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

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Summary

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- Main question of study:
  - What do BMI gains observed in people receiving INSTIs mean in terms of increased risks of diabetes mellitus (DM) that are traditionally associated with increased BMI.

- Main findings:
  - Time-updated natural log of BMI was strongly associated with DM and
  - Current use of INSTIs was associated with DM.
  - No evidence of interaction between BMI and DM in INSTI and non-INSTI users suggested that the risk increase with INSTIs is not dependent on BMI.

- Significance:
  - Understanding the extent to which BMI increases in people with HIV receiving INSTIs increases the risk of clinical endpoints such as DM will fill a current knowledge gap, and aid clinical management including clarifying the needs for monitoring weight more systematically in at risk individuals.

Background

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- Integrase strand transfer inhibitors (INSTIs) have high efficacy for suppressing human immunodeficiency virus (HIV) and a high genetic barrier to developing drug resistance. Hence, INSTIs have been recommended as the preferred first and second-line anti-retroviral therapy (ART) regimens to treat HIV.[1]

- INSTI use in people living with HIV has been linked to weight gain[2] and treatment emergent obesity with possible association with weight-related co-morbidities such as diabetes DM. [3,4]

- Body-mass-index (BMI) increases have also been associated with a higher risk of DM.[5,6]

References: ***1*** *WHO Guidelines Approved by the Guidelines Review Committee, 2021.* ***2*** *Bansi-Matharu et al. Lancet HIV, 2021.* ***3*** *Kerchberger et al. Clin Infect Dis.,2020* ***4*** *Lake et al. Clin Infect Dis.,2020* ***5*** *Achhra et al. JAIDS, 2018* ***6*** *Urrutia et al. Sci Rep. 2021*

Objectives

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- It remains uncertain what BMI gains seen in people receiving INSTIs mean in terms of increased risks of the clinical events that are traditionally associated with increased BMI.
- In this study we compared the association between BMI and risk of incident diabetes, between INSTI and non-INSTI-based regimens.

Methods

- The International Cohort Consortium of Infectious Disease (RESPOND) [1]
  - Involves 19 cohorts from Europe and Australia
  - Over 30,000 people with HIV in follow-up
  - Collects demographics, antiretroviral treatment (ART), blood pressure (BP), comorbidities (such as cardiovascular disease, cancer, fractures, DM) and laboratory parameters annually [2]

- Inclusion/exclusion criteria: RESPOND participants were included if they had CD4 and HIV RNA measurements 12 months before baseline and >2 BMI measurements during follow-up. Those with DM prior to baseline were excluded.
- Study baseline: latest of cohort entry or 1/1/2012, ART use, or first BMI.
- Study follow-up: From baseline to date of first DM, final follow-up, or 31st December, 2019.

References: **1** *Neesgaard et al. Microorganisms, 2020* **2** *RESPOND Manual of Operations V 1.7, 2021*

Methods

- DM was defined as:
  - Random blood glucose>11.1 mmol/L
  - HbA1c>6.5%/48 mmol/mol
  - Use of antidiabetic medication or clinical diagnosis.
- Covariates included in analysis:

Time fixed covariates	Time updated covariates
Sex	Natural log of Age (ln Age)
Mode of HIV acquisition	CD4 cell counts (cells/µL)
Ethnicity	HIV viral load (copies/mL)
Region	Natural log of BMI (ln BMI)
Hepatitis C virus co-infection	ART treatment (TAF, TDF, non-TAF/TDF)
Hepatitis B virus co-infection	INSTI use
Prior AIDS	Smoking
ART naive	High BP
Glucose (mmol/L)	Cholesterol (mg/dL)

TAF: Tenofovir alafenamide ; TDF: Tenofovir disoproxil fumarate;
High BP (blood pressure) defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg or initiation of anti-hypertensives

Methods

- Poisson regression was used to assess the association between time updated natural log of BMI, current INSTI/non-INSTI use, current TDF/TAF/no TDF or TAF use, and their interactions, on DM risk.

