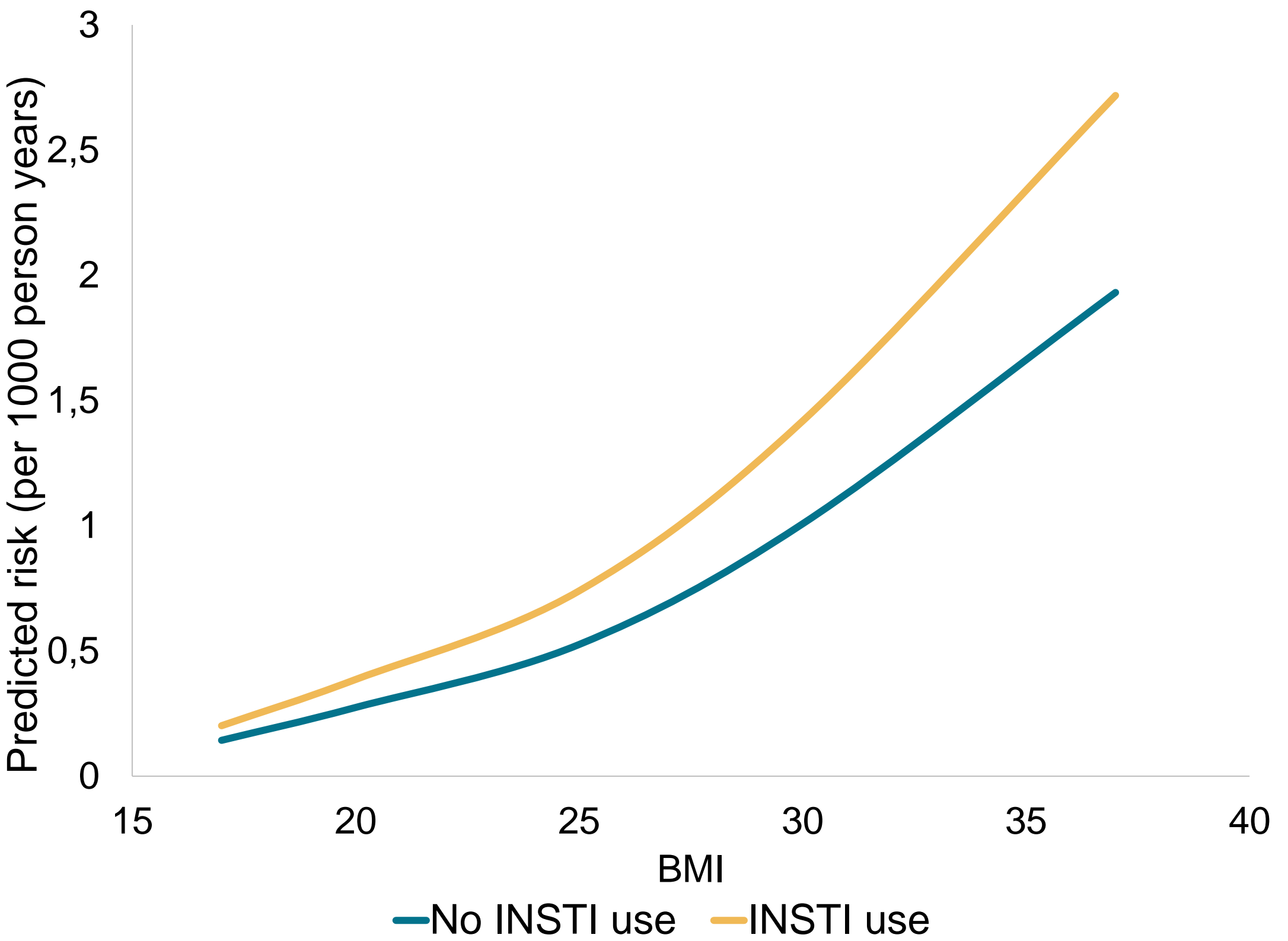


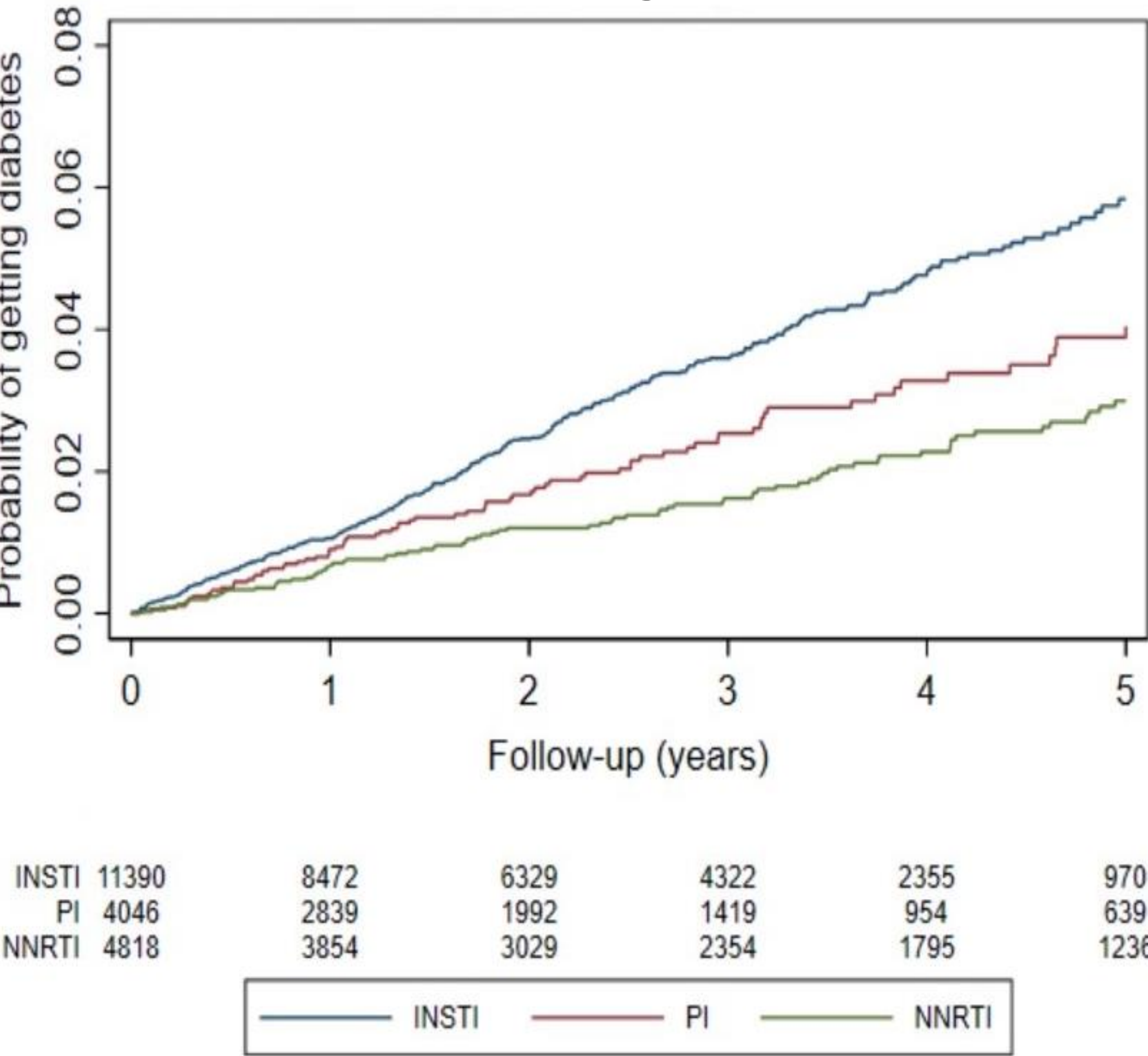
Figure 2 shows the predicted risk per 1000 person years of DM for BMI (antilog of log BMI among INSTI and non-INSTI users when adjusted for sex, natural log of age, HIV risk group, Ethnicity, CD4, hypertension, current TDF/TAF use. Among INSTI users 12% were on raltegravir (RAL), 60% on dolutegravir (DTG), and 28% on other INSTIs (elvitegravir (EVG/c), Bictegravir (BIC), Cabotegravir (CAB)).