- Sensitivity analyses using different fittings of ARV and BMI on DM :
  - Time-updated continuous BMI
  - 7% increases in BMI
  - Individual INSTIs
  - Cumulative use of INSTIs
  - Use of TAF/TDF with INSTIs
  - Short term DM risk score
  - Treatment Naïve/Treatment Experience with INSTI use

- Kaplan-Meier plot of incident DM among INSTI and non-INSTI users from the start of drug class to assess DM events shortly after starting INSTIs

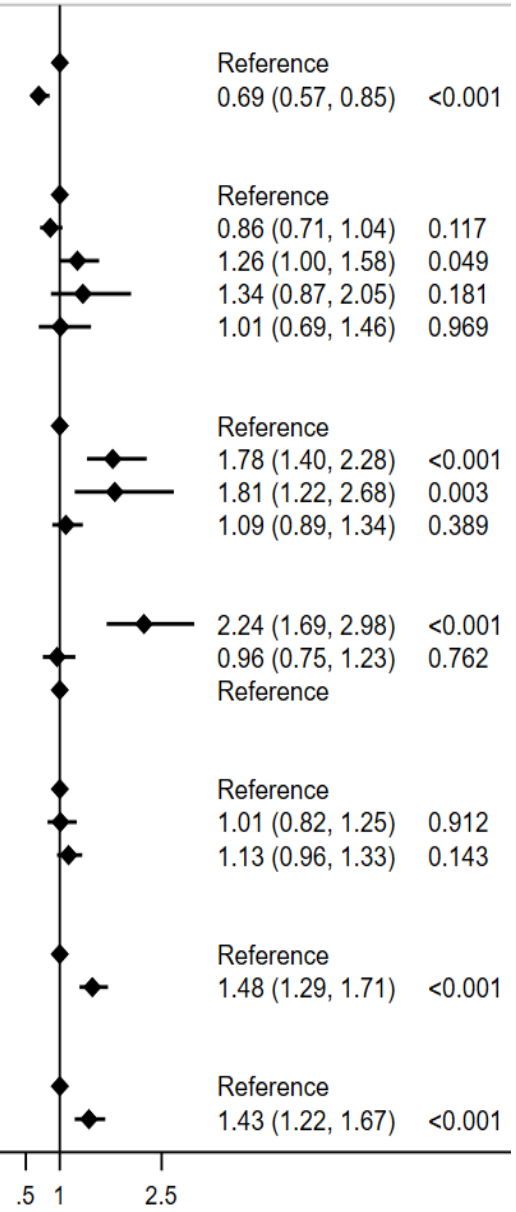
Participant characteristics

	Total participants	Participants diagnosed with DM
	n(%)	n(%)
Total	20865 (100)	785 (4)
Age (years) Median (IQR)	45 (37-52)	50 (44-57)
Sex		
Male	15529 (74)	617 (79)
HIV risk group		
Men who have sex with men(MSM)	9358 (45)	306 (39)
Ethnicity		
White	15161 (73)	546 (70)
CD4 cell count (cells/µL)		
Median (IQR)	551 (380-750)	562 (380-783)
HIV viral load (copies/mL)		
< 200	160967 (77)	649 (83)
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 naïve		
Yes	3184 (15)	72 (9)

- 107,641 person years of follow-up (median 4.8 years of follow-up)
- Overall crude rate of incident DM: **7.80/1000 PYS**

Main Results - Factors associated with onset 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



- Analyses was adjusted for natural log of age (IRR 7.3 per log increase, 95% CI (5.20, 10.20), p-value <0.001) and natural log of BMI (16.54 per log increase, 95% CI (11.33, 24.13), p-value <0.001)
- Interaction of ln BMI and INSTI-use: IRR 0.57, 95% CI (0.27, 1.18), p-value 0.130
- Absolute risk increase with INSTIs was 3/1000 person years

Abbreviations: MSM: Men who have sex with men; IDU: Injecting drug use; BP: blood pressure