Figure 3. Association of different fittings of ARVs and BMI on DM

	Adjusted IRR (95% CI)	p-value
Time-updated continuous BMI		
BMI 21-23 (vs <21)	1.25 (0.93, 1.67)	0.15
BMI 23-26 (vs <21)	1.47 (1.13, 1.91)	0.006
BMI 27-30 (vs <21)	2.38 (1.83, 3.10)	<0.001
BMI >30 (vs <21)	5.22 (4.00, 6.82)	<0.001
INSTI use (vs non-INSTI use)	1.48 (1.28, 1.70)	<0.001
7 % increase in current BMI		
7% BMI increase (vs no 7% BMI increase)	1.86 (1.48, 2.35)	<0.001
INSTI use (vs non-INSTI use)	1.37 (1.17, 1.60)	<0.001
Individual INSTIs		
DTG use (vs PI/NNRTIs)	1.54 (1.31, 1.82)	<0.001
RAL use (vs PI/NNRTIs)	1.72 (1.35, 2.19)	<0.001
Other INSTIs (vs PI/NNRTIs)	1.14 (0.88, 1.48)	0.315
Cumulative use of INSTIs		
0-1 year on INSTI (vs never)	1.19 (0.87, 1.62)	0.283
1-2 years on INSTI (vs never)	1.50 (1.16, 1.94)	0.002
2-3 years on INSTI (vs never)	1.47 (1.16, 1.87)	0.001
>3 years on INSTI (vs never)	1.19 (0.99, 1.42)	0.059
Using INSTI, TAF and TDF		
INSTI + TAF use (vs Other ART)	1.22 (0.95, 1.56)	0.12
INSTI +TDF use (vs Other ART)	1.26 (0.97, 1.65)	0.08
INSTI + no TDF /TAF use (vs Other ART)	1.34 (1.08, 1.66)	0.007
Other + TDF use (vs Other ART)	0.78 (0.64, 0.96)	0.02
Other + TAF use (vs Other ART)	0.86 (0.62, 1.20)	0.381
DM risk score per 100PYS		
DM risk per 100PYS	1.21 (1.11, 1.33)	<0.001
INSTI use (vs non-INSTI use)	1.58 (1.36, 1.83)	<0.001
TN/TE with INSTI use		
TE/non-INSTI (vs TE/INSTI)	1.14 (0.81, 1.59)	0.464
TN/non-INSTI (vs TE/INSTI)	1.57 (1.35, 1.81)	<0.001
TN/INSTI (vs TE/INSTI)	1.05 (0.74, 1.48)	0.804

Note: Each analyses was adjusted for natural log of age, sex, HIV risk group, Ethnicity, CD4, natural log of BMI (IRR≈17), high BP, current TDF/TAF use except for the analyses where TDF/ TAF use were combined with INSTI use.
TE: Treatment Experienced TN: Treatment Naive

Figure 4. Kaplan-Meier plot of incident DM among INSTI and non-INSTI users from start of drug class



INSTI	11390	8472	6329	4322	2355	970
PI	4046	2839	1992	1419	954	639
NNRTI	4818	3854	3029	2354	1795	1236

LIMITATIONS

- While the median BMI was 2/year, the observational nature of assessments may have made us unable to adequately adjust for increasing BMI.
- There is a potential for residual confounding caused by factors not collected in REPSOND such as steroids, diet and exercise.
- The definition of diabetes is not based on fasting status and may lead to under-diagnosis of DM in RESPOND.
- It was difficult to exclude channeling bias, though we found little evidence of it.

CONCLUSIONS

- In RESPOND, current use of INSTIs was associated with a 48% increased incidence of DM compared with PIs and NNRTIs, which was partially reduced when adjusted for BMI changes and other variables.
- Lack of an interaction between time updated log BMI and DM in INSTI and non-INSTI users, suggested that the risk increase with INSTIs is not dependent on BMI.
- There was little difference in DM risk between current TAF and TDF users and the effect did not increase with INSTI use.

References: 1 Kerchberger et al. Clin Infect Dis.,2020 2 Lake et al. Clin Infect Dis.,2020 3 Urrutia et al. Sci Rep. 2021 4 Neesgaard et al. Microorganisms, 2020,

Acknowledgements: Participating cohorts: CHU Saint-Pierre cohort, Austrian HIV Cohort, Australian HIV Observational Database, ATHENA cohort, EuroSIDA Cohort, Frankfurt HIV Cohort Study, Georgian National AIDS Health Information System, Nice HIV cohort, ICONA Cohort, Modena HIV Cohort, PISCIS cohort, Swiss HIV Cohort, InfCare Cohort, Royal Free HIV Cohort, San Raffaele Scientific Institute, University Hospital Bonn HIV cohort, University Hospital Cologne HIV cohort.

The RESPOND Study Group <https://www.chip.dk/Studies/RESPOND/Study-Group>

RESPOND Scientific Interest Groups <https://chip.dk/Research/Studies/RESPOND/SIGs>
The International Cohort Consortium of Infectious Disease (RESPOND) has received funding from Viiv Healthcare LLC, Gilead Sciences and Merck Sharp & Dohme. Additional support has been provided by participating cohorts contributing data in-kind and/or statistical support: Austrian HIV Cohort Study (AHIVCOS), The Australian HIV Observational Database (AHOD), CHU Saint-Pierre, University Hospital Cologne, EuroSIDA, Frankfurt HIV Cohort Study, Georgian National AIDS Health Information System (AIDS HIS), Modena HIV Cohort, San Raffaele Scientific Institute, Swiss HIV Cohort Study (SHCS), AIDS Therapy Evaluation in the Netherlands Cohort (ATHENA), Royal Free HIV Cohort Study. AHOD is further supported by grant No. U01-AI069907 from the U.S. National Institutes of Health, and GNT1050874 of the National Health and Medical Research Council, Australia.