Results

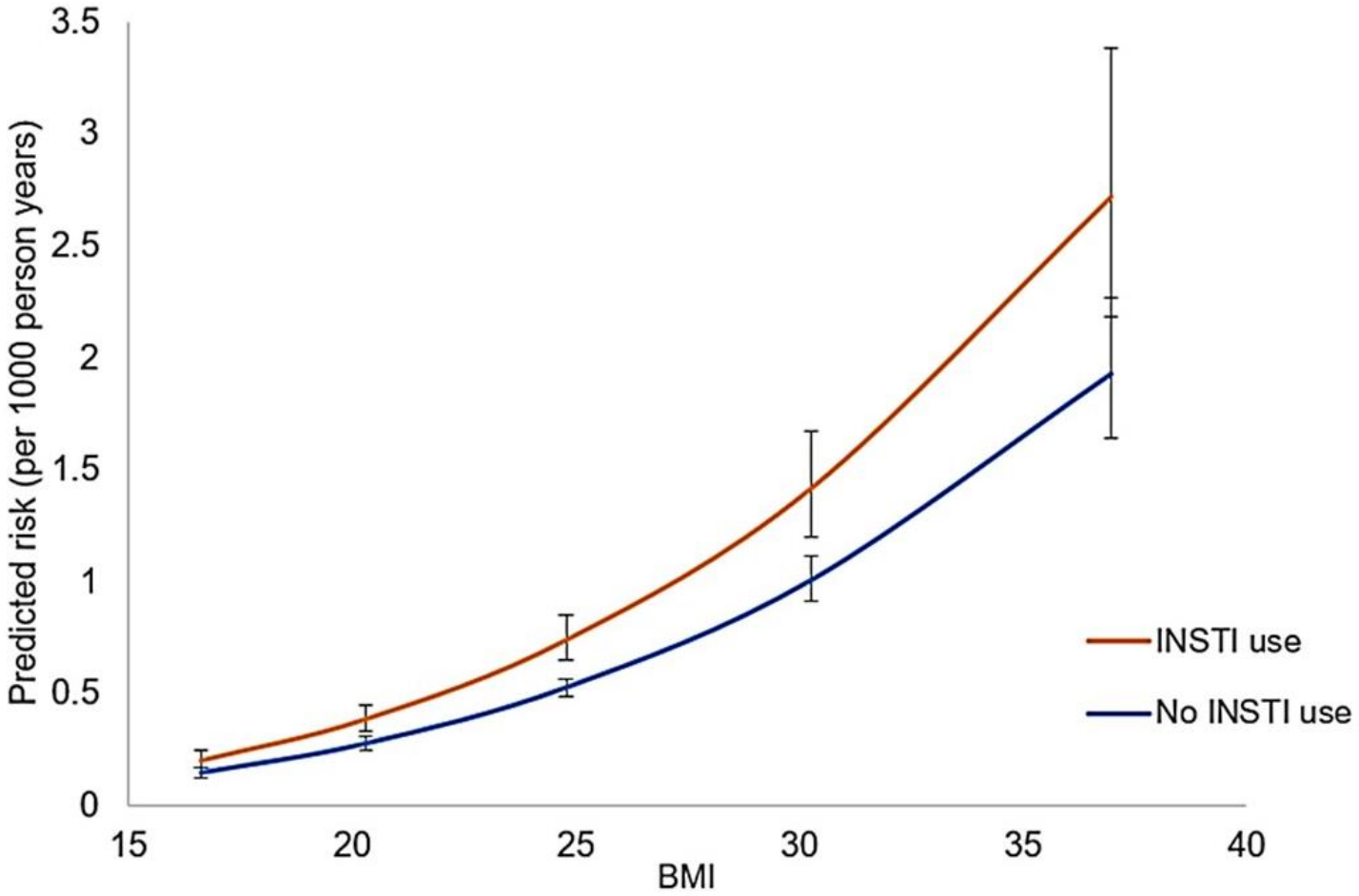
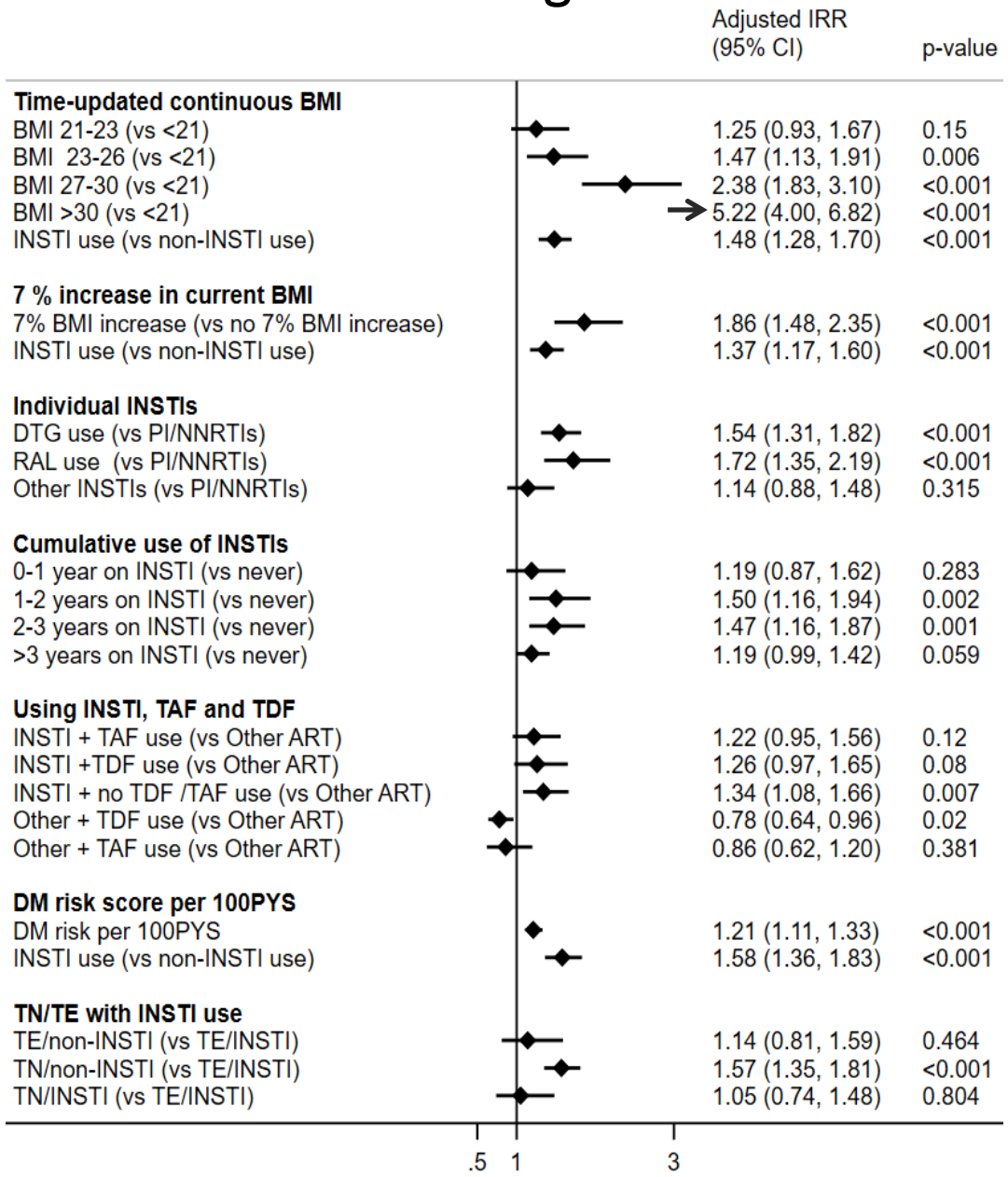


Figure shows the predicted risk per 1000 person years of DM for BMI (antilog of log BMI among INSTI and non-INSTI users when adjusted for sex, natural log of age, mode of HIV acquisition, Ethnicity, CD4, high BP, current TDF/TAF use. Among INSTI users 12% were on raltegravir (RAL), 60% on dolutegravir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

Sensitivity analyses: Association of different fittings of ARVs and BMI on DM



Each sensitivity 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

Results

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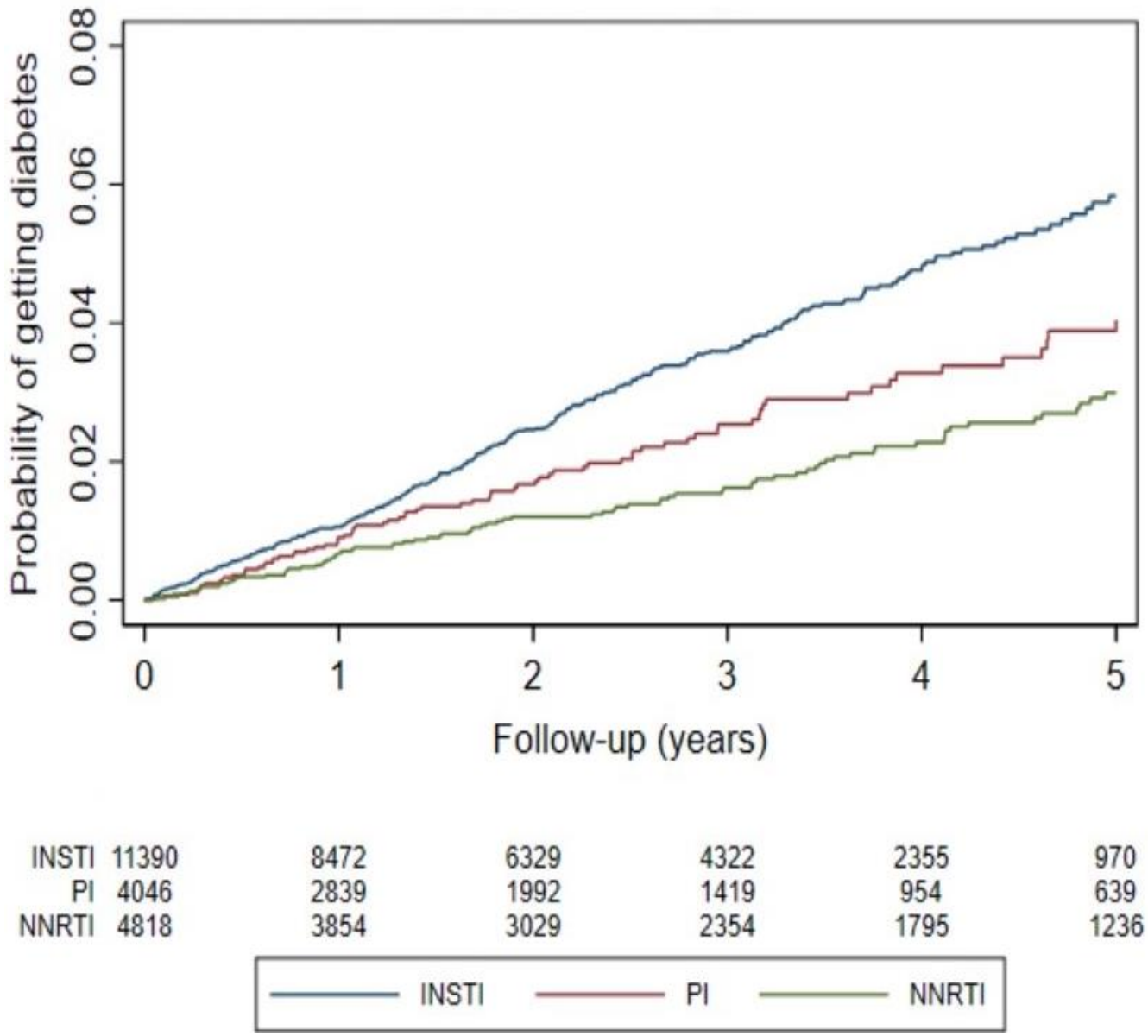
Kaplan-Meier plot of incident DM among INSTI and non-INSTI users from start of drug class



Overview

- Crude rate of DM of 7.3 per 1000 PYS was similar to cohorts with similar median year of follow-up.[1,2]
- A strong association was found between ln BMI and DM.
- Current INSTI use was also associated with risk of DM independently of 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*** *Bratu et al. Bmj Open.,2021* ***2*** *Urrutia et al. Sci Rep. 2021*

Limitations

- While the median number of BMI measurements 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 RESPOND 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.

Conclusion

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- In RESPOND, current use of INSTIs was associated with a 48% increased incidence of DM compared with PIs and NNRTIs, which was only? 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.
- With the clear association between INSTI use and the risk of DM found here, further studies on a possible biological mechanisms increasing DM in INSTI users are required.

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